Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015-26. DOI: 10.1056/NEJMoa1613683

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes. Please note that the statistical analysis plan is embedded in the protocol as section 8.

Table of Contents

Merck & Co., Inc., Kenilworth, N.J., U.S.A. (the Company) policy on posting of redacted study protocols on journal websites is described in Guidelines for Publication of Clinical Trials in the Scientific Literature on the www.merck.com website.

For publicly posted protocols, the Company redacts content that contains proprietary and private information.

This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

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

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

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

TITLE:

A Phase III Randomized Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer

IND NUMBER: 122753
EudraCT NUMBER: 2014-002009-40

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.0 TRIAL SUMMARY

Abbreviated Title	Ph 3 trial of Pembrolizumab (MK-3475) vs paclitaxel or vinflunine in recurrent/progressive metastatic urothelial cancer
Trial Phase	Phase III
Clinical Indication	Metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy
Trial Type	Interventional
Type of control	Active control without placebo
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	A) Pembrolizumab (MK-3475) 200 mg every 3 weeks B) Investigator's choice of: -Paclitaxel 175 mg/m^2 every 3 weeks OR -Vinflunine 320 mg/m^2 every 3 weeks
Number of trial subjects	Approximately 470 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 27 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 42 days, each subject will receive treatment based on the arm to which they have been randomized. Treatment on trial 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 withdrawals consent, pregnancy of the subject, noncompliance with trial treatment or procedures requirements, subject receives 24 months of trial treatment (pembrolizumab (MK-3475) arm only), or administrative reasons. Subjects on the pembrolizumab (MK-3475) arm who attain a complete response may consider stopping trial treatment if they meet criteria for holding therapy. Subjects receiving pembrolizumab (MK-3475) 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 they meet 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 (serious adverse events and events of clinical interest will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up every 6 weeks for disease status until disease progression is confirmed by the investigator/site radiologist, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival every 12 weeks until death, withdrawal of consent, or the end of the trial.
Randomization Ratio	1:1

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 randomized, active-controlled, multi-site, open-label trial of pembrolizumab (MK-3475) in subjects with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy, to be conducted in conformance with Good Clinical Practices.

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.

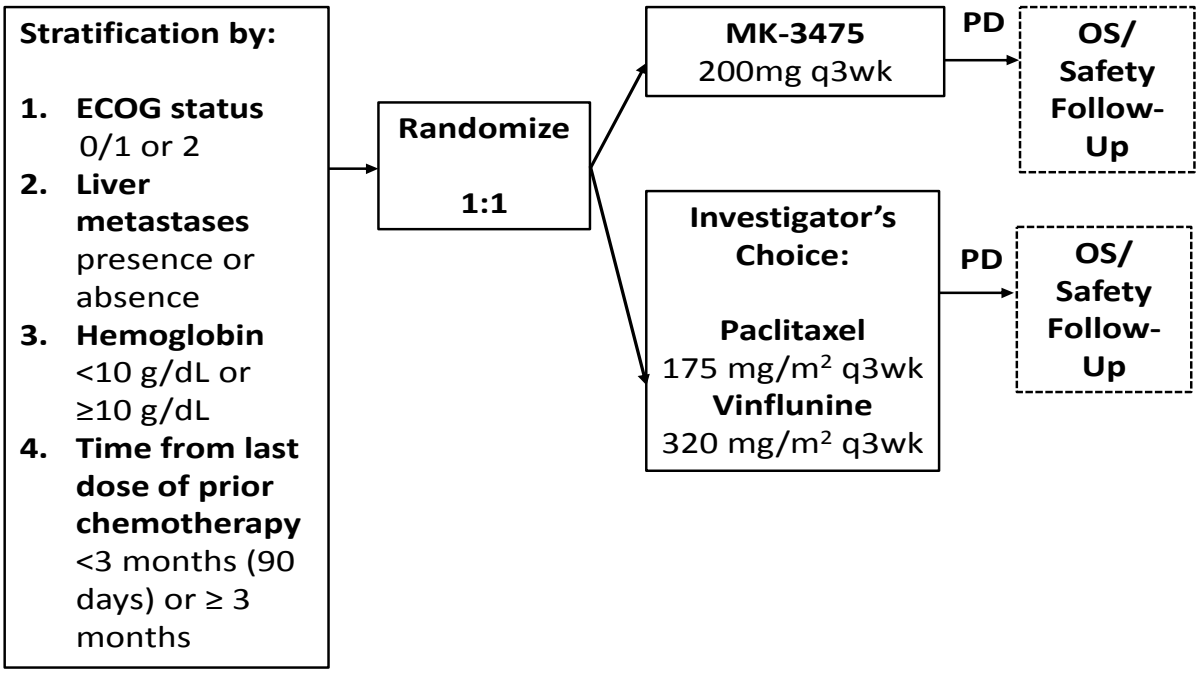


Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To evaluate the overall survival (OS) of subjects with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following

platinum-based chemotherapy (recurrent/progressive metastatic urothelial cancer), when treated with pembrolizumab (MK-3475) compared to paclitaxel or vinflunine.

Hypothesis: Pembrolizumab (MK-3475) prolongs OS in subjects with recurrent/progressive metastatic urothelial cancer compared to paclitaxel or vinflunine.

(2) **Objective:** To evaluate progression-free survival (PFS) per RECIST 1.1 by independent radiologists' review of subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475)compared to paclitaxel or vinflunine.

Hypotheses: Pembrolizumab (MK-3475) prolongs PFS by RECIST 1.1 (as assessed by blinded central radiology review) in subjects with recurrent/progressive metastatic urothelial cancer compared to paclitaxel or vinflunine.

3.2 **Secondary Objective(s) & Hypothesis(es)**

(1) **Objective**: To evaluate the safety and tolerability profile of pembrolizumab (MK-3475) in subjects with recurrent/progressive metastatic urothelial cancer.

(2) **Objective**: To evaluate PFS per modified RECIST 1.1 by independent radiologists' review of subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel or vinflunine.

Hypothesis: pembrolizumab (MK-3475) prolongs PFS by modified RECIST 1.1 (as assessed by blinded central radiology review) in subjects with recurrent/progressive metastatic urothelial cancer compared to paclitaxel or vinflunine.

(3) **Objective:** To evaluate the objective response rate (ORR) per RECIST 1.1. by independent radiologists' review in subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel or vinflunine.

Hypothesis: Pembrolizumab (MK-3475)improves ORR per RECIST 1.1. by independent radiologists' review in subjects with recurrent/progressive metastatic urothelial cancer compared to paclitaxel or vinflunine.

(4) **Objective:** To evaluate the objective response rate (ORR) per modified RECIST 1.1 by independent radiologists' review in subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel or vinflunine.

Hypothesis: Pembrolizumab (MK-3475) improves ORR per modified RECIST 1.1 by independent radiologists' review in subjects with recurrent/progressive metastatic urothelial cancer compared to paclitaxel or vinflunine.

(5) **Objective:** To evaluate response duration per RECIST 1.1 by independent radiologists' review in subjects with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel or vinflunine.

(6) **Objective:** To evaluate PFS, OS and ORR in a subgroup of subjects with high PD-L1 expression level and recurrent/progressive metastatic urothelial cancer treated with Pembrolizumab (MK-3475) compared to paclitaxel or vinflunine.

3.3 Exploratory Objectives

(1) **Objective:** To evaluate changes in health-related quality-of-life assessments from baseline in subjects with recurrent/progressive metastatic urothelial cancer using the EORTC QLQ-C30.

(2) **Objective:** To characterize utilities in previously-treated subjects with recurrent/progressive metastatic urothelial cancer using the EuroQol EQ-5D.

(3) **Objective:** To investigate the relationship between PD-L1 expression and response to pembrolizumab (MK-3475) treatment utilizing newly obtained or archival FFPE tumor tissue.

(4) **Objective:** To investigate the relationship between pembrolizumab (MK-3475) treatment and biomarkers predicting response (e.g., immunohistochemistry, proteomic signatures, genetic variation, and gene expression signatures) utilizing newly obtained or archival FFPE tumor tissue and blood.

(5) **Objective**: To evaluate progression free survival as assessed by RECIST 1.1 by investigator review in the next line of therapy (PFS2) in subjects treated with pembrolizumab (MK-3475) compared to paclitaxel or vinflunine.

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 (MK-3475) (previously known as 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.

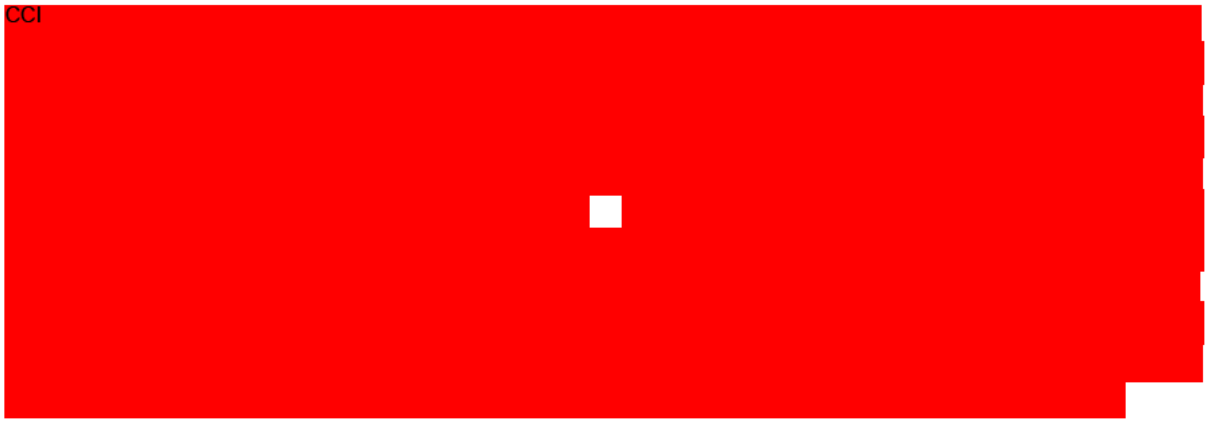
The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2; 3; 4; 5; 6]. 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 CD3ζ, PKCθ 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

CCI



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 (Protocol 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 tract 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 overall 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 tract 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.

4.1.4 Information on Other Trial-Related Therapy

The proposed choice of single agent paclitaxel or vinflunine for the control arm is based on common usage in the second-line setting, input from key opinion leaders, and prior precedence in 2nd line (2L) clinical trials. Therefore, these two agents will be used as standard treatment options in the comparator arm of this trial. This allows the investigator to select either option for subjects randomized to the standard therapy arm. See Section 4.2.2.1 for additional details.

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.

Subjects with metastatic urothelial cancer that has recurred or progressed following platinum-based chemotherapy present a challenge. Although a variety of chemotherapeutic agents are used in this setting, the prognosis of subjects with recurrent/progressive urothelial cancer is generally poor despite these therapies. The median survival in most series is 7 to 9 months, and the median PFS is 3 to 5 months, with limited treatment options and substantial morbidity. Single agent or combination therapy using conventional cytotoxic chemotherapy, combined with best supportive care, is palliative for subjects with recurrent/ progressive

urothelial cancer. The most widely used agents include taxanes (paclitaxel, docetaxel), pemetrexed, and, in the EU, vinflunine. There are no approved therapies for recurrent/progressive urothelial cancer in the US, while vinflunine is approved in the EU for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

After failure of first-line platinum-containing chemotherapy, objective responses to second-line cytotoxic chemotherapy are uncommon, particularly when contemporary response criteria are applied. Objective response rates of 5% to 28% have been reported with agents such as paclitaxel, docetaxel, pemetrexed and ifosfamide [29, 30, 31, 32], but few randomized, controlled studies have been conducted in the second-line setting. In single-arm studies, PFS and OS have been reported as 2-3 months and 7 months, respectively with paclitaxel [29, 30, 33]. In a Phase III trial, 370 previously treated patients were randomly assigned to either vinflunine or best supportive care [34]. Compared to best supportive care, treatment with vinflunine resulted in a 9% objective response rate and a trend towards increased overall survival that did not reach statistical significance in the ITT population (6.9 versus 4.6 months, hazard ratio 0.88, 95% CI 0.69-1.12).

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.

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

4.2.2 Rationale for Dose Selection/Regimen/Modification

CCI

[redacted]

CCI

[redacted]

4.2.2.1 Rationale for the Use of Comparator

While there is no accepted standard of care for recurrent/progressive metastatic urothelial cancer, taxanes, including paclitaxel, are widely utilized in this setting [35]. National Comprehensive Cancer Care guidelines state that, while no standard therapy exists for the second-line therapy of urothelial cancer, taxanes are preferred agents for palliation [36]. Data from single-arm, open label studies support the use of taxanes in subjects with progressive/recurrent urothelial cancer, but demonstrate the limited benefit of these chemotherapeutic regimens. An open-label study of paclitaxel in subjects with progressive/recurrent urothelial cancer demonstrated an ORR of 10% (95% CI 0%; 20%), a median PFS of 2.2 months and a median overall survival of 7.2 months [29]. Although no labeled dosing guidelines for these agents are available for subjects with urothelial cancer, paclitaxel has frequently been administered at Q3W doses of 175-250 mg/m^2 or equivalent weekly dosing to subjects with metastatic urothelial cancer, including in recent large Phase II and III clinical studies [37, 38].

In a Phase III trial, 370 previously treated urothelial cancer patients were randomly assigned to either vinflunine at 280-320mg/m^2 Q3W or best supportive care [34]. Compared to best supportive care, treatment with vinflunine resulted in a 9% objective response rate and a trend towards increased overall survival that did not reach statistical significance in the ITT population (6.9 versus 4.6 months, hazard ratio 0.88, 95% CI 0.69-1.12). PFS was 3 months in the vinflunine arm and 1.5 months in the arm that received best supportive care alone. In a multivariate Cox analysis, the addition of vinflunine was independently correlated with improved survival. On the basis of these data, vinflunine is has been approved in the EU as monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary

Overall survival (OS) is the gold standard endpoint to demonstrate superiority of antineoplastic therapy. Progression free survival (PFS) may be an acceptable scientific endpoint for a randomized Phase III trial to support accelerated approval in a population with a high unmet medical need and poor response to currently available therapies, such as in

subjects with recurrent/progressive urothelial cancer. RECIST 1.1 will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. Because the treatment assignment is unblinded, images will be read by independent radiologists blinded to treatment assignment to minimize bias in the response assessments. The first on-study radiographic imaging assessment will be performed at 9 weeks (± 7 days) after first dose of study treatment and then every 6 weeks (± 7 days) thereafter or more frequently if clinically indicated.

4.2.3.1.2 Secondary

4.2.3.1.2.1 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).

eEuroQoL EQ-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 [41]. Each dimension is rated on a three point scale from 1 (extreme problem) to 3 (no problem). The eEQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the patient 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 patient by qualified site personnel. The objective of the HEA form is for the site personnel to collect information from patients 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 recurrent/progressive 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. The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-neoplastic 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-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-neoplastic treatment should also be followed and recorded.

4.2.3.3 Planned Exploratory Biomarker Research

Additional biomarker research to identify factors important for pembrolizumab (MK-3475) therapy may also be pursued. For example, tumor and blood (including serum and plasma) samples from this study 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.

CCI

[redacted]

CCI

[redacted]

4.2.3.4 Future Biomedical Research

CCI

[redacted]

CCI

[redacted]

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 and Female subjects of at least 18 years of age with recurrent/progressive metastatic urothelial cancer 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 urothelial cancer of the renal pelvis, ureter, bladder, or urethra. Both transitional cell and mixed transitional/non-transitional cell histologies are allowed, but transitional cell

carcinoma must be the predominant histology. Subjects with non-urothelial cancer of the urinary tract are not allowed.

4. Have had progression or recurrence of urothelial cancer following receipt of a first-line platinum-containing regimen (cisplatin or carboplatin):

    a. Received a first-line platinum-containing regimen in the metastatic setting or for inoperable locally advanced disease;

    b. Received adjuvant platinum-containing therapy following cystectomy for localized muscle-invasive urothelial cancer, with recurrence/progression ≤12 months following completion of therapy.

    c. Received neoadjuvant platinum-containing therapy prior to cystectomy for localized muscle-invasive urothelial cancer, with recurrence ≤12 months following completion of therapy.

5. Have received no more than two prior lines of systemic chemotherapy for urothelial cancer. Subjects for whom the most recent therapy has been a non-platinum-based regimen following progression/recurrence on platinum-based therapy (i.e. third-line patients) are eligible if they have progressed/recurred on their most recent therapy.

6. Have provided tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. A newly-obtained biopsy is strongly preferred but not required if archival tissue is adequate for analysis. Adequacy of the archived or freshly-obtained biopsy specimen for PD-L1 biomarker analysis must be confirmed by the central laboratory during the screening period prior to enrollment.

7. Have measureable disease based on RECIST 1.1 as assessed by the investigator/site radiologist. Tumor lesions situated in a previously irradiated area are considered measureable 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. Subjects with an ECOG performance status of 2 must have a hemoglobin ≥10 g/dL, must not have liver metastases, and must have received the last dose of their last prior chemotherapy regimen ≥3 months (90 days) prior to enrollment.

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)	≤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 subjects 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.

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.

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 in or has participated in a study of an investigational agent or using an investigational device within 4 weeks prior to the first dose of trial treatment.

3. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

4. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

5. 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., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   Note: Subjects with ≤ Grade 2 neuropathy or ≤ 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.

6. 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; Gleason score ≤ 6, PSA undetectable.

7. 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 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.

8. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic or immunosuppressive agents. Subjects with vitiligo, diabetes Type I, or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study. Subjects with

hypothyroidism stable on hormone replacement or Sjøgren's syndrome will not be excluded from the study.

9. Has active cardiac disease, defined as:

    a. Myocardial infarction or unstable angina pectoris within 6 months of the first date of study therapy.

    b. History of serious ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation), high-grade atrioventricular block, or other cardiac arrhythmias requiring anti-arrhythmic medications (except for atrial fibrillation that is well controlled with antiarrhythmic medication); history of QT interval prolongation.

    c. New York Heart Association (NYHA) Class III or greater congestive heart failure, or left ventricular ejection fraction of < 40%.

10. Has evidence of interstitial lung disease or active non-infectious pneumonitis.

11. Has an active infection requiring systemic therapy.

12. Has a history of severe hypersensitivity reaction (e.g. generalized rash/erythema, hypotension, bronchospasm, angioedema or anaphylaxis) to paclitaxel or to other drugs formulated with polyoxyethylated castor oil, or to vinflunine or other vinca alkaloids.

13. Requires ongoing therapy with a medication that is a strong inhibitor of the CYP3A4 enzymes (a common list of such agents may be found in Section 12.9).

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

15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

17. Has received prior therapy with an anti-PD-1 or anti-PD-L1 agent, or with an agent directed to another co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137).

18. Has received paclitaxel as chemotherapy for urothelial cancer (for subjects in regions where vinflunine is not an approved therapy), OR has receive both prior paclitaxel

and vinflunine as chemotherapy for urothelial cancer (in regions where vinflunine is an approved therapy).

Note: The overall proportion of subjects receiving either vinflunine or paclitaxel in the control arm is capped at 70%. If this cap is reached, then subjects who have received prior therapy with the remaining available agent will be excluded.

19. Has a known history of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies).

20. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

21. Has received a live virus vaccine within 30 days of planned start of trial treatment.

22. 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(s) to be used in this trial are outlined below in Table 2.

Table 2 Trial Treatment

Drug	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 cycle	Experimental
Paclitaxel*	175 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	Active comparator
Vinflunine**	320 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	Active comparator
*In case of mild hepatic impairment (total bilirubin ≥1.25 ULN), paclitaxel should be started at a dose of 135 mg/m^2. ** In case of WHO/ECOG performance status (PS) of ≥1 or PS of 0 and prior pelvic irradiation, vinflunine should be started at the dose of 280 mg/m². In the absence of any hematological toxicity during the first cycle causing treatment delay or dose reduction, the dose will be increased to 320 mg/m² every 3 weeks for the subsequent cycles. See Section 5.2.1.2.1 for additional guidelines on dose modification for vinflunine, including starting doses in the setting of mild renal and hepatic impairment and in the elderly.					

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

All supplies indicated in Table 2 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased 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 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. There are no specific calculations or evaluation required to be performed in order to administer the proper dose to each subject.

Treatment on the standard treatment arm will be prepared and administered as per the approved product label. The body surface area (BSA) in m^2 should be calculated per local guidance.

5.2.1.2 Dose Modification for Pembrolizumab (MK-3475)

Pembrolizumab (MK-3475) will be withheld for drug-related Grade 4 hematologic and non-hematologic toxicities and severe or life-threatening AEs as per Table 3 below.

For subjects whose dose interval was increased due to toxicity, subjects may resume pembrolizumab (MK-3475) upon resolution of toxicity to Grade 0-1 or baseline. This dose would be considered Day 1 of the next cycle and should be in alignment with the new schedule.

Table 3 Dose Modification Guidelines for Drug-Related Adverse Events on the Pembrolizumab (MK-3475) Arm

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Hematological Toxicity	1, 2	No	N/A	N/A	N/A
	3 *Excludes Grade 3 neutropenia, anemia, and thrombo-cytopenia*	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
	4	Yes	Toxicity resolves to Grade 0-1 or baseline, After Sponsor consultation	N/A	Permanent Discontinuation
Non-hematological toxicity Note: Exception to be treated similar to grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue For additional information regarding irAEs reference Section 5.6.1.1 and 5.6.1.2.	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule (reference Section 5.6.1.2 for recommendations regarding pneumonitis) *Clinical AE does not resolve within 4 weeks:* May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion
	3	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
	4	Yes	Toxicity resolved to Grade 0-1 or baseline, after Sponsor consultation	N/A	Permanent Discontinuation
Note: Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with rechallenge of pembrolizumab (MK-3475) should be discontinued from trial treatment.					

In case toxicity does not resolve to Grade 0-1 within 12 weeks after the last infusion, trial treatment should be discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue in the trial only if asymptomatic and controlled. Increase in dosing interval of pembrolizumab (MK-3475) for intolerable Grade 2 drug-related adverse events may be considered after consultation with the Sponsor. For information on the management of adverse events, see Section 5.6.1.

5.2.1.2.1 Dose Modification for Standard Treatment Paclitaxel or Vinflunine

In general, treatment with paclitaxel or vinflunine will be withheld for drug-related Grade 4 hematologic toxicities and for non-hematologic toxicity ≥ Grade 3 and subsequent doses modified as per Table 4 below. Dose modifications will be applied for all subsequent doses. Specific dose modification guidance for paclitaxel and vinflunine is found below in Sections 5.2.1.2.2.1 and 5.2.1.2.2.2. Dose modifications for intolerable Grade 2 drug-related adverse events may be considered after consultation with the Sponsor. Dose modifications for paclitaxel or vinflunine should also be considered according to local product labels.

Table 4 Dose Modification Guidelines for Drug-Related Adverse Events on the Active Comparator Arm

Toxicity*	**Grade**	**Occurrence**	**Hold Treatment**	**Dose Modification**	**Treatment Discontinuation**
Neutropenia	Grade 1, 2, 3 or Grade 4 lasting ≤7 days	All	Hold treatment until neutrophils recover to >1500 cells/mm^3	N/A	N/A
	Grade 4 lasting > 7 days	1st occurrence	Hold treatment until neutrophils recover to >1500 cells/mm^3	Restart treatment at: Paclitaxel: 135 mg/m^2 Vinflunine: 280 mg/m^2	Treatment discontinuation should be considered
		2nd occurrence	Hold treatment until neutrophils recover to >1500 cells/mm^3	Restart treatment at: Paclitaxel: 100 mg/m^2 Vinflunine: 250 mg/m^2	Treatment discontinuation should be considered
		3rd occurrence	Yes	N/A	Yes
Thrombocytopenia	Grade 1, 2, 3	All	Hold treatment until platelets recover to >100,000 cells/mm^3	N/A	N/A
	Grade 4	1st occurrence	Hold treatment until platelets recover to > 100,000 cells/mm^3	Restart treatment at: Paclitaxel: 135 mg/m^2 Vinflunine: 280 mg/m^2	Treatment discontinuation should be considered
		2nd occurrence	Hold treatment until platelets recover to >100,000 cells/mm^3	Restart treatment at: Paclitaxel: 100 mg/m^2 Vinflunine: 250 mg/m^2	Treatment discontinuation should be considered
		3rd occurrence	Yes	N/A	Yes
Anemia	Grade 1, 2, 3	All	Until anemia resolves to Grade 1 or baseline	N/A	N/A
	Grade 4	1st occurrence	Until anemia resolves to Grade 1 or baseline	Restart treatment at: Paclitaxel: 135 mg/m^2 Vinflunine: 280 mg/m^2	Treatment discontinuation should be considered
		2nd occurrence	Until anemia resolves to Grade 1 or baseline	Restart treatment at: Paclitaxel: 100 mg/m^2 Vinflunine: 250 mg/m^2	Treatment discontinuation should be considered
		3rd occurrence	Yes	N/A	Yes
Non-hematological toxicity and other hematological toxicity not described above**	Grade 1, 2	All	No	None	N/A
	Grade 3, 4	1st occurrence	Yes, until toxicity resolves to Grade 0-1 or baseline	Restart treatment at: Paclitaxel: 135 mg/m^2 Vinflunine: 280 mg/m^2	Treatment discontinuation should be considered
		2nd occurrence	Yes, until toxicity resolves to Grade 0-1 or baseline	Restart treatment at: Paclitaxel: 100 mg/m^2 Vinflunine: 250 mg/m^2	Treatment discontinuation should be considered
		3rd occurrence	Yes	N/A	Yes

*See Table 5 and Table 6 for additional dose modifications for drug-related adverse events specific to vinflunine and paclitaxel, respectively.
**Subjects who experience suspected severe hypersensitivity reaction to paclitaxel or vinflunine (e.g. generalized rash/erythema, hypotension and/or bronchospasm, angioedema or anaphylaxis) should be discontinued from trial treatment. See Table 4 for guidelines on management of peripheral neuropathy.

In cases where the toxicity does not resolve to Grade 0-1 within 4 weeks after the last infusion (2 weeks for vinflunine), trial treatment should be discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 4 weeks may continue in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.6.1.

5.2.1.2.1.1 Specific Dose Modifications for Vinflunine

In case of WHO/ECOG performance status (PS) of ≥1 or PS of 0 and prior pelvic irradiation, vinflunine treatment should be started at the dose of 280 mg/m². In the absence of any hematological toxicity during the first cycle causing treatment delay or dose reduction, the dose will be increased to 320 mg/m² every 3 weeks for the subsequent cycles.

In subjects with moderate renal impairment (40 ml/min≤CrCl≤60 ml/min), the recommended dose is 280 mg/m² given once every 3 weeks. In subjects with renal impairment (30 ml/min≤CrCl<40 ml/min), the recommended dose is 250 mg/m² given once every 3 weeks.

The recommended dose of vinflunine is 250 mg/m² given once every 3 weeks in subjects with mild liver impairment (Child-Pugh grade A) or in subjects with a Prothrombin time ≥60% NV and 1.5xULN < Bilirubin ≤xULN and presenting at least one of the following criteria: transaminases > ULN and/or GGT > 5xULN .

The doses recommended in subjects ≥75 years old are as follows:
- in subjects at least 75 years old but less than 80 years, the dose of vinflunine to be given is 280 mg/m² every 3 weeks.
- in subjects 80 years old and beyond, the dose of vinflunine to be given is 250 mg/m² every 3 weeks.

In subjects who initiate vinflunine at 280 mg/m^2 and who experience an AE requiring dose modification, the dose should be reduced to 250 mg/m^2 following the 1st occurrence and resolution, and discontinued following a 2nd occurrence. In subjects who initiate vinflunine at 250 mg/m^2 and who experience an AE requiring dose modification, vinflunine should be discontinued.

Cases of Posterior Reversible Encephalopathy Syndrome (PRES) have been observed after administration of vinflunine. The typical clinical symptoms are, with various degrees: neurological (headache, confusion, seizure, visual disorders), systemic (hypertension), and gastrointestinal (nausea, vomiting). Radiological signs are white matter abnormalities in the posterior regions of the brain.
Vinflunine should be discontinued in subjects who develop neurological signs of PRES.
Specific dose modifications for subjects receiving vinflunine are detailed below in Table 5.

Table 5 Vinflunine Dose Modification for Drug-Related Adverse Events

Toxicity	**Dose Adjustment**				
	Initial Dose: Vinflunine 320 mg/m^2			**Initial Dose: Vinflunine 280 mg/m^2**	
	1st Event	**2nd Consecutive Event**	**3rd Consecutive Event**	**1st Event**	**2nd Consecutive Event**
Neutropenic fever (defined as T ≥100.5°F and ANC ≤ 1,000//L)	Vinflunine 280 mg/m^2	Vinflunine 250 mg/m^2	Discontinue treatment	Vinflunine 250 mg/m^2	Discontinue treatment
Mucositis or Constipation Grade 2 ≥5 days or Grade ≥3 any duration[1]					
Cardiac ischemia in patients with prior history of myocardial infarction or angina pectoris	Discontinue treatment	N/A	N/A	Discontinue treatment	N/A
[1]NCI CTC Grade 2 constipation is defined as requiring laxatives, Grade 3 as an obstipation requiring manual evacuation or enema, Grade 4 as an obstruction or toxic megacolon. Mucositis Grade 2 is defined as "moderate", Grade 3 as "severe" and Grade 4 as "life-threatening"					

5.2.1.2.1.2 Specific Dose Modifications for Paclitaxel

Paclitaxel should not be administered to subjects with baseline neutrophil counts of less than 1500 cells/mm^3. Subjects should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1500 cells/mm^3. Severe conduction abnormalities have been documented in <1% of subjects during paclitaxel therapy and in some cases requiring pacemaker placement. If subjects develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

In case of mild hepatic impairment (total bilirubin ≥1.25 ULN), paclitaxel should be started at a dose of 135 mg/m^2.

Dose modifications for subjects receiving paclitaxel are detailed below in Table 6.

Table 6 Paclitaxel Dose Modification for Drug-Related Adverse Events

Toxicity	**Grade**	**Occurrence**	**Hold Treatment**	**Dose Modification**	**Treatment Discontinuation**
Peripheral Neuropathy	Grade 1, 2		No	135 mg/m^2	N/A
	Grade 3, 4		Yes	N/A	Discontinue upon onset
Neutropenic fever (defined as T ≥100.5°F and ANC ≤ 1,000//L)		1	Hold until ANC ≥1,500/L	135 mg/m^2	
		2	Hold until ANC ≥1,500/L	100 mg/m^2	
		3	Yes	N/A	Yes

5.2.2 Timing of Dose Administration

Trial treatment of pembrolizumab (MK-3475) may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Trial treatment of paclitaxel or vinflunine may be administered up to 3 days before or after scheduled dosing date for administrative reasons per investigator's judgment.

All trial treatments will be administered on an outpatient basis.

5.2.2.1 Pembrolizumab (MK-3475)

Trial treatment of pembrolizumab (MK-3475) should be administered on Day 1 of each 3 week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

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 the preparation of the pembrolizumab (MK-3475) infusion fluid and administration of infusion solution.

5.2.2.2 Paclitaxel

Trial treatment of paclitaxel should be administered on Day 1 of each 3 week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

Paclitaxel 175 mg/m^2 will be administered as an IV infusion administered over 3 hours. See Section 5.2.1.2.1.2 for guidelines on adjustment of initial dose.

All subjects should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel. The appropriate premedication regimen may be determined by the investigator.

5.2.2.3 Vinflunine

Trial treatment of vinflunine should be administered on Day 1 of each 3 week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

Vinflunine 320 mg/m^2 will be administered as an IV infusion administered over 20 minutes. See Section 5.2.1.2.1.1 for guidelines on adjustment of initial dose.

5.2.3 Trial Blinding/Masking

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

Internal blinding of efficacy results will be maintained as follows: imaging data will be centrally reviewed, the central imaging vendor will be blinded to the subject treatment and the imaging results will be blinded to the clinical study team.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are two treatment arms. Subjects will be assigned randomly in a 1:1 ratio to pembrolizumab (MK-3475) OR investigator's choice of paclitaxel or vinflunine in an unblinded fashion. Within the control arm, the overall proportion of subjects receiving either vinflunine or paclitaxel will be capped at 70%.

5.4 Stratification

Randomization will be stratified according to the following factors:

1. Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2)
2. Presence or absence of liver metastases
3. Hemoglobin (≥ 10 g/dL vs. <10 g/dL)
4. Time from completion of most recent chemotherapy (<3 months or ≥3 months)*.

Note: Subjects with ECOG 2 may only be enrolled if liver metastases are absent, hemoglobin is ≥10 g/dL, and time from completion (last dose) of most recent chemotherapy is ≥ 3 months (90 days).

* 90 days.

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 28 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 considered on an exceptional case by case basis after consultation with Sponsor. The radiated lesion must be a non-target lesion per RECIST 1.1 and the subject must have clear measurable disease outside the radiated field.
- 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.
    - Note: It is acceptable for subjects receiving paclitaxel or vinflunine to receive live vaccines while participating in the trial.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  - Note: For subjects randomized to the paclitaxel or vinflunine arm, the use of glucocorticoids on trial treatment is acceptable and is required for premedication.

- Strong inhibitors of the CYP3A4 enzymes (a common list of such agents may be found in Section 12.8) for subjects receiving paclitaxel and vinflunine.
- QT/QTc-prolonging drugs for subjects receiving vinflunine (a common list of such agents may be found in Section 12.9).

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 for Pembrolizumab (MK-3475)

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

- Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.
  - In subjects with severe enterocolitis (Grade 3), pembrolizumab (MK-3475) will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
  - In subjects with moderate enterocolitis (Grade 2), pembrolizumab (MK-3475) should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with pembrolizumab (MK-3475), see Section 5.2.
  - All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.
- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Immune-related adverse events: Please see Section 5.6.1.1 below and the separate guidance document in the administrative binder regarding diagnosis and management of adverse experiences of a potential immunologic etiology.
- Management of Infusion Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

Table 7 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 7 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov.		

5.6.1.1 Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs)

Events of clinical interest of a potential immunologic etiology may be defined as an adverse event associated with drug exposure and is consistent with an immune phenomenon. IrAEs may be predicted based on the nature of the pembrolizumab (MK-3475) compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Of note, the requirement for reporting of ECIs applies to all arms, including comparators, of pembrolizumab (MK-3475) clinical trials.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on how to identify and evaluate irAEs has been developed and is included in the Event of Clinical Interest Guidance Document located in the Administrative Binder.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Section 7.2.3.2.

5.6.1.2 Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving pembrolizumab (MK-3475) and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 8.

Table 8 Recommended Approach to Handling Pneumonitis

Study Drug Associated Pneumonitis	Withhold / Discontinue pembrolizumab (MK-3475)?	Supportive Care
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2	Withhold pembrolizumab (MK-3475), may return to treatment if improves to Grade 1 or resolves within 12 weeks	Systemic corticosteroids are indicated. Taper if necessary.
Grade 3 and Grade 4	Discontinue pembrolizumab (MK-3475)	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. Refer to the Event of Clinical Interest Guidance Document for additional recommendations.

For Grade 2 pneumonitis that improves to ≤ Grade 1 within 12 weeks, the following rules should apply:

- First episode of pneumonitis
  - May increase dosing interval by one week in subsequent cycles

Second episode of pneumonitis – permanently discontinue pembrolizumab (MK-3475) if upon rechallenge subject develops pneumonitis ≥ Grade 2.

5.6.2 Supportive Care Guidelines for Paclitaxel and Vinflunine

Pre-medication(s) for paclitaxel will be given as per standard of care. Corticosteroid pre-treatment or post-treatment of paclitaxel is acceptable in concordance with the local label or standard of care.

Injection site reactions, including reactions secondary to extravasation, have been reported with paclitaxel. These reactions were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. More severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been reported. A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

In order to prevent constipation, laxatives and dietary measures including oral hydration are recommended from day 1 to day 5 or 7 after each vinflunine administration. Subjects at high risk of constipation (concomitant treatment with opiates, peritoneal carcinomas, abdominal masses, prior major abdominal surgery) should be medicated with an osmotic laxative from day 1 to day 7 administered once a day in the morning before breakfast.

Refer to the approved product label for additional supportive care guidance.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

MK 3475, paclitaxel and vinflunine may also have adverse effects on a fetus in utero. Furthermore, it is not known if these agents have transient adverse effects on the composition of sperm. Therefore, non-pregnant, non-breast-feeding women may only 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 be either 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).

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

5.7.4 Use in Nursing Women

It is unknown whether MK 3475, paclitaxel or vinflunine are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

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
- Radiographic disease progression as determined by local/site assessment
- Note: For unconfirmed radiographic disease progression, or confirmed progression with reduction in disease burden from baseline please see Section 5.8.1
- 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 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 Radiologic Progression

Immunotherapeutic agents such as pembrolizumab (MK-3475) may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

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 (≥ 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 9 below. Confirmatory imaging maybe performed as early as 28 days later; alternatively, the scan performed at the next scheduled time point (every 42 days + 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 9 Imaging and Treatment After 1st Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD	Repeat imaging at ≥ 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 ≥ 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 and site radiologist), an exception may be considered to continue treatment upon consultation with the Sponsor.

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 and PFS of the primary endpoint in this trial.

5.8.3 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study medication or before the initiation of a new antineoplastic treatment. Procedures and assessments performed at the Safety Follow-Up Visit and beyond should follow guidelines described in the Trial Flow Chart (Section 6.0). All AEs that occur within the 30-day safety follow-up visit should be recorded. Subjects with an AE >Grade 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new antineoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded. In subjects who start another cancer therapy before 30 days after discontinuation of study therapy, the Safety Follow-Up Visit should occur prior to the subject receiving another cancer therapy.

5.8.4 Duration of Follow-up

All subjects will be followed for at least 30 days after their last dose of trial treatment or until initiation of a new anti-cancer treatment, whichever occurs first. Subjects who are discontinued from the trial due to an unacceptable drug-related AE will be followed until the resolution of the AE to Grade 0-1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first. Subjects who discontinued study therapy without documented disease progression, should continue to be monitored for disease status by radiologic imaging according to the guidelines described in the Trial Flow Chart (Section 6.0) for post-treatment follow-up. Disease monitoring should continue to be assessed every 6 weeks (every 12 weeks following the 1st 12 months of trial treatment) until, 1) for approximately two years after the last dose of trial treatment, 2) start of a new antineoplastic therapy, 3) documented disease progression, or 4) until death, whichever occurs first.

5.8.5 Survival Follow-up

Subjects who discontinue from treatment should be contacted every three months to monitor overall survival. Guidelines are described in the Trial Flow Chart (Section 6.0) for post-treatment follow-up.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last trial 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. The trial may be stopped early for futility or safety at the recommendation of the Data Monitoring Committee (DMC).
2. Quality or quantity of data recording is inaccurate or incomplete
3. Poor adherence to protocol and regulatory requirements
4. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
5. Plans to modify or discontinue the development of the study drug

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 5	6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-42 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
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		
Trial Treatment Administration		X	X	X	X	X	X				
Post-study Anticancer Therapy Status										X	X
Survival Status											X
Clinical Procedures/Assessments											
Review Adverse Events[h]	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 and Weight[k]	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status[l]	X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory											
Pregnancy Test – Urine or Serum β-HCG[m]	X										

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 5	6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-42 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
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[j]		X[q]		
T3, FT4 and TSH[p]	X[o]		X		X		X[j]		X[q]		
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory											
Pharmacokinetics (pembrolizumab (MK-3475) arm only)[r]		X[r, s]	X[r]		X[r]				X[r]		
Anti-MK-3475 Antibodies (pembrolizumab (MK-3475) arm only)[r]		X[r]	X[r]		X[r]				X[r]		
Blood for Future Biomedical Research[t]		X									
Correlative Blood Samples[u]		X		X				X			
Blood for Genetics[v]		X									
Efficacy Measurements											
Tumor Imaging	X[w]				X[x]		X[x]	X[y]		X[b]	

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 5	6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-42 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Tumor Tissue Collection											
Archival or Newly Obtained Tissue Collection for biomarker analysis[z]	X										
Patient Reported Outcomes											
EuroQol EQ-5D		X[aa]	X[aa]	X[aa]	X[j, aa]		X[j, aa]	X[aa]	X[y]		
EORTC QLQ-C30		X[aa]	X[aa]	X[aa]	X[j, aa]		X[j, aa]	X[aa]	X[y]		
Health Economic Assessment (HEA)			X[aa]	X[aa]	X[j, aa]		X[j, aa]	X[aa]	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 (for pembrolizumab (MK-3475) arm only) 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 after 1st dose and every 6 weeks thereafter (42 days + 7 days) regardless of any treatment delays.
b. In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the central imaging vendor, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression by the central imaging vendor, the subject should be contacted by telephone every 12 weeks to assess for survival status.
d. In general, the window for each visit is ± 3 days unless otherwise noted. Cycle 1 treatment must be given within 3 days of randomization.
e. Written consent must be obtained prior to performing any protocol specified procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 42 days prior to the first dose of trial treatment). Screening number will be assigned when the trial informed consent is signed.
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.
g. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for AEs as defined in Section 7.2.
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.

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 5	6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-42 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks

j. Full PE at Screening Visit; 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.
l. ECOG PS at Screening to be performed ≤ 10 days prior to Day 1 of trial treatment visit.
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.
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.
o. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
p. For the paclitaxel/vinflunine arm, CBC, LFTs and chemistry should be collected on Days 1, 8 and 15of each 3 week cycle. For the pembrolizumab (MK-3475) arm, CBC, LFTs and chemistry should be collected on Day 1 of each 3 week cycle. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests. For Cycle 1, the Screening samples are sufficient if performed within 10 days. For subjects with a baseline estimated creatinine clearance below the normal institutional laboratory range, a baseline measured creatinine clearance should be performed.
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.
r. Pembrolizumab (MK-3475) arm only. Pre-dose trough PK and anti- pembrolizumab (MK-3475) antibody samples will be collected at Cycles 1, 2, 4, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug, and 3 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab (MK-3475). Additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab (MK-3475) infusion at Cycles 1 and 8.
s. An additional single PK sample should be drawn between 72 and 168 hours after Cycle 1 dosing.
t. Informed consent for future biomedical research samples must be obtained before the DNA sample is collected. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw) as the last sample drawn or at a later date as soon as the informed consent is obtained. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
u. Whole blood sample, serum sample, plasma sample for correlative studies should be collected prior to Cycle 1, at Cycle 3 and again at treatment discontinuation. Blood for serum and blood for plasma to be collected only prior to Cycle 1 Day 1. See Procedures Manual.
v. This sample should be drawn for planned, exploratory genetic analysis of DNA unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection.
w. The initial tumor imaging will be performed within 28 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management

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 5	6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-42 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks

are acceptable for use as the screening scan if they are of diagnostic quality and performed within 42days prior to the first dose of trial treatment.

x. The first on-study imaging time point will be performed at 9 weeks (± 7 days) after first dose of trial treatment 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.

y. 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.

z. Baseline tumor tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy (FNA not adequate) must be provided to the central vendor prior to randomization. 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.

aa. Electronic patient reported outcomes (ePROs) are to be administered prior to all study procedures 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.

6.2 Second Course Phase (Retreatment) for Pembrolizumab (MK-3475) Arm Only

Trial Period:	Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	1	2	3	4	To be repeated beyond 6 cycles: 5	To be repeated beyond 6 cycles: 6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
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
Survival Status										X
Clinical Procedures/Assessments										
Review Adverse Events[h]	X	X	X	X	X	X	X	X[i]	X[i]	
Full Physical Examination	X[j]									
Directed Physical Examination		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[s]		
Chemistry Panel[o]	X[n]	X	X	X	X	X	X	X[s]		
Urinalysis	X									
T3, FT4 and TSH[o]	X[n]		X[j]		X[j]			X[s]		
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory										
Pharmacokinetics[p]	X	X			X			X[p]	X[p]	
Anti-MK-3475 Antibodies[p]	X	X			X			X[p]	X[p]	
Efficacy Measurements										
Tumor Imaging[q]	X				X		X[r]		X	

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.

b. In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.

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

c. After the start of new anti-cancer treatment or documented disease progression by the central imaging vendor, the subject should be contacted by telephone every 12 weeks to assess for survival status.
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 intolerability 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 AEs 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 Screening Visit; 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.
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, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
p. Pembrolizumab (MK-3475) only. Pre-dose trough PK and anti- pembrolizumab (MK-3475) antibody samples will be collected at Cycles 1, 2, 4, every 4 cycles thereafter, 30 days after discontinuation of study drug, and 3 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab (MK-3475).
q. 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 dose of trial treatment 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 pembrolizumab (MK-3475) cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. The Sponsor will collect radiological assessments for analysis by a central imaging vendor. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual.
r. 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.
s. Unresolved labs that are drug-related AEs should be followed until resolution. Labs do not need to be repeated after 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. 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.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. 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 and record in the trial database.

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

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

Investigators must choose a standard treatment (paclitaxel or vinflunine) prior to randomization and document the selection in the trial database (See Data Entry Guidelines).

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

Interruptions from the protocol specified treatment for greater than 12 weeks between pembrolizumab (MK-3475) doses on the pembrolizumab (MK-3475) treatment arm 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) or comparator infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab (MK-3475) or comparator administered.

The instructions for preparing and administering pembrolizumab (MK-3475) will be provided in the Pharmacy Manual. Treatment with paclitaxel or vinflunine will be prepared and administered as per the approved product label.

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 clinical indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.7). 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 Section 5.6.1.1 and the separate 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 12-Lead Electrocardiogram

A standard 12-lead ECG will be performed using local standard procedures once at screening visit as described in Section 6 – Trial Flow Chart. Clinically significant abnormal findings should be recorded as medical history.

7.1.2.3 Physical Exam

7.1.2.3.1 Full Physical Exam

The investigator or clinical designee will perform a complete physician exam during the screening period (See Trial Flow Chart Section 6.0). Clinically significant abnormal findings should be recorded as medical history. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3.2 Directed Physical Exam

The investigator or qualified designee will perform a directed physical exam as clinically indicated prior to Day 1 of each treatment cycle starting with Cycle 2. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.4 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.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.5) at screening (within ≤10 days prior the dosing on Day 1 Cycle 1) and prior to the dosing on Day 1 of each treatment cycle and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Process for image collection and transmission to the central vendor can be found in the Site Imaging Manual. Tumor imaging may be performed by computed tomography (CT) or magnetic resonance imaging (MRI), but the same imaging technique should be used in a subject throughout the trial.

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging must be performed within 42 days prior to the first dose of trial treatment. The investigator/site radiologist must review pre-trial images to confirm the subject has measurable disease per RECIST 1.1. The baseline imaging scan should also be submitted to the central imaging vendor.

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 42 days prior to the first dose of trial treatment. The same imaging technique should be used in a subject throughout the trial.

7.1.2.6.2 Tumor Imaging During Trial

The first imaging assessment should be performed at 9 weeks (63 days + 7 days) from the first dose of trial treatment. Subsequent imaging should be performed every 6 weeks (42 days + 7 days) or more frequently if clinically indicated. After the first 12 months on trial therapy, the imaging interval should be decreased to every 12 weeks (+ 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, whichever is clinically indicated.

Imaging should continue to be performed until disease progression is assessed by the investigator, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, 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 7.1.2.5.3.

7.1.2.6.3 Assessment of Disease

For the purposes of the primary study endpoints, RECIST 1.1 (Appendix 12.7) will be applied by the central imaging vendor as the primary measure for assessment of tumor response and date of disease progression. Subjects on the pembrolizumab (MK-3475) arm 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 to subjects on the control arm as well. All scans, including confirmatory scans, should be submitted to the central imaging vendor for retrospective evaluation.

Imaging during the follow-up period is to be repeated every 6 weeks (42 + 7 days), or every 12 weeks 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.

Local reading (investigator assessment with site radiology reading) based on RECIST 1.1 will be used to determine subject eligibility. Confirmatory scans performed per modified RECIST 1.1 will be evaluated by local reading for the purpose clinical decision-making. The central imaging vendor will receive all images from the sites, and a retrospective analysis of subject eligibility and treatment response by modified RECIST 1.1, will also be performed by a central vendor.

7.1.2.7 Tumor Tissue Collection and Correlative Blood Sampling

Either an archival FFPE tumor sample or 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 prospectively in this trial. The tumor tissue must be received by the central vendor and be deemed adequate for evaluation prior to subject randomization. If new scientific data emerge that indicate that an existing biopsy or surgical specimen is suboptimal for identification of subjects, only new biopsies will be acceptable for determination of 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.

Blood for correlative biomarker studies should be collected prior to Cycle 1, at Cycle 3 and at treatment discontinuation.

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 prior to all other study procedures in the following order: EuroQol EQ-5D first then EORTC QLQ-C30 at the time points specified in the Trial Flow Chart.

The health economic assessment (HEA) form will be completed via an interview with the patient 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 10.

Table 10 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)	Aspartate aminotransferase (AST)	Specific gravity	Total thriiodothyronine (T3) (or Free T3)[b]
Red Blood Cell Count	Bicarbonate	Microscopic exam, if abnormal results are noted	Free tyroxine (T4)
Absolute Neutrophil Count	Calcium	Urine pregnancy test[a]	Thyroid Stimulating Hormone (TSH)
Absolute Lymphocyte Count	Chloride		PK (for subjects on the pembrolizumab (MK-3475) arm only)
	Creatinine[c]		Anti- pembrolizumab (MK-3475) Antibodies (for subjects on the pembrolizumab (MK-3475) arm only)
	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		
	Carbon dioxide (CO_2 or bicarbonate)[b]		
	Uric acid		

[a] Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
[b] If considered standard of care in your region
[c] For subjects with a baseline calculated creatinine clearance below the normal institutional laboratory range, a baseline measured creatinine clearance should be prefomed.

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.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

To further evaluate pembrolizumab (MK-3475) immunogenicity and pembrolizumab (MK-3475) exposure in this indication, and also to evaluate exposure of the 200 mg fixed dosing regimen, sample collections for analysis of anti-drug antibodies (ADA) and PK are currently planned as shown in the Trial Flowchart (Sections 6.1.1 and 6.2). However, if ongoing ADA and PK results continue to be consistent with existing ADA and PK data (mainly in melanoma and NSCLC), it can be decided to discontinue further sample collection in this study after evaluation of the first 65-70 patients (i.e. 50% of pembrolizumab (MK-3475) treated).

7.1.3.2.1 Blood Collection for Serum Pembrolizumab (MK-3475)

Sample collection, storage and shipment instructions for serum PK samples will be provided in the Procedures Manual. PK samples should only be drawn for subjects in the pembrolizumab (MK-3475) arm.

7.1.3.2.2 Blood Collection for Anti- pembrolizumab (MK-3475) Antibodies

Sample collection, storage and shipment instructions for anti- pembrolizumab (MK-3475) antibody samples will be provided in the Procedures Manual. Anti- pembrolizumab (MK-3475) antibody samples should only be drawn for subjects in the pembrolizumab (MK-3475) arm.

7.1.3.3 Future Biomedical Research

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

- DNA for future use
- Leftover tumor tissue

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 on the pembrolizumab (MK-3475) arm 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 (PPD), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

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

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 42 days prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

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 42 days prior to the first dose trial treatment except for the following:

- 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 42 days of the first dose of study

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

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 on the pembrolizumab (MK-3475) arm 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 MK-3745. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
    - Stopped initial treatment with pembrolizumab (MK-3475) after attaining an investigator-determined confirmed CR according to RECIST 1.1
        - Was treated for at least 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.
- 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.
- 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-Treatment Visits

7.1.5.3.1 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 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 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. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression determined by the central imaging vendor, 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 the 3-month Follow-up visits, and any subsequent visits for imaging that may occur until PD is identified. Once the subject stops the imaging assessments for this protocol (e.g. for PD or starting a new antineoplastic therapy), the subject moves into the survival follow-up phase and should be contacted by telephone every 3 months to assess for survival status. Post-study treatments and the subject's response to them will also be collected.

7.2 Assessing and Recording Adverse Events

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

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

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

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

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and 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.

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 any dose of 1,000 mg or greater (≥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. An overdose for all other trial treatments will be defined as any dose exceeding the prescribed dose by 20%. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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 from the time the consent is signed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic

media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

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

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

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

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

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

3. Additional adverse events:

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

   ECIs 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 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, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours either by electronic or paper media.

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 11 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) 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 cancer; or	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to 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:	
	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

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product 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; (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 trial? 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 RE-EXPOSURE 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 AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

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

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

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

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities) **Injection site redness or swelling from the day of vaccination through Day 5 post-vaccination will be evaluated by maximum size.**
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose 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 cancer; or	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the test vaccine to be discontinued?	
Relationship to test vaccine	Did the test vaccine cause the adverse event? The determination of the likelihood that the test vaccine 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 vaccine and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the test vaccine and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test vaccine caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the test vaccine such as: reliable history, acceptable compliance assessment (e.g., diary), seroconversion or identification of vaccine virus in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the test vaccine? Is the time of onset of the AE compatible with a vaccine-induced effect?
	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 test vaccine (continued)	**The following components are to be used to assess the relationship between the test vaccine and the AE: (continued)**	
	Dechallenge	(not applicable for vaccines)
	Rechallenge	Was the subject reexposed to the test vaccine in this trial? 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 vaccine trial.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST VACCINE, OR IF REEXPOSURE TO THE TEST VACCINE POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Vaccine Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test vaccine or vaccine 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 criteria as guidance (not all criteria must be present to be indicative of a vaccine relationship).**
Yes, there is a reasonable possibility of vaccine relationship.		There is evidence of exposure to the test vaccine. The temporal sequence of the AE onset relative to the administration of the test vaccine is reasonable. The AE is more likely explained by the test vaccine than by another cause.
No, there is not a reasonable possibility of vaccine relationship		Subject did not receive the test vaccine OR temporal sequence of the AE onset relative to administration of the test vaccine is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 Trial Governance and Oversight

7.3.1 Scientific Advisory Committee

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

7.3.2 Executive Oversight Committee

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

7.3.3 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.1.4 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

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

Key elements of the statistical analysis plan are summarized below; details are provided in Section 8.2 of the protocol. Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months) will be the stratification variables in all stratified analyses.

8.1.1 Efficacy Analyses

The intention-to-treat (ITT) population will serve as the primary analysis population in this study. The primary efficacy endpoints are progression-free-survival (PFS) (i.e., time from randomization to documented progressive disease or death due to any cause, whichever occurs first) and overall survival (OS) (i.e., time from randomization to death due to any cause). The primary analyses of PFS will be based on blinded independent central review using RECIST 1.1. Supportive analyses based on investigator's assessments using RECIST 1.1 will also be performed. The secondary endpoints include PFS per modified RECIST 1.1 (see Section 8.2.3.1for definition) and objective response rate (ORR) per RECIST 1.1 and modified RECIST 1.1 based on independent central review.

An outline of the efficacy analysis strategy is presented in Table 12 below.

Table 12 Primary Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Progression-free survival (RECIST 1.1) by independent radiologists' review	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Model based (censored at last assessment)
Overall survival	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Model based (censored at last contact date)
Secondary:			
Progression-free survival (Modified RECIST 1.1) by independent radiologists' review	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Model based (censored at last assessment)
Objective response rate (RECIST 1.1) by independent radiologists' review	Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered non-responders
Objective response rate (Modified RECIST 1.1) by independent radiologists' review	Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered non-responders

8.1.2 Safety Analyses

The All-Patients-as-Treated (APaT) population will be employed for safety analyses. P-values and 95% confidence intervals for between-treatment differences in the rate of patients with Tier-1 events will be calculated using the stratified Miettinen and Nurminen method [40].

8.1.3 Power and Sample Size

The study will randomize approximately 470 patients, stratified by 1) Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), 2) presence/absence of liver metastases, 3) hemoglobin (≥ 10 g/dL vs. <10 g/dL) and 4) time from completion/discontinuation of most recent prior therapy (<3 months or ≥3 months) with a 1:1 ratio into the pembrolizumab (MK-3475) arm and the standard treatment arm. The study is event-driven and sample size calculation is driven by survival events.

The first PFS analysis will be conducted after enrollment is complete, approximately 160 PFS events are observed between the pembrolizumab (MK-3475) arm and the paclitaxel or vinflunine arm, and at least 300 subjects have at least 4 months of follow-up. With ~160 PFS events, the study has ~96% power to demonstrate superiority in PFS of pembrolizumab (MK-3475) relative to the paclitaxel or vinflunine arm at the alpha = 0.4% (one-sided) level if the true hazard ratio is 0.50. A p-value less than 0.4% (one-sided) for PFS approximately

corresponds to an observed hazard ratio of < 0.657 (or approximately at least 6.08 months of median PFS in the pembrolizumab (MK-3475) arm vs. 4 months of median PFS in the paclitaxel or vinflunine arm). The sample size calculation is based on the following assumptions: 1) progression-free survival follows an exponential distribution with a median of 4 months in the standard therapy arm, 2) the true hazard ratio between pembrolizumab (MK-3475) and standard therapy is 0.5, 3) an enrollment period of 11 months, and 4) a yearly dropout rate of 5%.

The final OS analysis will be carried out after approximately 356 deaths have occurred between the pembrolizumab (MK-3475) arm and the paclitaxel or vinflunine arm, or all patients have been followed up for 24 months, whichever occurs first, barring early stopping for futility or efficacy. With 356 events, the study provides 90% power to demonstrate superiority in OS of pembrolizumab (MK-3475) relative to standard therapy at the alpha=2.0% (one-sided) level if the true HR is 0.7. Success for OS at the final analysis approximately corresponds to an observed hazard ratio of < 0.80 (or approximately at least 10 months of median OS in the pembrolizumab (MK-3475) arm vs. 8 months of median OS in the paclitaxel or vinflunine arm). The sample size calculation is based on the following assumptions: 1) overall survival follows an exponential distribution with a median of 8 months in the control arm; 2) the hazard ratio for OS between pembrolizumab (MK-3475) and control is 0.70 (deemed to be clinically meaningful in this population); 3) an enrollment period of 11 months and a minimum of 16 months follow-up after enrollment completion; and 4) a yearly drop-out rate of 2%.

The second PFS analysis will be conducted at the time of the final analysis of OS only if the pembrolizumab (MK-3475) arm is not demonstrated to have a superior PFS at the first PFS analysis.

The family-wise type I error rate for this study is strongly controlled at 2.5% (one-sided) with 0.5% allocated to the PFS analysis and 2.0% allocated to the overall OS hypothesis. There are two planned analyses of PFS and three planned analyses of OS. If the pembrolizumab (MK-3475) arm is demonstrated to have a superior PFS to the paclitaxel or vinflunine arm at any PFS analysis, then 0.5% alpha will be rolled into the OS hypothesis (i.e. the OS hypothesis will be tested at 2.5%) and allocation to each analysis will be based on the specified spending function. If the PFS and OS hypotheses are successful, then the secondary endpoints will be tested sequentially at the alpha=2.5% level.

8.1.4 Interim Analysis

The first interim analysis for OS will be conducted at the time of the first PFS analysis. Table 13 summarizes the timing, sample size and decision guidance for the interim analysis. Results of the interim analysis will be reviewed by an external data monitoring committee (DMC). Further details of interim analyses are provided in Section 8.2.9 Interim Analysis as well as in the DMC Charter. Another interim analysis for OS will be performed about 8 months after the first OS interim analysis.

Table 13 Summary of Timing, Sample Size and Decision Guidance at the Interim Analysis

	Interim analysis 1 (the first analysis of PFS)	Interim analysis about 8 months after the first PFS analysis
Endpoints	PFS and OS	OS
Sample size the first PFS analysis is based upon	About 160 PFS events and 130 deaths	Number of OS events at 8 month after the first PFS analysis
Stop early for futility	PFS HR>0.657 AND OS HR>1.24	OS HR determined by Hwang-Shih-DeCani beta-spending function with gamma parameter -8
Stop early for efficacy	P-value for OS <0.1% (one-sided) corresponding to approximate observed HR <0.588.	OS HR determined by Hwang-Shih-DeCani alpha-spending function with gamma parameter -4

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.

Although the trial is open label, the analysis and reporting team will be blinded to the treatment assignments and PD-L1 biomarker result to ensure data integrity. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment. The official, final database will not be unblinded for any analysis until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete. Depending on the recommendation of the DMC, the Sponsor may prepare a regulatory submission. The analysis and reporting team would be unblinded to treatment group assignment at the time that a regulatory submission is prepared and would remain unblinded for the remainder of the study until the final OS analysis.

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

The first PFS analysis, described in Section 8.2.9, occurs prior to the final OS analysis. The results of the first PFS analysis will not be shared with the Investigators prior to the completion of the study. Access to the allocation schedule for this study will be restricted to an external unblinded statistician and, as needed, a scientific programmer performing the analysis, who will have no other responsibilities associated with the study.

Treatment-level results at the first PFS analysis will be provided by an external unblinded statistician to the eDMC. Key enrollment metrics and study data will also be monitored by the external unblinded statistician to inform the timing of the first PFS and OS analyses as needed. Limited additional SPONSOR personnel may be unblinded to the treatment level results of the first PFS analyses, if required, in order to act on the recommendations of the

eDMC or facilitate regulatory filing after the PFS analysis. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician.

The eDMC will serve as the primary reviewer of the results of the first PFS analyses and will make recommendations for discontinuation of the study or modification to an executive committee of the SPONSOR. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the eDMC Charter.

Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol violators, or data validation efforts after the PFS analyses.

8.2.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3. The study is considered to have met its primary objective if pembrolizumab (MK-3475) is superior to the paclitaxel or vinflunine arm either in PFS or in OS at the interim analysis or final analysis.

8.2.3 Analysis Endpoints

8.2.3.1 Efficacy Endpoints

Primary

Progression-free survival - RECIST 1.1 by blinded independent radiologists' review

Progression-free-survival (PFS) is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded independent radiologists' review or death due to any cause, whichever occurs first. See Section 8.2.5.1.1 for definition of censoring.

A supportive analysis of PFS will be conducted using site radiology review.

Overall Survival

Overall Survival (OS) is defined as the time from randomization to death due to any cause. Patients without documented death at the time of the final analysis will be censored at the date of the last follow-up.

Secondary

Objective Response Rate (ORR) – RECIST 1.1 by blinded independent radiologists' review

Objective response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR). Responses are based upon blinded central radiologists' review per RECIST 1.1.

A supportive analysis of ORR will be conducted using site radiology review.

PFS/ORR – modified RECIST 1.1 by blinded independent radiologists' review

PFS and ORR per modified RECIST 1.1 are defined as specified for the respective endpoints using RECIST 1.1 above, with the exception that a confirmation assessment of PD (at least 4 weeks after the initial PD assessment) is required for subjects who remain on treatment following a documented PD per RECIST 1.1. Subjects who discontinue treatment following a documented PD assessment per RECIST 1.1 will be counted as having disease progression on the date of the documented PD assessment. See Section 8.2.5.1.1 for definition of censoring.

Supportive analyses will be conducted using site radiology review.

Response Duration – RECIST 1.1 by blinded independent radiologists' review

For subjects who demonstrated CR or PR, response duration is defined as the time from first documented evidence of CR or PR until disease progression or death. Response duration for subjects who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment. Response duration will be calculated for RECIST 1.1 based on blinded independent radiologists' review and site review.

Exploratory

Exploratory endpoints of this study include but not limit to PFS2, disease control rate, and response to treatment by biomarker subgroups. Patient-reported outcomes (PROs) while on treatment and post-discontinuation will be examined.

An exploratory analysis of PFS2, defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever first, will be carried out. If progression after next-line therapy cannot be measured, a PFS event is defined as end or discontinuation of next-line treatment or death from any cause, whichever occurs first. Patients alive and for whom a PFS event has not been observed will be censored at the last time known to be alive and without second disease progression.

8.2.3.2 Safety Endpoints

Safety measurements are described in Section 7.

8.2.4 Analysis Population

8.2.4.1 Efficacy Analysis Population

The analysis of primary efficacy endpoints are based on the intention-to-treat (ITT) population, i.e., subjects will be included in the treatment group to which they are randomized. Details on the approach to handling missing data are provided in Section 8.2.5 Statistical Methods.

8.2.4.2 Safety Analysis Populations

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized subjects who received at least 1 dose of study treatment. Subjects will be included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data. Subjects who take incorrect trial treatment for the entire treatment period will be included in the treatment group corresponding to the trial treatment actually received. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial 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.

8.2.5 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 8.2.5.2. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 8.2.6, Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses.

8.2.5.1 Statistical Methods for Efficacy Analyses

The family-wise type I error rate for this study is strictly controlled at 2.5% (one-sided) that allows the trial to declare positive in PFS or OS in the ITT population.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints and multiple analyses is described in Section 8.2.6 and Section 8.2.9.

8.2.5.1.1 Progression-Free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox

model with Efron's method of tie handling and with a single treatment covariate will be reported. The same stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model. A sensitivity analysis based on multivariate Cox PH model with treatment, stratification factors and other factors as covariates will also be provided.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint, we will perform two sensitivity analyses with a different set of censoring rules. The first sensitivity analysis is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of new anticancer treatment, whichever occurs later, to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 14. In case there is an imbalance between the treatment groups on disease assessment schedules or censoring patterns, we will also perform the following two additional PFS sensitivity analyses: 1) a PFS analysis using time to scheduled tumor assessment visit from randomization as opposed to actual tumor assessment time; 2) Finkelstein (1986)’s likelihood-based score test for interval-censored data, which modifies the Cox proportional hazard model for interval censored data, will be used as a supportive analysis for the PFS endpoint [41]. The interval will be constructed so that the left endpoint is the date of the last disease assessment without documented PD and the right endpoint is the date of documented PD or death, whichever occurs earlier.

Table 14 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥ 2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Progressed at date of documented PD or death

8.2.5.1.2 Overall Survival (OS)

The Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. The same stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model. A sensitivity analysis based on multivariate Cox PH model with treatment, stratification factors and other factors as covariates will also be provided.

Subjects in the standard therapy arm may discontinue treatment earlier compared to subjects in the pembrolizumab (MK-3475) arm due to disease progression, and they may switch to another anti PD-1 treatment following confirmation of progressive disease. As an exploratory analysis, the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1989) will be used to adjust for the effect of crossover to other PD-1 therapies on OS. The RPSFT model provides a randomization-based estimate of treatment effect (RBEE) corrected for the bias induced by crossover. The 95% confidence intervals of the hazard ratio for OS after adjustment of the cross-over effect will be provided. The Kaplan-Meier estimates of the OS rate at 3 months, 6 months (when most cross-overs are likely to occur) and other time points of interest will also be compared between the two treatment groups to explore the confounding effect of subsequent treatments. To further account for the possible confounding effect, a sensitivity analysis of OS that censors subjects at the time of initiation of new therapy will be performed and an OS analysis that treats initiation of new therapy as a time-dependent binary covariate will also be conducted. In case the proportional hazards

assumption doesn't hold, Fleming and Harrington's weighted log-rank test or other methods, as appropriate, will be conducted, after proper adjustment of the crossover effect over time.

8.2.5.1.3 Objective Response Rate (ORR)

Stratified Miettinen and Nurminen's method will be used for comparison of the objective response rates between the treatment groups. A 95% confidence interval for the difference in response rates between the pembrolizumab (MK-3475) arm and the standard therapy arm will be provided. The same stratification factors used for randomization (see Section 5.4) will be applied to the analysis. Sensitivity analyses will be performed for comparison of ORR based on investigator's assessment.

8.2.5.1.4 Response Duration

If sample size permits, response duration 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. Response duration will be assessed using RECIST 1.1 separately by independent radiologists' review and by site radiology review.

A summary of the primary analysis strategy for the primary and secondary efficacy endpoints is provided in Table 15.

8.2.5.1.5 Exploratory Aanalyses

An exploratory analysis of PFS2, defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever first, will be carried out. If progression after next-line therapy cannot be measured, a PFS event is defined as end or discontinuation of next-line treatment or death from any cause, whichever occurs first. Patients alive and for whom a PFS event has not been observed should be censored at the last time known to be alive and without second disease progression.

EORTC QLQ-C30 and EQ-5D changes will be summarized as part of the exploratory analysis. Longitudinal and descriptive data analysis will be used to evaluate patient-reported outcomes. Several approaches will be considered to address the issue of informative missing data: (i) truncating the analysis observation period at the visit closest to median duration of treatment in the comparator arm, (ii) hierarchical pattern mixture models incorporating reason for missingness (a model that treats disease progression as a time-varying covariate) and (iii) multiple imputation methods. The difference in PRO score for progressed patients compared to patients with no radiographic evidence of tumor progression will be evaluated within each treatment arm. For HEA, descriptive statistics by treatment group will include total counts of each type of healthcare contact, as well as the total number of hospital days. The detailed PRO analysis plan will be included in a separate document.

An exploratory analysis of PFS and OS by PD-L1 score, either as a dichotomous or continuous variable, as well as PFS2 will be conducted using the same methods as the primary analysis.

Table 15 Efficacy Analysis Methods for Primary and Secondary Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Primary or Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis:				
PFS (RECIST 1.1) by independent radiologists' review	P	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 14
PFS (RECIST 1.1) by independent radiologists' review – Sensitivity Analyses 1& 2	S	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 14
OS	P	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Model based (censored at last date)
OS using RPSFT model	S	Testing: Stratified Log-rank test using Rank Preserving Structural Failure Time (RPSFT) model	ITT	Model based (censored at last date)
OS	S	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at time of initiation of new therapy or last assessment date
OS	S	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method using initiation of new therapy as time-dependent covariate	ITT	Censored at last assessment date
Secondary Hypothesis :				
Objective response rate (RECIST 1.1) by independent radiologists' review	P	Stratified Miettinen and Nurminen method	ITT	Patients with missing data are considered non-responders
PFS (modified RECIST 1.1) by independent radiologists' review	P	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 14
Objective response rate (modified RECIST 1.1) by independent radiologists' review	P	Stratified Miettinen and Nurminen method	ITT	Patients with missing data are considered non-responders
Response duration (RECIST 1.1) by independent radiologists' review	P	Summary statistics using Kaplan-Meier method	All responders in ITT	Non-responders are excluded in analysis

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, vital signs, and ECG measurements.

Time to Grade 3-5 AE

Time to first Grade 3-5 AE is defined as the time from the first day of study drug to the first event of Grade 3-5 AE. For patients without a Grade 3-5 AE, the time to first Grade 3-5 AE is censored at 30 days post last study dose. The Kaplan-Meier method will be used to estimate the curve of time to first Grade 3-5 AE. The treatment difference in time to first Grade 3-5 AE will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. The same stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model.

As a binary analysis, the p-value and 95% confidence interval for between-treatment difference (pembrolizumab (MK-3475)-standard treatment) in the percentage of patients with Grade 3-5 AE overall as well as per cycle for the first four cycles of pembrolizumab (MK-3475) and standard therapy will be calculated using the stratified Miettinen and Nurminen method. Further, the between-treatment difference in the Grade 3-5 AE incidence density adjusted for treatment exposure will also be analyzed using the stratified Miettinen and Nurminen method. In this analysis, the exposure-adjusted incidence rate is calculated as:

Incidence rate = 100* (total number of patients with ≥1 event post-randomization / total patient-years of exposure).

For patients who had an event, the patient-years of exposure will be calculated as the number of days from the first day of initiating study drug to the date of the first event. For patients without an event, the patient-years of exposure will be calculated as the number of days from the first day of initializing study drug to 30 days post last study dose (same as in the time-to-event analysis). The total patient-years of exposure for a treatment group will be the sum of the patient-years of exposure of all patients in the treatment group. Notice that when time to first Grade 3-5 AE follows the exponential distribution, the relative incidence rate between each pembrolizumab (MK-3475) arm and the standard therapy arm corresponds to the hazard ratio estimate from the time to event analysis.

Tiered Approach for Other Safety Analyses

The analysis of safety results will follow a tiered approach (Table 16). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence

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

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format. In addition, summary statistics for the difference between treatment groups will also be provided, along with nominal p-values for between-group differences. Mean change from baseline over time will be plotted with the corresponding standard errors.

To properly account for the potential difference in follow-up time between the study arms, which is expected to be longer in the pembrolizumab (MK-3475) arm, an analysis of Tier 1 AE and Grade 3-5 AE will be based on the time to first event using the same time-to-event analysis methods as for OS (i.e., the stratified log-rank test will be used for testing the time to AEs, and the stratified Cox model with Efron's tie handling method will be used for estimating the hazard ratio and its 95% confidence interval). For other AEs with potentially differential follow-up time, such analysis may also be explored.

In addition, the p-value and 95% confidence interval for between-treatment difference in the percentage of subjects with Grade 3-5 AE overall as well as per cycle for the first four cycles, and the between-treatment difference in the Grade 3-5 AE incidence density adjusted for treatment exposure (AE duration is defined as from first dose of study drug to 30 days after last dose of study drug) will be calculated using the stratified Miettinen and Nurminen method.

Further, pre-specified adverse events of clinical interest outlined in the separate pembrolizumab (MK-3475) ECI and irAE guidance document will be collected as Tier 1

events. P-values and 95% confidence intervals will be provided for between treatment differences in the percentage of subjects with these events.

Based on emerging external data, the analysis strategy for safety parameters may be modified to improve the integrity and efficiency of the design. Should this happen, the change will be documented elsewhere, if not in a protocol amendment, at the earliest time before any unblinding of the data.

Table 16 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Outlined in the separate pembrolizumab (MK-3475) ECI and irAE guidance document	X	X	X
Tier 2	Any AE		X	X
	Any Grade 3-5 AE		X	X
	Any Serious AE		X	X
	Onset and Duration of First Grade 3-5 AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Any Grade3-5 and Drug-Related AE		X	X
	Dose Modification due to AE		X	X
	Discontinuation due to AE		X	X
	Death		X	X
	Specific AEs, SOCs (including ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs (incidence <4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects randomized, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables. The reasons for exclusion from the ITT population (if any) will be summarized.

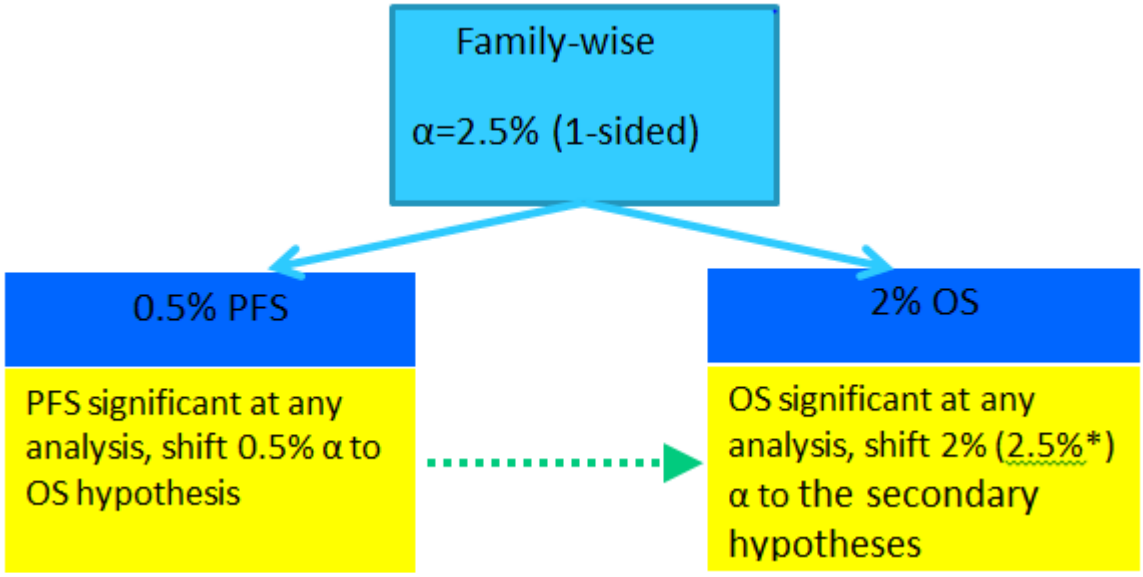
8.2.6 Multiplicity

The family-wise type I error rate for this study is strongly controlled at 2.5% (one-sided) with 0.5% allocated to the PFS hypothesis and 2.0% allocated to the OS hypothesis. There are two planned analyses of PFS and three planned analyses of OS.

If the pembrolizumab (MK-3475) arm is demonstrated to have a superior PFS to the control arm at any PFS analysis, then 0.5% alpha will be rolled into the OS hypothesis (i.e. the OS

hypothesis will be tested at 2.5%) and allocation to each OS analysis will be based on the spending function used (Figure 2).

For the PFS hypothesis, a Hwang-Shih-DeCani alpha-spending function with the gamma parameter (4) is constructed to implement group sequential boundaries that control the type I error rates. For the OS hypothesis, a Hwang-Shih-DeCani alpha-spending function with the gamma parameter (-4) and beta-spending function with the gamma parameter (-8) are constructed to implement group sequential boundaries that control the type I error rate as well as allow for non-binding futility analysis. Two interim analyses for OS are planned in this trial and further details of the interim analysis strategy can be found in Section 8.2.9.



* If PFS is also significant at any analysis.

Figure 2 Type I Error Reallocation Strategy Following Closed Testing Principle

The secondary hypotheses will be tested sequentially with alpha level of 2.5% in the order listed below if pembrolizumab (MK-3475) arm is superior to paclitaxel or vinflunine in PFS AND the pembrolizumab (MK-3475) arm is superior to paclitaxel or vinflunine in OS at any analysis:

(1) PFS (modified RECIST 1.1) by independent radiologists' review
(2) ORR (RECIST 1.1) by independent radiologists' review
(3) ORR (modified RECIST 1.1) by independent radiologists' review

If the pembrolizumab (MK-3475) arm is only superior to paclitaxel or vinflunine in OS at any analysis, then the above secondary hypotheses will be tested sequentially with alpha level of 2.0%.

8.2.7 Sample Size and Power Calculation

The study is event-driven and plans to randomize approximately 470 subjects with 1:1 ratio into the pembrolizumab (MK-3475) arm and the paclitaxel or vinflunine arm.

PFS analysis: The first PFS analysis will be conducted after: (1) enrollment is complete, (2) approximately 160 PFS events are observed between the pembrolizumab (MK-3475) arm and the paclitaxel or vinflunine arm, and (3) after at least 300 subjects have 4 months of follow-up or more. All subjects with at least 4 months of follow-up at the time of the database lock for the first PFS analysis will be included. With ~160 PFS events, the study has ~96% power to demonstrate superiority in PFS of pembrolizumab (MK-3475) relative to the paclitaxel or vinflunine arm at the alpha = 0.4% (one-sided) level if the true hazard ratio is 0.50. A p-value less than 0.4% (one-sided) for PFS approximately corresponds to an observed hazard ratio of < 0.657 (or approximately at least 6.08 months of median PFS in pembrolizumab (MK-3475) vs. 4 months of median PFS in paclitaxel or vinflunine). The sample size calculation is based on the following assumptions: 1) progression-free survival follows an exponential distribution with a median of 4 months in the standard therapy arm, 2) the true hazard ratio between pembrolizumab (MK-3475) and standard therapy is 0.5, 3) an enrollment period of 11 months, and 4) a yearly dropout rate of 5%. Any change to the timing, along with its rationale, will be documented in a memo to the study file before the database lock.

The second analysis of PFS per RECIST 1.1 by independent radiology review will be performed at the time of the final OS analysis. It is expected that approximately 415 PFS events would have been observed between the two arms at this analysis.

OS analyses: At the time of the first PFS analysis, an interim analysis for OS will also be conducted with at least 130 OS events. If there are fewer than 130 OS events at the time, the PFS analysis may be delayed for up to 2 months or when the target OS number is reached, whichever occurs first. The purpose of the OS interim analysis is to determine if the risk/benefit ratio to the trial population as a whole is unacceptable and subsequently whether the trial may be stopped early at the recommendation of the DMC. Another interim analysis for OS will be performed about 8 months after the first OS interim analysis. Further details of the interim analysis strategy, including efficacy and futility rules, are given in Section 8.2.9.

The final OS analysis will be conducted after ~356 deaths have occurred between the pembrolizumab (MK-3475) arm and the paclitaxel or vinflunine arm, if the trial is not stopped early for efficacy or futility. The timing of final OS analysis is expected to be about 16 months after enrollment completion. With 356 events at the final analysis, the study provides 90% power to demonstrate superiority in OS of pembrolizumab (MK-3475) relative to standard therapy at the alpha=2.0% (one-sided) level if the true HR is 0.7. Success for OS at the final analysis approximately corresponds to an observed hazard ratio of < 0.80 (or approximately at least 10 months of median OS in pembrolizumab (MK-3475) vs. 8 months of median PFS in paclitaxel or vinflunine). The sample size calculation is based on the following assumptions: 1) OS follows an exponential distribution with a median of 8 months

in the standard therapy arm, 2) hazard ratio between pembrolizumab (MK-3475) and standard therapy is 0.7, 3) an enrollment period of 11 months and a minimum of 16 months follow-up after enrollment completion; and 4) a yearly drop-out rate of 2%.

The assumptions for the median PFS of 4 months and the median OS of 8 months in the standard therapy arm are based on weighted average of median PFS and median OS estimates from 2L trials of single agents [29, 30, 32, 33, 34, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62].

The sample size and power calculation were performed in the software EAST and R (package "gsDesign").

8.2.8 Subgroup Analyses and Effect of Baseline Factors

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

- Age category (≤65 vs. >65 years)
- PD-L1 subgroup (positive vs. negative)
- High PD-L1 subgroup (to be defined based on emerging external data)
- Sex (female vs. male)
- Race (white vs. non-white)
- ECOG status (0 / 1 vs. 2)
- Geographic region of enrolling site (East Asia vs. non-East Asia and EU vs. non-EU)
- Prior platinum therapy (carboplatin vs. cisplatin)
- Setting of most recent prior therapy (neoadjuvant vs. adjuvant vs. 1L metastatic vs. 2L metastatic)
- Presence or absence of liver metastases at baseline
- Baseline hemoglobin (≥ 10 g/dL vs. <10 g/dL)
- Time from completion/discontinuation of most recent prior therapy to baseline (<3months vs. ≥3 months)
- Histology (transitional cell vs. mixed transitional/non-transitional histology)
- Smoking status (never vs. former vs. current)
- Brain metastasis status (prior brain metastasis vs. no prior brain metastasis)
- Investigators' choice of paclitaxel or vinflunine
- Burden of disease in terms of baseline tumor volume

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

Additionally, patients with high PD-L1 expression level (cut-off point to be determined) are of special interest in this study. Once data from the ongoing pembrolizumab (MK-3475) studies provide reliable estimates of the cut-off point and the prevalence of high PD-L1

expression level becomes available, the objective on this subpopulation may be elevated to a primary one with a primary hypothesis. Such a change, if any, will be made and documented before any interim analysis and unblinding of the biomarker data including details of the assay to be used and the criteria for classification as PD-L1 positive or negative. Analysis methods as described in [63, 64] or a more conservative Bonferroni approach will be considered for testing the joint primary hypotheses on the subpopulation and the overall population.

8.2.9 Interim Analysis

There are two planned PFS analyses and three planned OS analyses. The futility bounds of this study are non-binding and the bounds are considered guidance rather than strict bounds. Results of the first PFS analysis and the interim analysis of OS will be reviewed by a data monitoring committee (DMC). Further details of interim analyses are provided below and will be incorporated into the DMC Charter.

8.2.9.1 PFS Analysis and Interim OS Analysis

The first PFS analysis will take place when enrollment is complete, approximately 160 PFS events have been observed between the MK arm and the paclitaxel or vinflunine arm, and at least 300 subjects have 4 months or more of follow-up. The first PFS analysis is expected to occur ~11 months after study start and may be delayed for 2-3 months to ensure that at least 300 subjects have ≥4 months of follow-up. In addition, if there are less than 130 OS events between two arms at the time, the analysis may be delayed for up to 2 months or until when the target OS number is reached, whichever occurs first. If there are fewer than 130 events following the delay, then the spending function for OS will be adjusted to adjust for the smaller number of events. The primary objective of this analysis is to demonstrate superiority of pembrolizumab (MK-3475) in PFS and exclude detrimental effect of pembrolizumab (MK-3475) on OS.

For PFS hypothesis, a Hwang-Shih-DeCani alpha-spending function with the gamma parameter (4) is constructed to implement group sequential boundaries that control the type I error rates. The pembrolizumab (MK-3475) arm will be compared to the paclitaxel or vinflunine arm. An approximate observed HR of ~0.657 or less would demonstrate PFS superiority at $\alpha = 0.4\%$ (one-sided). This hazard ratio approximately corresponds to at least 2.1-month improvement over the median PFS from 4 months in the paclitaxel or vinflunine arm. However, because immunotherapies have been shown to impact PFS curves at later time points (i.e., the tail of the curve), the observed difference in medians may be an underrepresentation of the treatment effect.

The study will also examine OS at the planned PFS analysis. For OS, a Hwang-Shih-DeCani alpha-spending function with the gamma parameter (-4) and beta-spending function with gamma (-8) are constructed to implement group sequential boundaries that control the type I error rate as well as allow for non-binding futility analysis. Table 17 summarizes the efficacy and futility rules for the OS analysis.

If at least 130 OS events are observed at the time of the first PFS analysis, an interim OS analysis will be conducted at the level determined by the spending function boundaries and the actual number of OS events at the time of the final PFS analysis. As shown in Table 17 an approximate observed hazard ratio < ~0.59, i.e., at least 5.6-month improvement in median OS, would demonstrate OS superiority at the interim analysis. A futility analysis will be conducted at the same time and an observed hazard ratio > 1.24 will approximately meet the criterion for futility. The boundaries for OS hypothesis testing will be re-calculated if actual monitoring schedule is altered. If there are fewer than 130 OS events even after a 2 month delay, or if more than 130 events have occurred at the time of the first PFS analysis, the alpha and beta spending functions will be adjusted to accommodate the revised interim analysis timing using the fraction of total OS events.

Additional interim analyses of OS will be performed about 8 months after the first PFS analysis. The purpose of the additional OS analyses is to determine whether the trial may be stopped early for efficacy or futility at the recommendation of the DMC and to mitigate the risk of dilution of treatment effect due to potential crossover of subjects in the control arm to other PD-1 therapies. Assuming an 11 months enrollment with the final OS analysis approximately 16 months following enrollment completion, this could result in the first IA at approximately 11 months, the second IA at approximately 19 months and the final analysis at 27 months. The second IA of OS will not be performed if more than 90% (~320 events) of the final planned OS events have occurred by 8 months after the first IA. Table 17 summarizes the timing, sample size and decision guidance for the planned PFS and OS analyses under this hypothetical scenario. The actual boundaries will be determined from the actual number of PFS or OS events at the time of the specified IA using the alpha- and beta-spending functions.

The final OS analysis will be conducted after ~356 OS events are observed at the alpha level determined by the spending function boundaries and actual number of OS events.

Table 17 Summary of Timing, Sample Size and Decision Guidance at the Planned PFS and OS Analyses

Analysis	Criteria for Conduct of Analysis	Value	Efficacy	Futility
First PFS Analysis/ Interim OS Analysis 1	Approx. 11 mos OS Events: 130 PFS Events: 160 All Subjects Enrolled	OS: Z statistic	3.03	-1.21
		OS: p value (1-sided)	0.001	0.886
		OS: HR at bound	0.588	1.236
		PFS: Z statistic	2.65	
		PFS: p value (1-sided)	0.004	
		PFS: HR	0.657	
Interim OS Analysis 2	Approx. 19 mos OS Events : 277 All Subjects Enrolled	OS: Z statistic	2.59	0.39
		OS: p value (1-sided)	0.005	0.348
		OS: HR at bound	0.746	0.903
Final OS Analysis / Second PFS analysis	Approx. 27 mos OS Events: 356 PFS Events: 415	OS: Z statistic	2.11	2.11
		OS: p value (1-sided)	0.017	0.017
		OS: HR at bound	0.800	0.800
		PFS: Z statistic	3.01	
		PFS: p value (1-sided)	0.0013	
		PFS: HR	0.744	

*The first PFS analysis will be conducted after enrollment is complete, 160 PFS events are observed, and at least 300 subjects have ≥4 months of follow-up. This analysis may be delayed 2-3 months to ensure that at least 300 subjects have ≥4 months of follow-up

8.2.9.2 Final OS Analysis

The final analysis will take place when approximately 356 deaths have occurred between the pembrolizumab (MK-3475) arm and the paclitaxel or vinflunine arm which is expected to occur ~27 months after study start. The approximate observed hazard ratio for OS superiority is < 0.80, which corresponds to at least ~2-month improvement in median OS. If the required number of OS events is not observed by the time that the trial has been open for 27 months (assuming ~16 months of follow-up after enrollment completion), the spending function will be adjusted for the number of events observed at that time. Likewise, if the timing of events occurs faster than anticipated, the test boundary at the final analysis will be adjusted to use the remaining Type I error not spent at earlier analyses. A 95% confidence interval will be provided for the hazard ratio to characterize the OS effect in case the superiority is not demonstrated. As an exploratory analysis, RPSFT model will be used to adjust for the potential crossover effect to other PD-1 therapies.

The second PFS analysis will be conducted at the time of the final analysis of OS.

8.2.10 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the study. Compliance with trial treatment administration will be measured by subjects: 1) receiving unscheduled study agent infusions/injections; 2) missing an infusion/injection. Numbers and percentages of subjects and infusion/injection visits with any deviation in these measures will be reported for the ITT population.

8.2.11 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles. Dose intensity will also be summarized as appropriate.

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 18.

Table 18 Product Descriptions

Product Name & Potency	Dosage Form
pembrolizumab (MK-3475) 100 mg/ 4 mL	Solution for Infusion
Vinflunine 250 mg/ 10 mL	Solution for Infusion
Paclitaxel 100 mg/ 16.7 mL	Solution for Infusion

The paclitaxel and vinflunine will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements. All other products will be provided locally by the trial site, subsidiary or designee.

The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

9.2 Packaging and Labeling Information

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

Subjects will receive open label pembrolizumab (MK-3475) vials, vinflunine kits and paclitaxel kits. Each kit of vinflunine and paclitaxel will contain one vial.]

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return.

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 Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 **Quality Management System**

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

10.6 **Data Management**

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

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

10.7 **Publications**

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

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

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

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although

publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

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

11.0 LIST OF REFERENCES

1. Disis ML. Immune regulation of cancer. J Clin Oncol 2010; 28(29):4531-8.

2. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8):793-800.

3. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nature 2002;2:116-26.

4. Brown JA, Dorfman DM, Ma F-R, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 2003;170:1257-66.

5. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

6. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Caner Res 2007;13(6):1757-61.

7. Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007;26:373-400.

8. Usubütün A, Ayhan A, Uygur MC, Ozen H, Toklu C, Ruacan S. Prognostic factors in renal cell carcinoma. J Exp Clin Cancer Res 1998;17(1):77-81.

9. Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund L-T. Prognostic effect of epithelial and stromal symphocyte infiltration in non-small cell lung cancer. Clin Cancer Res 2008;14(16):5220-7.

10. Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen p, Lardon F, et al. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol 2010;11:19.

11. Diez M, Pollán M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, et al. Histopathologic prognostic score in colorectal adenocarcinomas. Anticancer Res 1998;18:689-94.

12. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313:1960-4.

13. Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol 2010;15:544-51.

14. Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, et al. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori 2008;94:426-30.

15. Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. J Cutan Pathol 2010;37(Suppl 1):48-53.

16. Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. Lancet 2009;10:840-841.

17. Hillen F, Baeten CIM, van de Winkel A, Creytens D, van der Schaft DWJ, Winnepenninckx V, et al. Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. Cancer Immunol Immunother 2008;57:97-106.

18. Lee HE, Chae SW, Lee YJ, Kim MA, Lee HS, Lee BL, et al. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. Br J Cancer 2008;99(10):1704-11.

19. Leffers N, Gooden MJM, de Jong RA, Hoogeboom B-N, ten Hoor KA, Hollema H, et al. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother 2009;58:449-59.

20. Nishimura H, Honjo T, Minato N. Facilitation of β selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med 2000;191(5):891-7.

21. Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, et al. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Intern 2010;107:1500-6.

22. Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma V-M. Prognostic value of tumour-infiltrating lynmphocytes (TILs) in colorectal cancer. J Pathol 1997;182:318-24.

23. Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.

24. Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.

25. Ölcher M, Braun M, Friedrichs N, Rudlowski C, Bercht E, Fimmers R, et al. Foxp3+ cell infiltration and granzyme B+/Foxp3+ cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59:909-19.

26. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. PNAS 2001;98(24):13866-71.

27. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisted. Annu Rev Immunol 2005;23:515-48.

28. Jemal A, Bray F, Center MM, Ferlay J, Ward E, and Forman D. Global Cancer Statistics. CA Cancer J Clin 2011;61:69-90.

29. Vaughn DJ, Broome CM, Hussain M, Gutheil JC and Markowitz AB. Phase II Trial of Weekly Paclitaxel in Patients With Previously Treated Advanced Urothelial Cancer. Journal of Clinical Oncology. 2002;20(4):937-940.

30. McCaffrey JA, Hilton S, Mazumdar M, Sadan S, Kelly WK, Scher HI and Bajorin DF. Phase II Trial of Docetaxel in Patients With Advanced or Metastatic Transitional-Cell Carcinoma. Journal of Clinical Oncology. 1997;15(5):1853-1857.

31. Witte RS, Elson P, Bono B, Knop R, Richardson RR, Dreicer R, and Loehrer Sr. PJ. Journal of Clinical Oncology. 1997;15(2):589-593.

32. Sweeney CJ, Roth BJ, Kabbinavar FF, Vaughn DJ, Arning M, Curiel RE, Obasaju CK, et al. Phase II Study of Pemetrexed for Second-Line Treatment of Transitional Cell Cancer of the Urothelium. Journal of Clinical Oncology. 2006;24:3451-3457.

33. Joly F, Houede N, Noal S, Chevreau C, Priou F, Chinet-Charrot P, Rolland F, Flechon A, et al. Clinical Genitourinary Cancer. 2009;7(2):E28-E33.

34. Bellmunt J, Theodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, Caty A, Carles J, et al. Journal of Clinical Oncology. 2009;27(27):4454-4461.

35. Sonpavde G, Sternberg CN, Rosenberg JE, Hahn NM, Galsky MD, and Vogelzang NJ. Second-line systemic therapy and emerging drugs for metastatic transitional-cell carcinoma of the urothelium. Lancet Oncol. 2010;11(9):861-870.

36. NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 2.2014, NCCN.org

37. Bellmunt J, von der Maase H, Mead GM, Skoneczna I, De Santis M, Daugaard G, Boehle A, Chevreau C, et al. Randomized Phase III Study Comparing Paclitaxel/Cisplatin/Gemcitabine and Gemcitabine/Cisplatin in Patients With Locally Advanced or Metastatic Urothelial Cancer Without Prior Systemic Therapy: EORTC Intergroup Study 30987. Journal of Clinical Oncology. 2012;30:1107-1113.

38. Wong Y-N, Litwin S, Vaughn D, Cohen S, Plimack ER, Lee J, Song W, Dabrow M, et al. Phase II Trial of Cetuximab With or Without Paclitaxel in Patients With Advanced Urothelial Tract Carcinoma. Journal of Clinical Oncology. 2012;30(28):3545-3551.

39. Rabin R and de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-343.

40. Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985; 4: 213–226.

41. Finkelstein DM (1986). A proportional hazards model for interval-censored failure time data. *Biometrics* 42**,** 845-54.

42. Akaza H, Naito S, Usami M, Miki T, Miyanaga N, Taniai H and the Japanese Gemcitabine Study Group. Efficacy and Safety of Gemcitabine Monotherapy in Patients with Transitional Cell Carcinoma after Cisplatin-Containing Therapy: A Japanese Experience. Jpn J Clan Oncol 2007;37(3)201-206.

43. Albers P Onkologie 2002 Albers P, Siener R, Haertlein M, Fallahi M, Haeutle D, Perabo FGE, Steiner G, Blatter J and Mueller SC. Gemcitabine Monotherapy as Second-Line Treatment in Cisplatin-Refractory Transitional Cell Carcinoma – Prognostic Factors for Response and Improvement of Quality of Life. Onkologie 2002;25:47-52.

44. Bellmunt J Cancer Invest 2002 Bellmunt J, Cos J, Cleries R, Perez M, Ribas A, Eres N, Murio JE, Margarit C, and Baselga J. Feasibility trial of methotrexate-paclitaxel as a second line therapy in advance urothelial cancer. Cancer Invest 2002;20(5-6):673-685.

45. Culine S, Theodore C, De Santis M, Bui B, Demkow T, Lorenz J, Rolland F, Delgado F-M, et al. A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. British Journal of Cancer 2006;94:1395-1401.

46. Dreicer R, Li S, Manola J, Haas N, Roth B, and Wilding G. Phase 2 Trial of Epothilone B Analog BMS-247550 (Ixabepilone) in Advanced Carcinoma of the Urothelium (E3800): A Trial of the Eastern Cooperative Oncology Group. Cancer 2007; 100:759-63.

47. Fechner G, Siener R, Reimann M, Kobalz L, Albers P, and Members of the German Association of Urologic Oncology (AUO) Bladder Cancer Study Group. Randomised phase II trial of gemcitabine and paclitaxel second-line chemotherapy in patients with transitional cell carcinoma (AUO Trial AB 20/99). J Clin Pract 2006;60(1):27-31.

48. Gallagher DJ, Milowsky MI, Gerst SR, Ishill N, Riches J, Regazzi A, Boyle MG, Trout A, et al. Phase II Study of Sunitinib in Patients With Metastatic Urothelial Cancer. Journal of Clinical Oncology 2010;28(8):1373-1379.

49. Kanai K, Kikuchi E, Ohigashi T, Miyajima A, Nakagawa K, Nakashima J, and Oya M. Gemcitabine and paclitaxel chemotherapy for advanced urothelial carcinoma in patients who have received prior cisplatin-based chemotherapy. Int J Clin Oncol 2008;(13):510-514.

50. Ko Y-J, Canil CM, Mukherjee SD, Winquist E, Elser C, Eisen A, Reaume MN, Zhang L, et al. Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicenter, phase 2 study. Lancet Oncology 2013;14(8):769-776.

51. Krege S, Rembrink V, Borgermann CH, Otto T, and Rubben H. Docetaxel and Ifosfamide as Second Line Treatment for Patients with Advanced or Metastatic Urothelial Cancer After Failure of Platinum Chemotherapy: A Phase 2 Study. The Journal of Urology 2001;165:67-71.

52. Lin C-C, Hsu C-H, Huang C-Y, Keng J-Y, Tsai Y-C, Huang K-H, Cheng A-L and Pu Y-S. Gemcitabine and ifosfamide as a second-line treatment for cisplatin-refractory metastatic urothelial carcinoma: a phase II study. Anti-Cancer Drugs 2007;18:487-491.

53. Lorusso V, Pollera CF, Antimi M, Luporini G, Gridelli C, Frassineti GL, Oliva C, Pacini M, et al. A Phase II Study of Gemcitabine in Patients with Transitional Cell Carcinoma of the Urinary Tract Previously Treated with Platinum. Eu J Can 1998;34(8):1208-1212.

54. Milowsky MI, Iyer G, Regazzi AM, Al-Ahmade H, Gerst SR, Ostrovnaya I, Gellert LL, Kaplan R, et al. Phase II study of everolimus in metastatic urothelial cancer. BJU 2013;112:462-470.

55. Prozanto P, Vigani A, Pensa F, Vanoli M, Tani F, and Vaira F. Second Line Chemotherapy with Ifosfamide as Outpatient Treatment for Advanced Bladder Cancer. Am J of Clin Oncol 1997; 20(5):519-521.

56. Sternberg CN, de Mulder PHM, Theodore C, Fossa SD, Van Oosterom AT, Witjes F, Spina M, van Groeningen CJ, et al. Randomized Phase III Trial of High-Dose-Intensity Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (MVAC) Chemotherapy and Recombinant Human Granulocyte Colony-Stimulating Factor Versus Classic MVAC in Advanced Urothelial Tract Tumors: European Organization for Research and Treatment of Cancer Protocol No. 30924. Journal of Clinical Oncology. 2001;19:2638-2646.

57. Suyama T, Ueda T, Fukasawa S, Imamura Y, Nakamura K, Miyasaka K, Sazuka T, Egoshi K-I, et al. Combination of Gemcitabine and Paclitaxel as Second-line Chemotherapy for Advanced Urothelial Carcinoma. Jpn J Clin Oncol 2009;39(4):244-250.

58. Sweeney CJ, Williams SD, Finch DE, Bihrle R, Foster RS, Collins M, Fox S, Roth BJ. A Phase II Study of Paclitaxel and Ifosfamide for Patients with Advanced Refractory Carcinoma of the Urothelium. Cancer 1999;86:514-518.

59. Takahashi T, Higashi S, Nishiyama H, Segawa T, Nakamura E, Kinoshita H, Itoh N, Yamamoto S, et al. Biweekly Paclitaxel and Gemcitabine for Patients with Advanced Urothelial Cancer Ineligible for Cisplatin-Based Regimen. Jpn J Clin Oncol 2006;36(2):104-108.

60. Vaishampayan UN, Faulkner JR, Small EJ, Redman BG, Keiser WL, Petrylak DP, Crawford ED. Phase II Trial of Carboplatin and Paclitaxel in Cisplatin-Pretreated Advanced Transitional Cell Carcinoma. Cancer 2005;104:1627-1632.

61. Vaughn DJ, Srinivas S, Stadler WM, Pili R, Petrylak D, Sternberg CN, Smith, DC, Ringulette S, et al. Vinflunine in Platinum-Pretreated Patients With Locally Advanced or Metastatic Urothelial Carcinoma. Cancer 2009;115:4110-7.

62. Witte RS, Manola J, Burch PA, Kuzel T, Weinshel EL, and Loeher, Sr. PJ. Topotecan in previously treated advanced urothelial carcinoma: an ECOG phase II trial. Investigational New Drugs 1998;16:191-195.

63. Chen C, Beckman RA. Hypothesis testing in a confirmatory phase III trial with a possible subset effect. Stat Biopharm Res 2009;1(4):431-40.

64. Wang S-J, O'Neil RT, Hung HMJ. Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset. Pharmaceut Statist 2007;6:227-44.

65. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 2004;291(3):335-42.

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 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 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 (PPD) 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

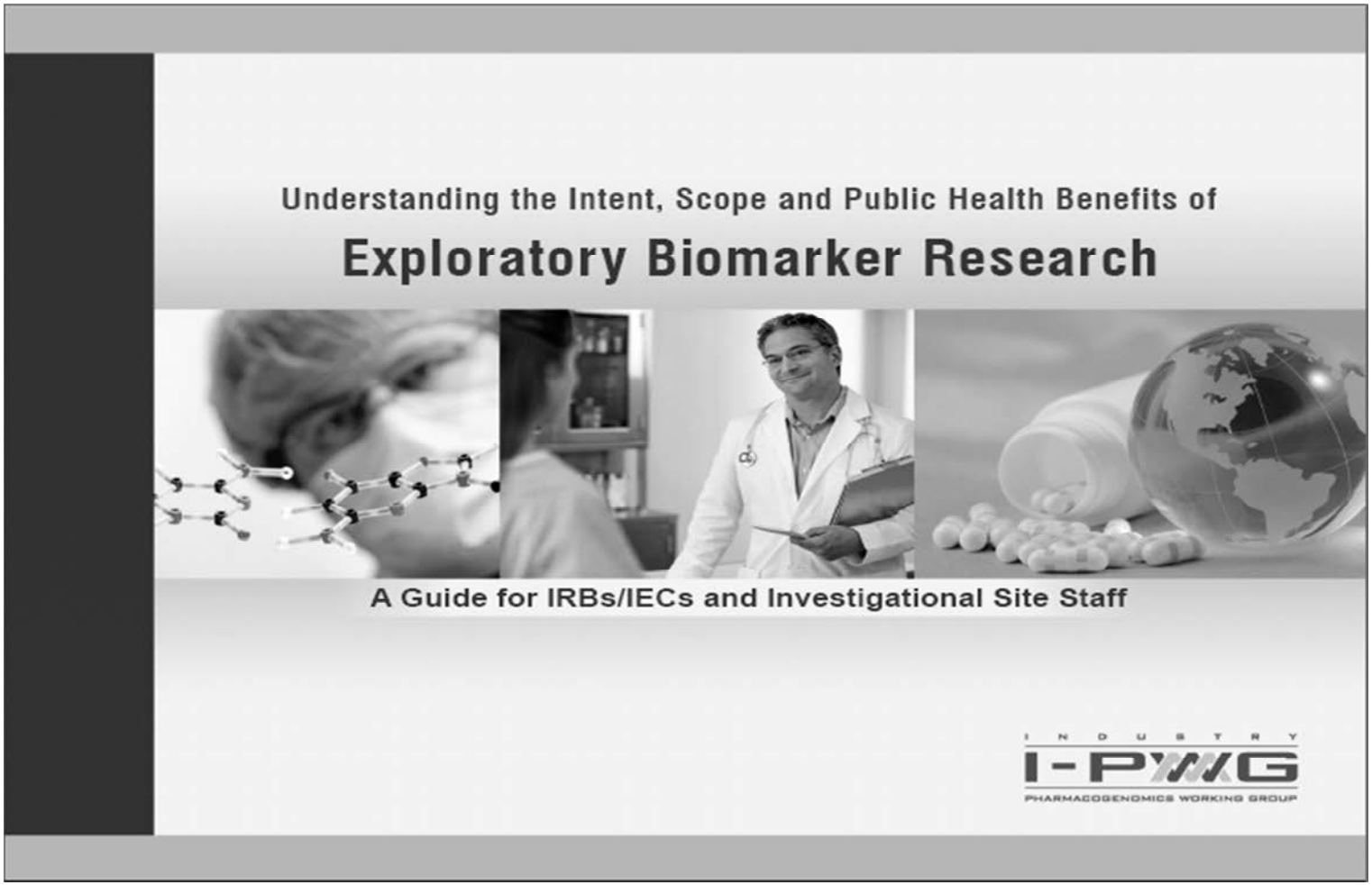
Any questions related to the future biomedical research should be e-mailed directly to PPD.

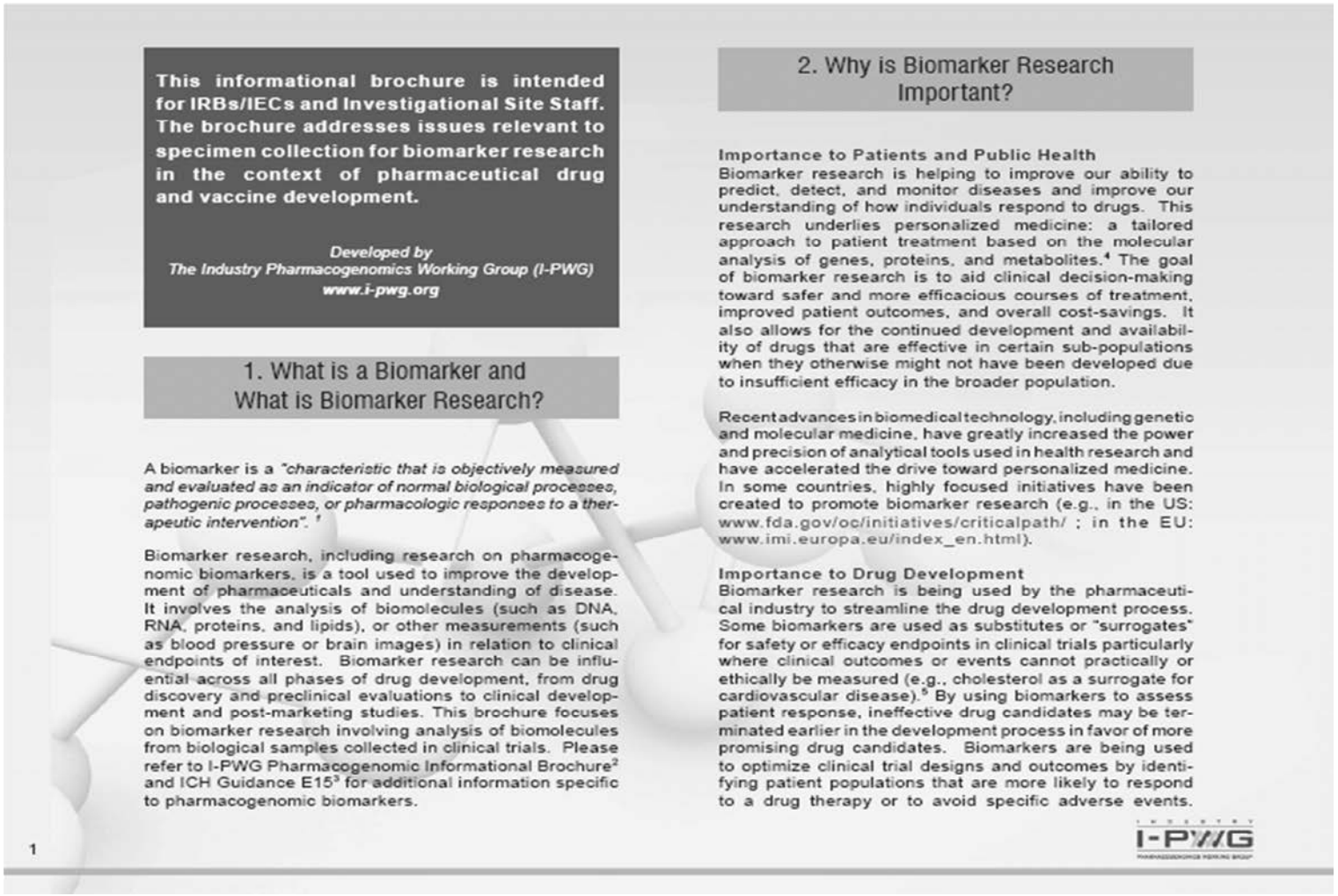
14. References

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

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

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





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

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

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

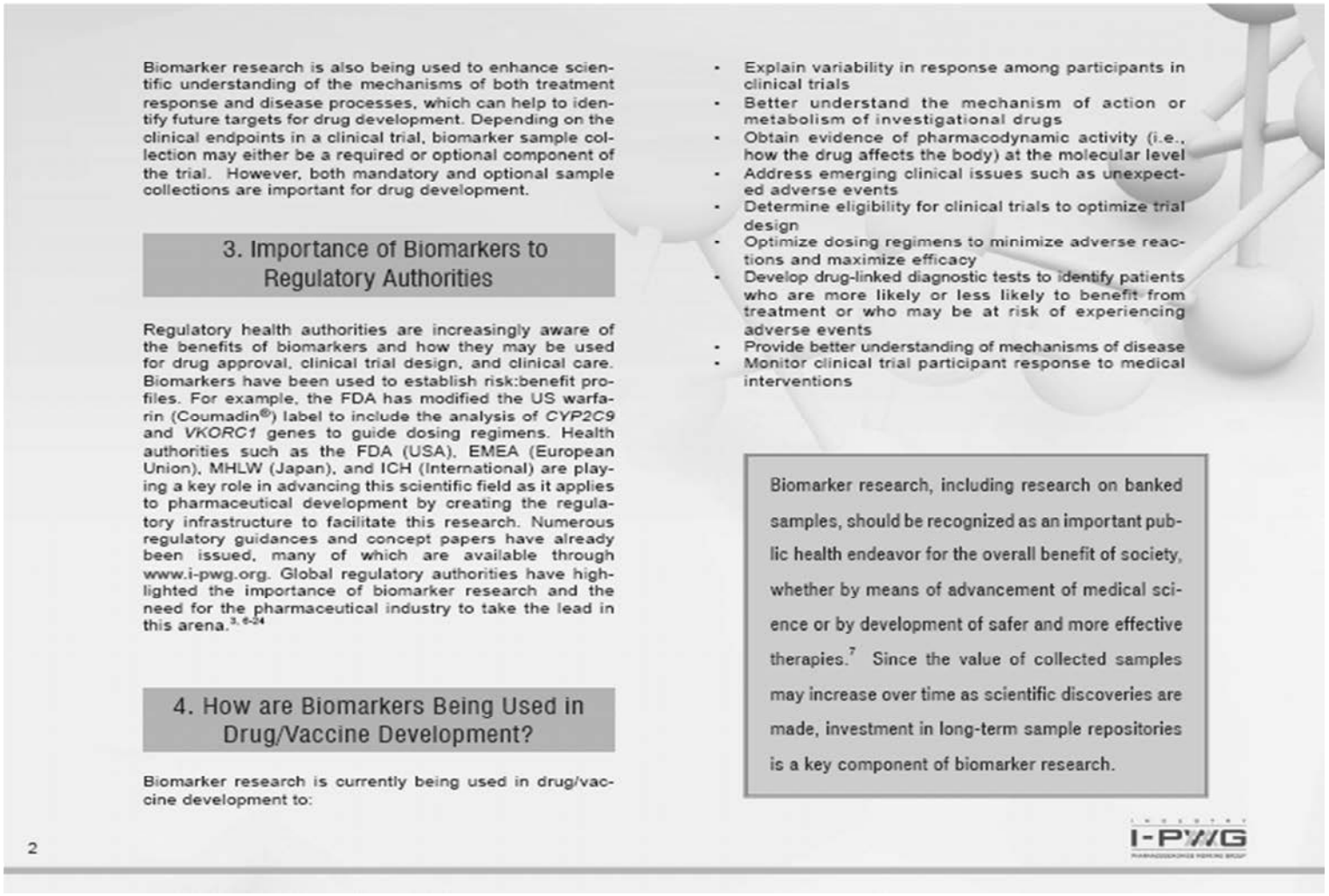
Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to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

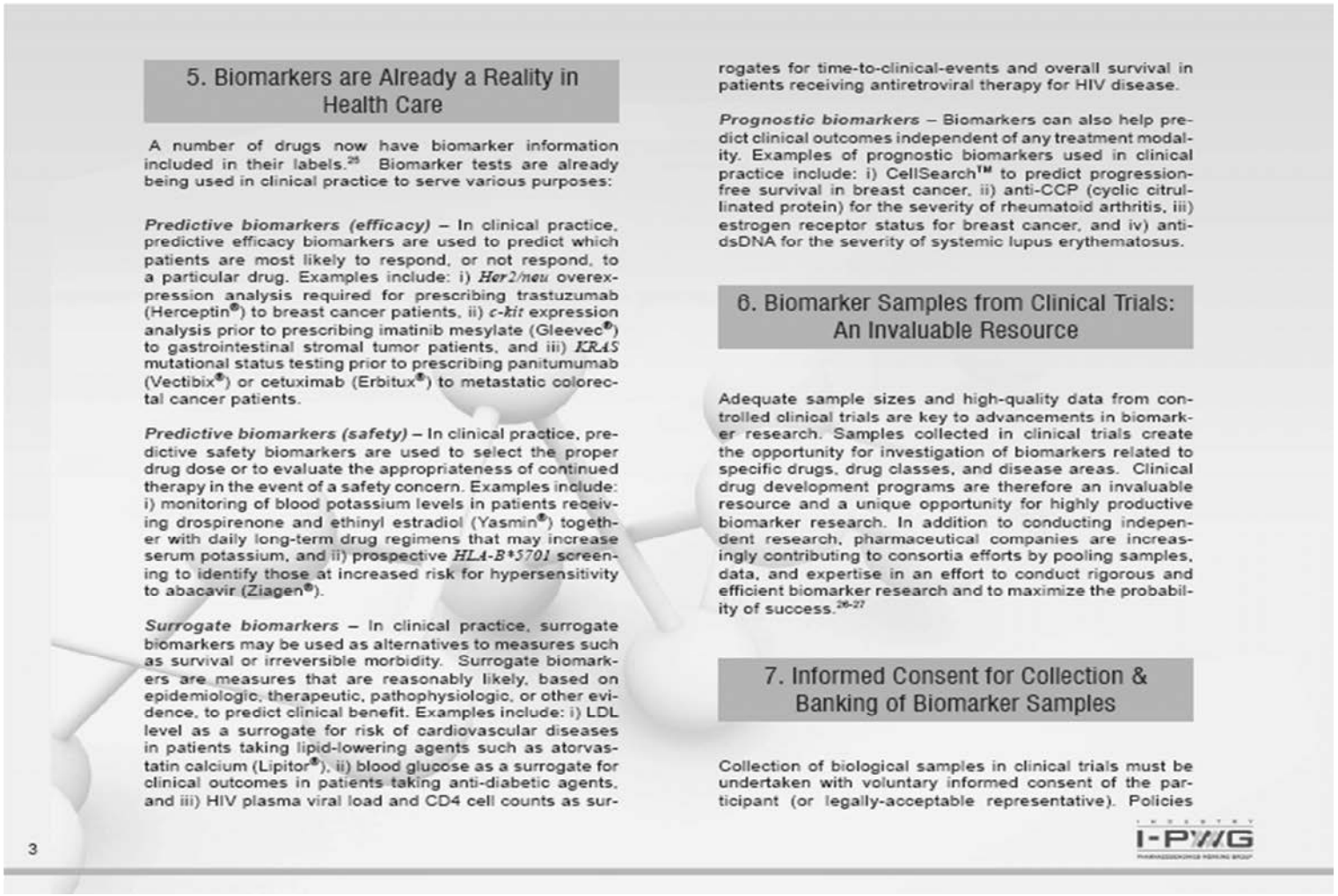
Importance to Drug Development

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

1

I-PWG


Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of CYP2C9 and VKORC1 genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3,6-24]
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.
I-PWG
2



5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

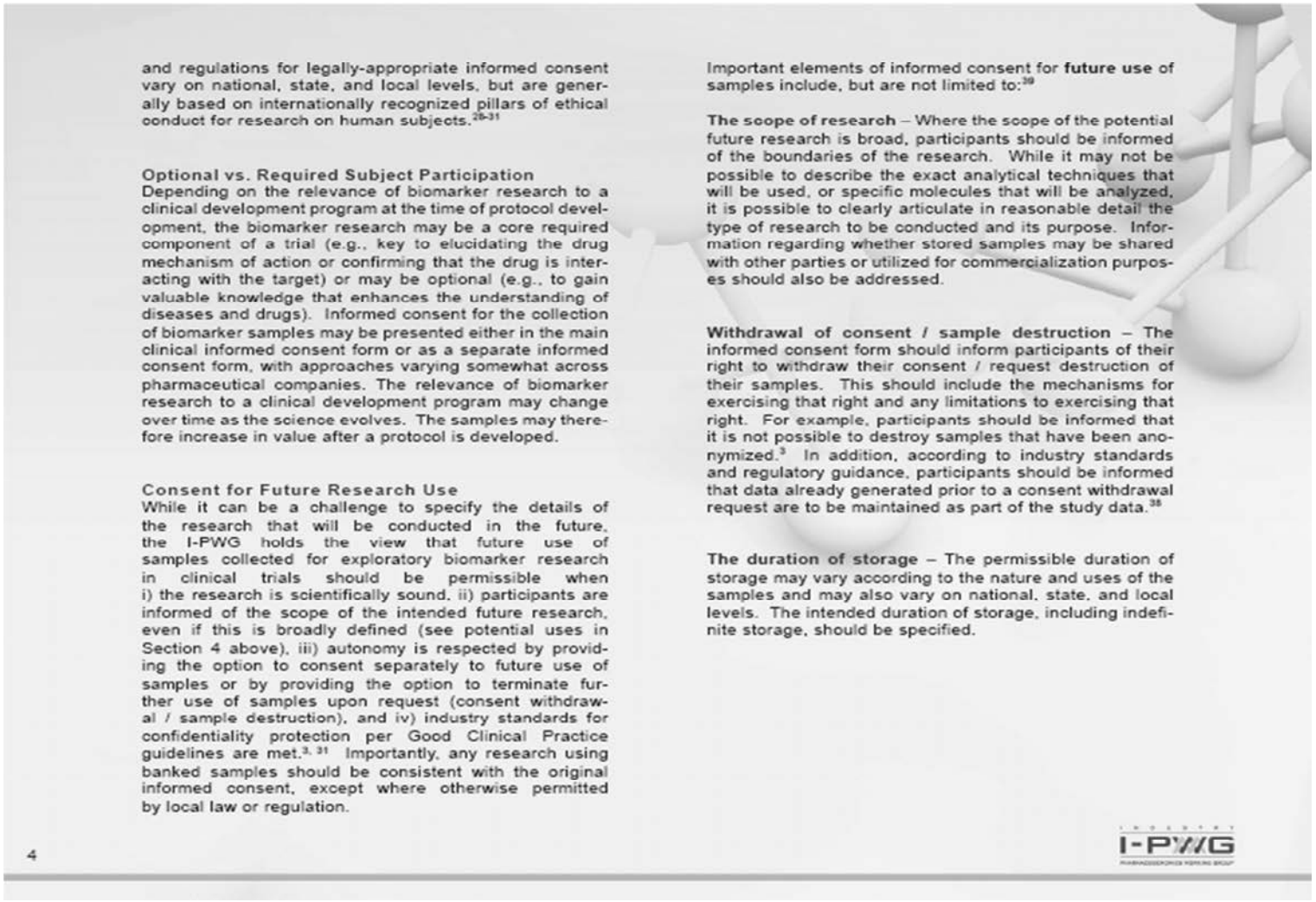
Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

3

I-PWG



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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

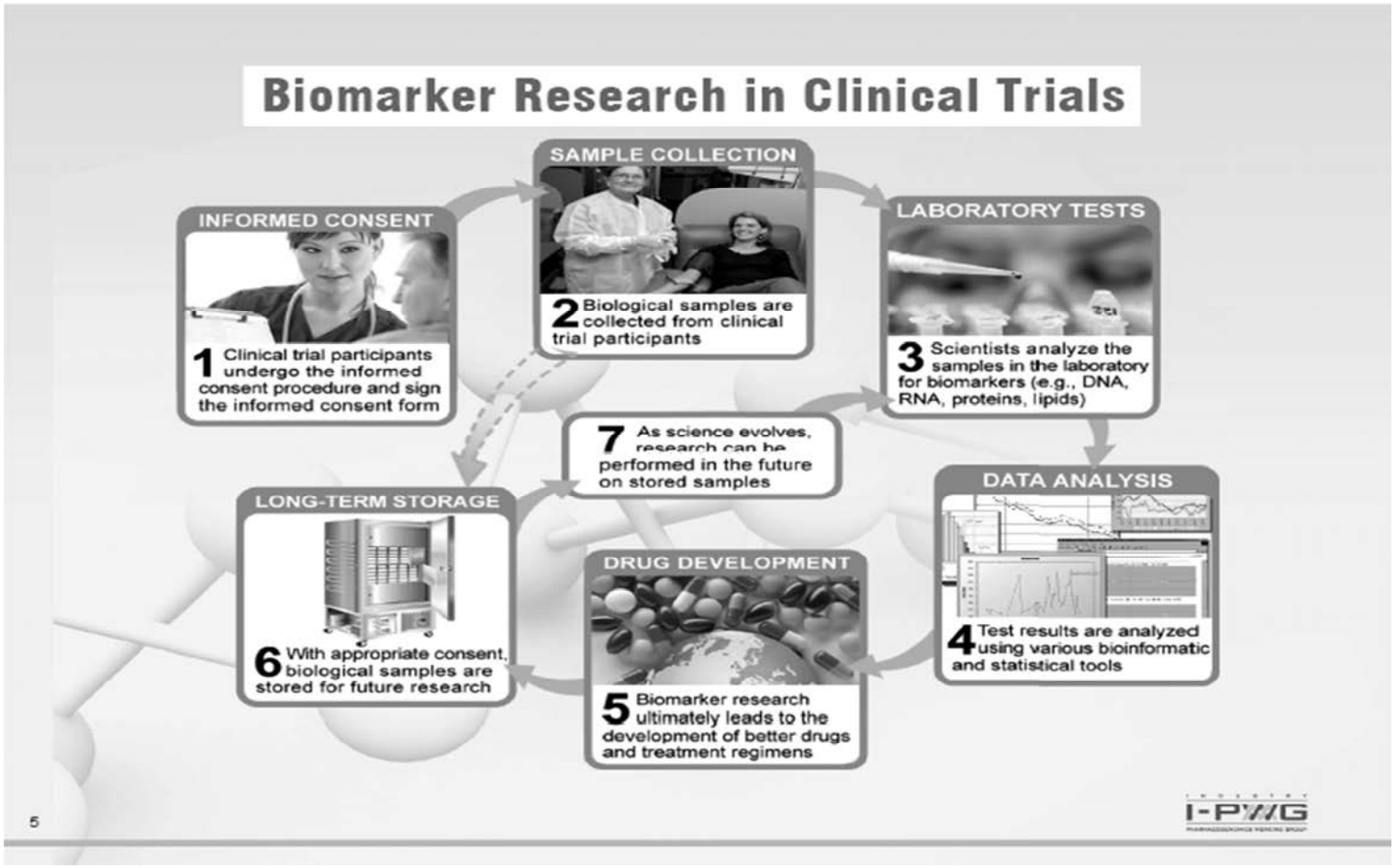
The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible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

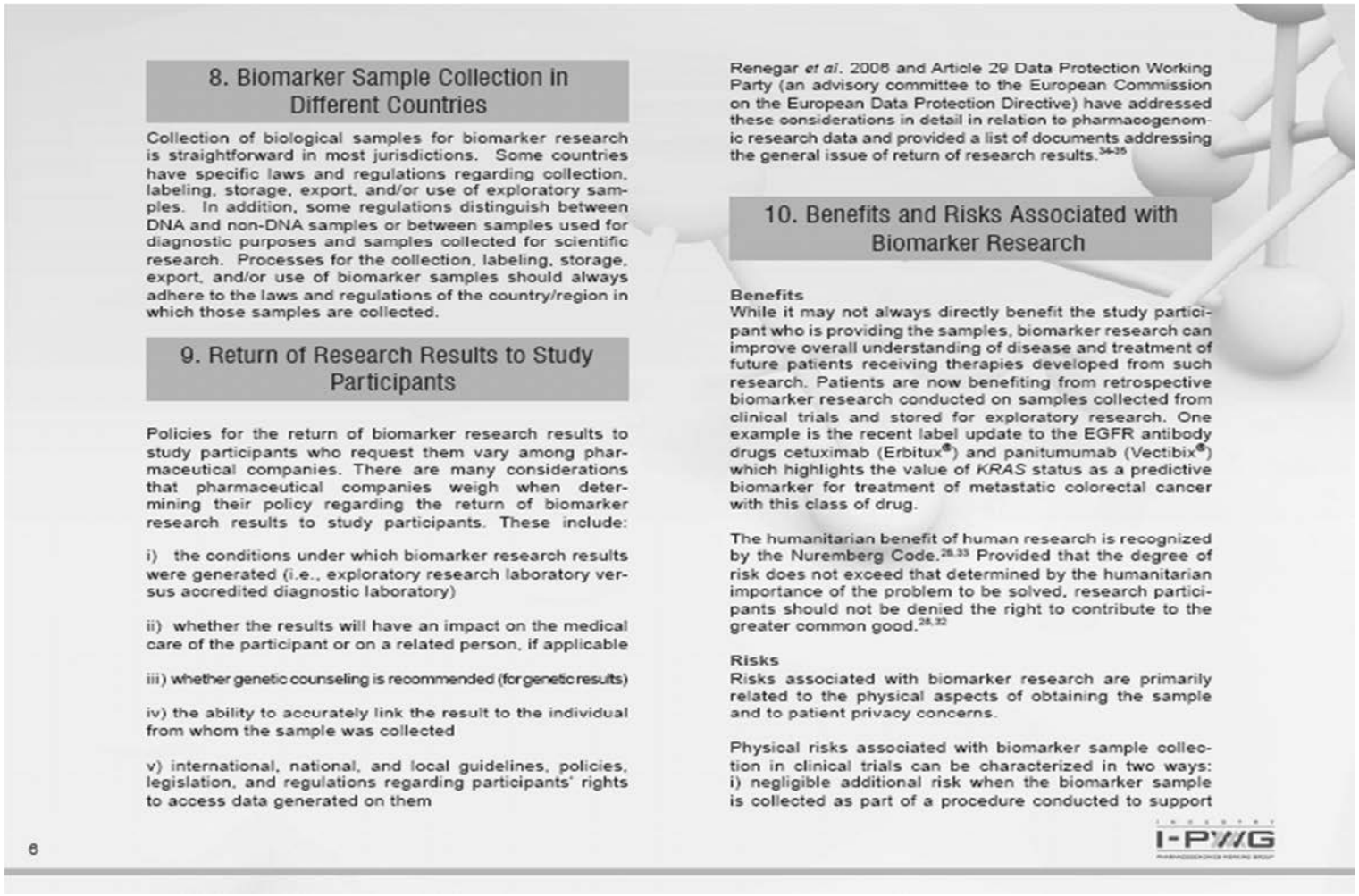
Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants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

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

4

I-PWG


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



8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

Renegar *et al*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

6

I-PWG

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [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).[35-37]

12.Where to Get More Information?

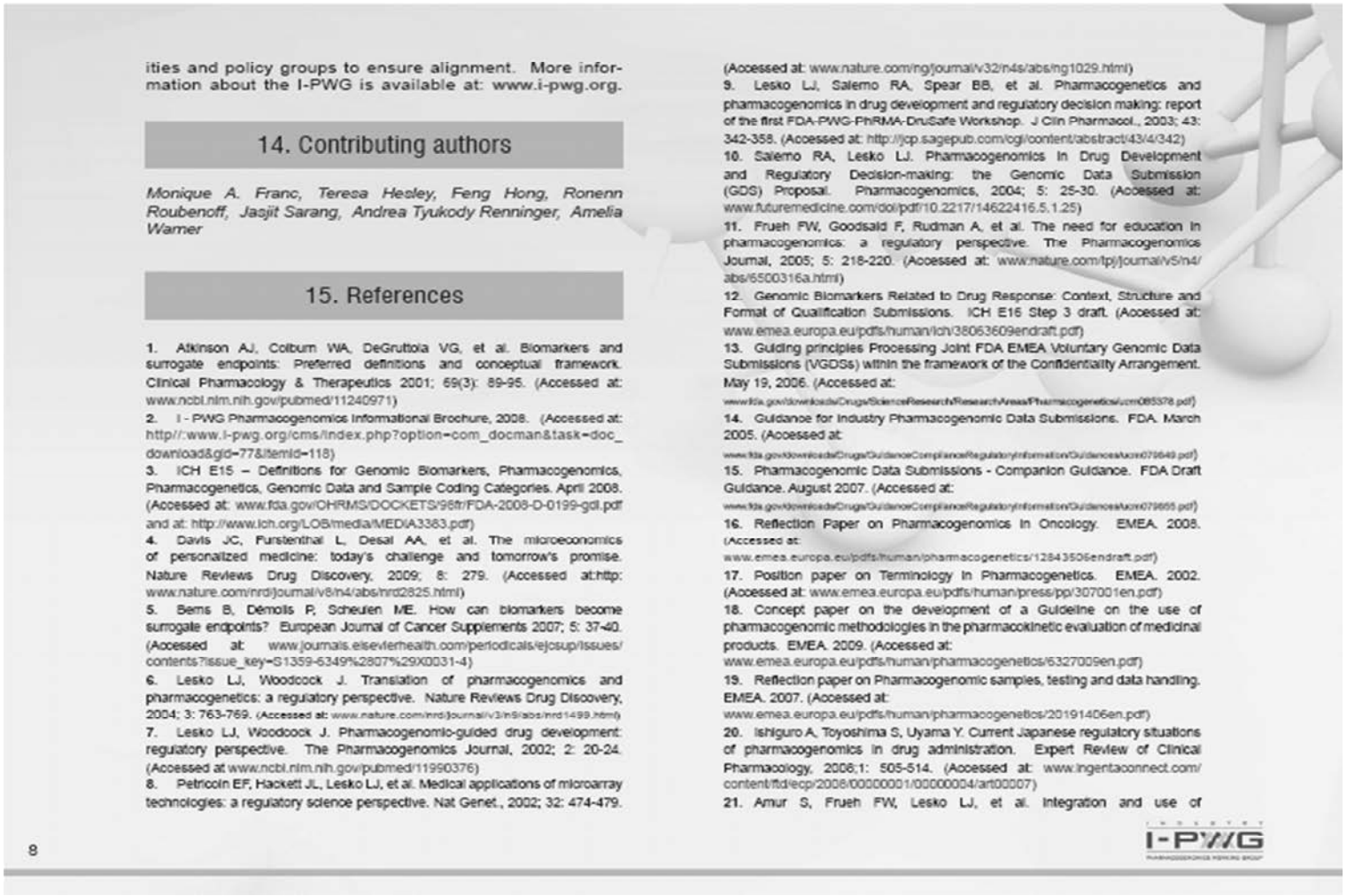
Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

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

7

I-PWG



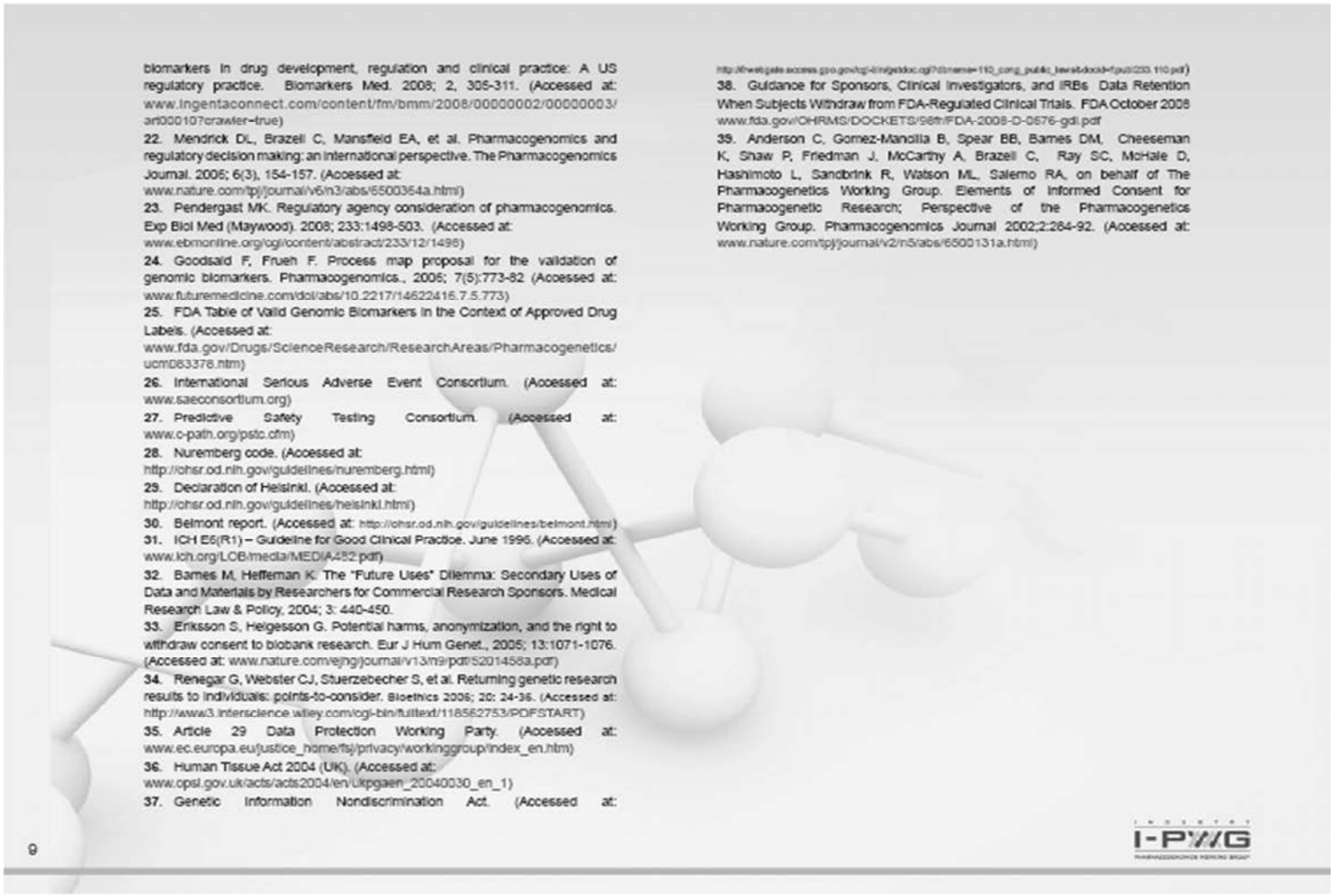
ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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

15. References

1. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics 2001; 69(3): 89-95. (Accessed at: www.ncbi.nlm.nih.gov/pubmed/11240971)
2. I - PWG Pharmacogenomics Informational Brochure, 2008. (Accessed at: http//:www.i-pwg.org/cms/index.php?option=com_docman&task=doc_download&gid=77&Itemid=118)
3. ICH E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)
4. Davis JC, Furstenthal L, Desai AA, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nature Reviews Drug Discovery, 2009; 8: 279. (Accessed at:http: www.nature.com/nrd/journal/v8/n4/abs/nrd2825.html)
5. Bems B, Demolis P, Scheulen ME. How can biomarkers become surrogate endpoints? European Journal of Cancer Supplements 2007; 5: 37-40. (Accessed at: www.journals.elsevierhealth.com/periodicals/ejcsup/issues/contents?issue_key=S1359-6349%2807%29X0031-4)
6. Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews Drug Discovery, 2004; 3: 763-769. (Accessed at: www.nature.com/nrd/journal/v3/n9/abs/nrd1499.html)
7. Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. The Pharmacogenomics Journal, 2002; 2: 20-24. (Accessed at www.ncbi.nlm.nih.gov/pubmed/11990376)
8. Petricoin EF, Hackett JL, Lesko LJ, et al. Medical applications of microarray technologies: a regulatory science perspective. Nat Genet., 2002; 32: 474-479. (Accessed at: www.nature.com/ng/journal/v32/n4s/abs/ng1029.html)
9. Lesko LJ, Salerno RA, Spear BB, et al. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PhRMA-DruSafe Workshop. J Clin Pharmacol., 2003; 43: 342-358. (Accessed at: http://jcp.sagepub.com/cgi/content/abstract/43/4/342)
10. Salerno RA, Lesko LJ. Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal. Pharmacogenomics, 2004; 5: 25-30. (Accessed at: www.futuremedicine.com/doi/pdf/10.2217/14622416.5.1.25)
11. Frueh FW, Goodsaid F, Rudman A, et al. The need for education in pharmacogenomics: a regulatory perspective. The Pharmacogenomics Journal, 2005; 5: 218-220. (Accessed at: www.nature.com/tpj/journal/v5/n4/abs/6500316a.html)
12. Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions. ICH E16 Step 3 draft. (Accessed at: www.emea.europa.eu/pdfs/human/ich/3806360endraft.pdf)
13. Guiding principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement. May 19, 2006. (Accessed at: www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085378.pdf)
14. Guidance for Industry Pharmacogenomic Data Submissions. FDA. March 2005. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079849.pdf)
15. Pharmacogenomic Data Submissions - Companion Guidance. FDA Draft Guidance. August 2007. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079865.pdf)
16. Reflection Paper on Pharmacogenomics in Oncology. EMEA. 2008. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf)
17. Position paper on Terminology in Pharmacogenetics. EMEA. 2002. (Accessed at: www.emea.europa.eu/pdfs/human/press/pp/307001en.pdf)
18. Concept paper on the development of a Guideline on the use of pharmacogenomic methodologies in the pharmacokinetic evaluation of medicinal products. EMEA. 2009. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/6327009en.pdf)
19. Reflection paper on Pharmacogenomic samples, testing and data handling. EMEA. 2007. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)
20. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. Expert Review of Clinical Pharmacology, 2008;1: 505-514. (Accessed at: www.ingentaconnect.com/content/ftd/ecp/2008/00000001/00000004/art00007)
21. Amur S, Frueh FW, Lesko LJ, et al. Integration and use of



biomarkers in drug development, regulation and clinical practice: A US regulatory practice. Biomarkers Med. 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/bmm/2008/00000002/00000003/art00010?crawler=true)

22. Mendrick DL, Brazell C, Mansfield EA, et al. Pharmacogenomics and regulatory decision making: an international perspective. The Pharmacogenomics Journal. 2006; 6(3), 154-157. (Accessed at: www.nature.com/tpj/journal/v6/n3/abs/6500364a.html)

23. Pendergast MK. Regulatory agency consideration of pharmacogenomics. Exp Biol Med (Maywood). 2008; 233:1498-503. (Accessed at: www.ebmonline.org/cgi/content/abstract/233/12/1498)

24. Goodsaid F, Frueh F. Process map proposal for the validation of genomic biomarkers. Pharmacogenomics., 2006; 7(5):773-82 (Accessed at: www.futuremedicine.com/doi/abs/10.2217/14622416.7.5.773)

25. FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. (Accessed at: www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)

26. International Serious Adverse Event Consortium. (Accessed at: www.saeconsortium.org)

27. Predictive Safety Testing Consortium. (Accessed at: www.c-path.org/pstc.cfm)

28. Nuremberg code. (Accessed at: http://ohsr.od.nih.gov/guidelines/nuremberg.html)

29. Declaration of Helsinki. (Accessed at: http://ohsr.od.nih.gov/guidelines/helsinki.html)

30. Belmont report. (Accessed at: http://ohsr.od.nih.gov/guidelines/belmont.html)

31. ICH E6(R1) – Guideline for Good Clinical Practice. June 1996. (Accessed at: www.ich.org/LOB/media/MED/A482.pdf)

32. Barnes M, Heffernan K. The "Future Uses" Dilemma: Secondary Uses of Data and Materials by Researchers for Commercial Research Sponsors. Medical Research Law & Policy, 2004; 3: 440-450.

33. Eriksson S, Helgesson G. Potential harms, anonymization, and the right to withdraw consent to biobank research. Eur J Hum Genet., 2005; 13:1071-1076. (Accessed at: www.nature.com/ejhg/journal/v13/n9/pdf/5201458a.pdf)

34. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2006; 20: 24-36. (Accessed at: http://www3.interscience.wiley.com/cgi-bin/fulltext/118562753/PDFSTART)

35. Article 29 Data Protection Working Party. (Accessed at: www.ec.europa.eu/justice_home/fsj/privacy/workinggroup/index_en.htm)

36. Human Tissue Act 2004 (UK). (Accessed at: www.opsi.gov.uk/acts/acts2004/en/ukpgaen_20040030_en_1)

37. Genetic Information Nondiscrimination Act. (Accessed at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:pub1233.110.pdf)

38. Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials. FDA October 2008 www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0576-gdl.pdf

39. Anderson C, Gomez-Mancilla B, Spear BB, Barnes DM, Cheeseman K, Shaw P, Friedman J, McCarthy A, Brazell C, Ray SC, McHale D, Hashimoto L, Sandbrink R, Watson ML, Salerno RA, on behalf of The Pharmacogenetics Working Group. Elements of Informed Consent for Pharmacogenetic Research; Perspective of the Pharmacogenetics Working Group. Pharmacogenomics Journal 2002;2:284-92. (Accessed at: www.nature.com/tpj/journal/v2/n5/abs/6500131a.html)


www.i-pwg.org

12.4 **Abbreviations**

Abbreviation/Term	Definition
2L	Second Line
AE	Adverse Event
ADA	Anti-Drug Antibodies
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ß-HCG	Beta Human Chorionic Gonadotropin
BSA	Body Surface Area
CBC	Complete Blood Count
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
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOC	Executive Oversight Committee
ePRO	Electronic Patient Reported Outcomes
ERC	Ethics Review Committee
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HCV	Hepatitis C
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
ISS	International Staging System
ITIM	Immunoreceptor Tyrosine-based Switch Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITT	Intent-to-Treat
IV	Intravenous
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
Kg	kilogram
mAb	Monoclonal Antibody

Abbreviation/Term	Definition
mcL	Millimeters
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.
NA or N/A	Not Applicable
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PFS	Progression Free Survival
PGt	Pharmacogenetic
PK	Pharmacokinetic
PK/PD	Pharmacokinetic-Pharmacodynamic
PO	Oral Administration
PR	Partial Response
PSA	Prostate Specific Antigen
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
TIL	Tumor-Infiltrating Lymphocytes
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WHO	World Health Organization

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.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

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

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

12.7 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.

12.8 **Strong Inhibitors of CYP3A4**

Strong inhibitors of CYP3A4 include:

- Clarithromycin
- Indinavir
- Itraconazole
- Ketoconazole
- Nefazodone
- Nelfinavir
- Ritonavir
- Saquinavir

This appendix is not intended to be a comprehensive list of strong CYP3A4 inhibitors, but to provide a practical list of commonly prescribed medications that should be avoided in subjects participating in this study. Additional guidance for investigators on potential strong CYP3A4 inhibitors of clinical significance may be found at http://medicine.iupui.edu/flockhart/.

The web-based resources are intended as guidance for the investigators and not necessarily as a list of prohibited medications.

12.9 QT Prolongation Medications

FDA DRUG PRODUCT LABELS QT PROLONGATION				
Boxed Warnings	**Warnings & Precautions**	**Adverse Reactions**	**Clinical Pharmacology**	**Clinical Studies**
Arsenic Trioxide	Amiodarone	Citalopram	Ambrisentan	Citalopram
Droperidol	Arsenic Trioxide	Clarithromycin	Azilsartan Medoxomil	Dofetilide
Ibutilide	Azithromycin	Dronedarone	Azithromycin	
Itraconazole	Bisacodyl	Droperidol	Citalopram	
Ketoconazole	Ciprofloxacin	Erythromycin	Crizotinib	
Nilotinib	Citalopram	Fesoterodine	Darifenacin	
Vandetanib	Clarithromycin	Fluoxetine	Desvenlafaxine	
	Clozapine	Granisetron	Dexlansoprazole	
	Cyclophosphamide	Ketoconazole	Dolasetron	
	Dasatinib	Mirtazapine	Eltrombopag Olamine	
	Dofetilide	Ondansetron	Etravirine	
	Dolasetron	Oxybutynin	Everolimus	
	Droperidol	Risperidone	Ezogabine	
	Erythromycin	Sertraline	Fexofenadine	
	Ezogabine	Sotalol	Ibutilide	
	Famotidine	Vandetanib	Ixabepilone	
	Fluconazole	Venlafaxine	Ketoconazole	
	Fluoxetine		Levetiracetam	
	Gemifloxacin		Mexiletine	
	Granisetron		Moxifloxacin	
	Haloperidol		Nilotinib	
	Ibutilide		Olopatadine	
	Iloperidone		Plerixafor	
	Itraconazole		Pseudoephedrine	
	Ketoconazole		Quinidine	
	Levofloxacin		Ranolazine	
	Lopinavir/Ritonavir		Telbivudine	
	Methadone		Teriflunomide	
	Nabilone		Tolterodine	
	Nilotinib		Vandetanib	
	Ofloxacin		Voriconazole	
	Ondansetron			
	Paroxetine			
	Pimozide			
	Posaconazole			
	Propafenone			
	Quinine Sulfate			
	Ranolazine			
	Romidepsin			

FDA DRUG PRODUCT LABELS QT PROLONGATION				
Boxed Warnings	**Warnings & Precautions**	**Adverse Reactions**	**Clinical Pharmacology**	**Clinical Studies**
	Sevoflurane			
	Solifenacin			
	Sorafenib			
	Sotalol			
	Sunitinib			
	Tacrolimus			
	Tolterodine			
	Vandetanib			
	Vardenafil			
	Vemurafenib			
	Voriconazole			
	Ziprasidone			

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	

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)
1.0	Trial Summary	Docetaxel was added as a comparator in the control arm.
3.0	Objective(s) & Hypothesis(es)	
4.1.4	Information on Other Trial-Related Therapy	
4.2.2.1	Rationale for the Use of Comparator	
5.2	Trial Treatment(s)	
5.2.1.2.1	Dose Modification for Standard Treatment with Paclitaxel, Docetaxel or Vinflunine	
5.2.1.2.1.3	Specific Dose Modifications for Docetaxel	

Section Number (s)	Section Title(s)	Description of Change (s)
5.2.2.3	Docetaxel	Docetaxel was added as a comparator in the control arm.
5.3	Randomization or Treatment Allocation	
5.5.2	Prohibited Concomitant Medications	
5.6.2	Supportive Care Guidelines for Paclitaxel, Docetaxel and Vinflunine	
5.7.3	Use in Pregnancy	
5.7.4	Use in Nursing Women	
8.1.3	Power and Sample Size	
8.2.2	Hypotheses/Estimation	
8.2.5.1.1	Progression-Free Survival (PFS)	
8.2.6	Multiplicity	
8.2.7	Sample Size and Power Calculation	

Section Number (s)	Section Title(s)	Description of Change (s)
8.2.8	Subgroup Analyses and Effect of Baseline Factors	Docetaxel was added as a comparator in the control arm.
8.2.9.2	Final OS Analysis	
9.1	Investigational Product	
9.2	Packaging and Labeling Information	

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)
2.2	Trial Diagram	A note was added stating the overall proportion of subjects receiving vinflunine in the control arm is capped at approximately 35%.
4.2.2	Rationale for Dose Selection/Regimen	Background information pertaining to Keynote 001 information was added.
3.2	Secondary Objective(s) & Hypothesis(es)	Objective 7 was added to evaluate PFS per RECIST 1.1 from randomization to specific time points (6 months, 12 months) by independent radiologists' review.
5.1.2	Subject Inclusion Criteria	Inclusion criterion 4 was updated to include a note pertaining to primary chemoradition and study eligibility.
5.1.2	Subject Inclusion Criteria	Inclusion criterion 5 was updated to include a Note pertaining to primary chemoradiation for unresectable muscle-invasive bladder cancer and study eligibility.
5.1.2	Subject Inclusion Criteria	The wording for inclusion criterion 6 was updated.

Section Number (s)	Section Title(s)	Description of Change (s)
5.1.2	Subject Inclusion Criteria	Footnote b "Docetaxel will only be a comparator option for subjects with a total bilirubin ≤1x ULN, and an AST ≤ 1.5x ULN if alkaline phosphatase is also >2.5x ULN" was added to Table 1.
5.1.2	Subject Inclusion Criteria	Inclusion criteria 11 and 12 were updated to include the timing for abstinence from last dose for added paclitaxel, docetaxel or vinflunine.
5.1.2	Subject Inclusion Criteria	Inclusion criterion 11 was updated to include a note clarifying that abstinence is an acceptable conceptive method if it is the established and preferred contraception for the subject.
5.1.3	Subject Exclusion	Exclusion criterion 12 was updated to exclude subjects with severe hypersensitivity reaction to docetaxel or other drugs formulated with polysorbate 80.
5.1.3	Subject Exclusion	Exclusion criterion 18 was updated to exclude subjects who have received docetaxel as a prior chemotherapy for urothelial cancer.
5.2	Trial Treatment(s)	Table 2 was updated to include docetaxel. A note was added stating the overall proportion of subjects receiving vinflunine in the control arm is capped at approximately 35%.
5.2.1.2	Dose Modification for Pembrolizumab (MK-3475	Table 3 was updated to clarify the timing for restarting treatment following a Grade 4.
5.3	Randomization or Treatment Allocation	The cap for vinflunine was updated to approximately 35% of the control arm.
5.5.1	Acceptable Concomitant Medications	The timing for recording concomitant medications was updated to 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment
5.6.2	Supportive Care Guidelines for Paclitaxel, Docetaxel and Vinflunine	This section was updated to include supportive care guidelines for docetaxel

Section Number (s)	Section Title(s)	Description of Change (s)
5.7.2	Contraception	This section was update to include the timing for using birth for paclitaxel, docetaxel and vinflunine.
5.7.2	Contraception	A note clarifying that abstinence is an acceptable conceptive method if it is the established and preferred contraception for the subject was added.
5.8.5	Survival Follow-up	This section was updated to clarify timing for Survival Follow-up.
5.10	Beginning and End of the Trial	This section was updated to clarify the timing for the beginning and ending of the trial.
6.1	Initial Treatment Phase	The trial flowchart was updated to include the separation of the screening visits (Day -42 – Day -1, Day -28- Day -1 and Day -10- Day -1).
6.1	Initial Treatment Phase	The timing for the collection of correlative samples was updated.
6.1	Initial Treatment Phase	The timing for the collection of Thyroid Function Tests was updated to every 6 weeks.
6.1	Initial Treatment Phase	Footnote letter “j was removed from the following assessments in the trial flowchart: Urinalysis, T3, FT4 and TSH, EuroQol EQ-5D, EORTC QLQ-C30 and Health Economic Assessment (HEA).
6.1	Initial Treatment Phase	Footnote letter “y” was removed from the following assessments in the trial flowchart: EuroQol EQ-5D, EORTC QLQ-C30 and Health Economic Assessment (HEA).
6.1	Initial Treatment Phase	Footnote letter “u” was updated to “Whole blood sample for correlative studies should be collected prior to Cycle 1, at Cycle 3 and again at treatment discontinuation. Blood for serum and blood for plasma to be collected only prior to Cycle 1 Day 1. See Procedures Manual.
6.1	Initial Treatment Phase	Visit windows for the Post-treatment visits were added as follows: Safety Follow-up: 30 days post discon ± 3 days, Follow Up Visits Every 6 weeks post discon ±7 days and Survival Follow-up Every 12 weeks ±7 days.
6.1	Initial Treatment Phase	The timing for the Correlative Samples was updated. Footnote letter u was updated to reflect the timing.

Section Number (s)	Section Title(s)	Description of Change (s)
6.1	Initial Treatment Phase	Footnote letter b was updated to "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 central imaging vendor, (3) death, or (4) the end of the study, whichever occurs first".
6.1	Initial Treatment Phase	Height was added within the trial flowchart as an assessment to obtain at Visit 1 only. This information is also reflected in footnote letter k.
6.1	Initial Treatment Phase	Footnote z was added to incorporate bone scans as well as the timing of the bone scans.
6.1	Initial Treatment Phase	Footnote aa was updated to clarify the adequacy of the biopsy specimen for biomarker analysis
6.2	Second Course Phase (Retreatment) for Pembrolizumab (MK-3475) Arm Only	Height was added within the trial flowchart as an assessment to obtain at Visit 1 only. This information is also reflected in footnote letter k.
6.2	Second Course Phase (Retreatment) for Pembrolizumab (MK-3475) Arm Only	Footnote letter j was removed from T3, FT4 and TSH.
7.1.2.6.	Tumor Imaging and Assessment of Disease	Clarification on the use of CT scan vs. MRI was provided. CT scan is the preferred modality for this study and should be used for routine imaging whenever possible, with MRI being reserved for situations in which a contraindication to CT scanning exists.
7.1.2.6.1	Initial Tumor Imaging	The timing for the initial tumor imaging was updated to 28 days prior to the first dose of trial treatment.
7.1.2.6.1	Initial Tumor Imaging	The inclusion of bone scan assessments were added.
7.1.2.6.3	Bone Scans	Additional information pertaining to the use of bone scans was added.

Section Number (s)	Section Title(s)	Description of Change (s)
7.1.2.7	Tumor Tissue Collection and Correlative Blood Sampling	The timing for the collection of Correlative Samples was updated.
7.1.5.1	Screening	The timing for the screening procedures to be completed was updated to 28 days prior to the first dose trial treatment.
7.1.5.1	Screening	The Day -42- Day -1 screening procedures were added.
7.1.5.2.1	Second Course Phase (Retreatment Period)	A note stating that abstinence is acceptable if this is the established and preferred contraception for the subject was added.
7.1.5.3.1	Safety Follow-up Visit	The section was updated to include a ±3 day visit window.
7.1.5.3.2	Follow-up Visits	The section was updated to include that After 1 year, the imaging time point will occur every 12 weeks (±7 days).
7.1.5.3.3	Survival Follow-up	The timing for survival follow-up was clarified.
7.2	Assessing and Recording Adverse Events	Table 11 “Evaluating Adverse Events” was updated to reflect assessing and recording adverse events for Oncology studies.
8.2.9.1	PFS Analysis and Interim OS Analysis	This section was updated to include the following “Primary analysis and at least 130 PFS events for sensitivity analysis 1 have been observed between the MK arm and the paclitaxel indicate that the first PFS analysis will take place when enrollment is complete, approximately 160 PFS events for primary analysis and at least 130 PFS events for sensitivity analysis 1 have been observed.
11.0	List of References	Reference 66 was added.

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
3.1 3.2 4.2.1 4.2.3.1.1	Primary Objective (s) and Hypothesis (es) Secondary Objective(s) & Hypothesis(es) Rationale for the Subject Population Primary (Endpoints)	PFS and OS in patients with PD-L1 positive and PD-L1 strongly positive tumors have been elevated to co-primary objectives.	Emerging evidence suggests that PD-L1 status may correlate to outcomes of patients with urothelial cancer treated with pembrolizumab and other agents in the PD-1/PD-L1 axis.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0	Trial Summary	The duration of the trial was updated	The duration of the trial was updated to reflect the Sponsor's estimate of the time it will take from the time the first subject signs the informed consent until the last subject's last visit.
3.2; 7.1.2.6.4 8.1.1 8.2.3.1 8.2.5.1.5 8.2.6	Secondary Objective(s) & Hypothesis(es) Assessment of Disease Assessment of Disease Efficacy Analyses Efficacy Endpoints Exploratory Analyses Multiplicity	Modified RECIST was updated to exclude the 1.1 as a reference.	Modified RECIST was updated to clarify that it is a. set of modifications developed by the Sponsor and to distinguish from the RECIST 1.1 published paper

2.2; 5.12; 5.2;	Trial Diagram Subject Inclusion Criteria Trial Treatments	The hepatic test parameter (ALT) was added for Docetaxel.	This change was made based on a request from an agency.
4.1.3	Ongoing Clinical Trials	KEYNOTE 012 study information was updated.	Updated information for KEYNOTE 012 was available and implemented into this amendment.
4.1.4	Information on Other Trial-Related Therapy	The number of agents for the standard treatment options in the comparator arm of this trial was updated from two to three.	The number of agents for the standard treatment options in the comparator arm was rectified in this amendment.
4.2.2	Rationale for Dose Selection/ Regimen/Modification	CCI [redacted]	CCI [redacted]

4.2.3.1.1; 6.1; 7.1.5.1 7.1.2.6.2; 7.1.2.6.3	Primary Initial Treatment Phase Screening Tumor Imaging During Trial Bone Scans	The first on-study radiographic imaging assessment was updated to be performed at 9 weeks (±7 days) after randomization and then every 6 weeks (±7 days) thereafter or more frequently if clinically indicated.	This update was made to take into account the subjects who are randomized and receive the first dose of study treatment up to 3 days after randomization.
4.2.3.1.3.1	Patient Reported Outcomes	Additional information pertaining to the timing as to when the EORTC QLQ-C30 is to be assessed was added.	The time point information was added to be consistent with the information provided for the two other Patient Reported Outcomes assessments.
4.2.3.1.3.1	Patient Reported Outcomes	The three levels listed for the five health state dimensions in the eEuroQoL-5D were corrected. Each dimension as three levels: no problems, some problems, extreme problems.	The description of the three levels listed for the five health state dimensions in the eEuroQoL-5D was not accurate and has been corrected.
4.2.3.3	Planned Exploratory Biomarker Research	Additional information pertaining to Gene analysis research was added.	To provide additional information as to how Gene Analyses contributes to research for this study.
5.1.2	Subject Inclusion Criteria	The first note pertaining to Inclusion Criterion #4 was updated.	This updated was made to clarify the lines of therapy for primary chemoradition in regards to surgical candiates.

5.1.2	Subject Inclusion Criteria	“e.g” was added prior to cisplatin , carboplatin”	"e.g" was added adjacent to cisplatin and carboplatin, as the aforementioned drugs, are examples, not the sole representatives, of platinum compounds - a class of drugs that also includes oxaliplatin, nadeplatin and others
5.1.2	Subject Inclusion Criteria	The second note pertaining to Inclusion Criterion #4 was updated.	This note was updated to clarify that subjects with locally advanced unresectable disease who subsequently become eligible for surgery after platinum-containing therapy (and remain eligible at the time of study enrollment) should not be included in the study.
5.1.2	Subject Inclusion Criteria	Inclusion Criterion #5 was updated to include Metastatic as the type of urotherial cancer for the inclusion criteria.	Metastatic was added to clarify the type of urotherial cancer required for inclusion in the study.
5.1.2	Subject Inclusion Criteria	PTT was added to Table 1 Adequate Organ Function Laboratory Values	This update was made to allow for PTT to be collected if aPTT is not measured.
5.1.2 5.7.2 7.1.5.2.1	Subject Inclusion Criteria Contraception Second Course Phase (Retreatment Period)	Clarification of abstinence as a method of contraception was added.	This update was made to clarify abstinence as a method of contraception.

5.1.3; 5.5.2; 12.8	Subject Exclusion Criteria Prohibited Concomitant Medications Strong Inhibitors and Inducers of CYP3A4	The exclusion of strong CYP3A4 inducers was added.	The update was made to prohibit the use of CYP3A4 inducers.
5.2; 9.1	Trial Treatments Investigational Product	The requirement for trial sites to record locally sourced product information at the site was updated.	The update was made to permit trial sites to record locally sourced product information according to local agency requirements.
5.2.1.2	Dose Modification for Pembrolizumab (MK-3475)	The Dose Modification for Pembrolizumab (MK-3475) was updated.	The change was made to align with current Pembrolizumab (MK-3475) program standards.
5.2.3	Trial Blinding/Masking	The language pertaining to the blinding of open label trial was updated.	The change was made to align with the new standard language on the blinding of open label trials.
5.5.2	Prohibited Concomitant Medications	The requirements for use of Radiation therapy was updated.	The requirement for use of radiation to only non-target lesions was updated to allow symptom control to any lesion.

5.5.2	Prohibited Concomitant Medications	Systemic glucocorticoids was added.	Clarification was made on the type of glucocorticoids (Systemic) that is permitted to be utilized for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology.
5.5.2	Prohibited Concomitant Medications	The permission to use prophylactic corticosteroids, inhaled steroids or local injection of corticosteroids was added.	This update was made to allow for the use of the steroids specified.
5.6.1	Supportive Care Guidelines for Pembrolizumab (MK-3475)	The Supportive Care Guidelines for Pembrolizumab (MK-3475) was updated.	The change was made to align with current Pembrolizumab (MK-3475) program standards.
5.7.2	Contraception	This section was updated to include cryopreservation of sperm details for male subjects randomized to the paclitaxel, docetaxel or vinflunine treatment arm.	The inclusion of the guidance for cryopreservation was added to correspond to the approved labels for paclitaxel, docetaxel and vinflunine regarding the possibility of infertility.
6.1; 7.1.5.1	Initial Treatment Phase Screening	The timing for obtaining Informed Consent for Future Biomedical Research was updated.	The timing was updated to correspond with the timing of obtaining Informed Consent.

6.1	Initial Treatment Phase	The timing for when the Subject Identification Card will be provided was updated.	Subjects are provided with Subject Identification Card at the time informed consent is obtained. This update was made to be consistent with section 7.1.1.3 Subject Identification Card of the protocol.
6.1; 7.1.3.3	Initial Treatment Phase Future Biomedical Research	The assessment for Blood for Future Biomedical Research (FBR) use was updated.	The Blood for Future Biomedical Research was updated to clarify the use for FBR samples.
6.1	Initial Treatment Phase	The timing for the Safety Follow-up visit was updated.	The timing for when the Safety Follow-Up visit should occur was further clarified.
6.1	Initial Treatment Phase	Footnote letter b was updated to reflect that the investigator/site radiologist will assess disease progression.	The footnote was updated to correspond with the assessment of disease progression throughout the protocol.
6.1; 7.1.2.6; 7.1.2.6.3	Initial Treatment Phase; Tumor Imaging and Assessment of Disease; Bone Scans	Instructions were added that plain X-ray evaluation should be obtained for symptomatic sites with negative bone scan evaluations.	These instructions were added based on agency feedback that was received.
6.1; 7.1.2.8	Initial Treatment Phase Patient Reported Outcomes (PROs)	The timing of ePRO questionnaires was updated.	This timing was updated to clarify the timing to which the questionnaires are to be administered.

6.1	Initial Treatment Phase	Footnote "bb" was added to the EuroQol EQ-5D, EORTC QLQ-C30 and Health Economic Assessment (HEA) assessments at the Safety Follow-Up Time point.	Footnote "bb" was added to be consistent with the text within the footnote.
6.2	Second Course Phase (Retreatment) for Pembrolizumab (MK-3475) Arm Only	The time point for Tumor Imaging was updated	The time point for Tumor Imaging was updated to reflect the 6 week (42 ±7 days) from the first dose of trial treatment imaging schedule.
7.1.2.1	Adverse Event (AE) Monitoring	The reference to the NCI CTCAE Version 4.0 was updated.	The reference to the NCI CTCAE Version 4.0 was corrected.
7.1.2.6	Tumor Imaging and Assessment of Disease	The requirement for sending unscheduled images related to disease progression to the central vendor was added.	This requirement was included to ensure all images that support the assessment of disease progression (schedule and unscheduled) are provided to the central imaging vendor for complete evaluations.
7.1.2.6.1	Initial Tumor Imaging	Information pertaining to brain imaging intervals was added for subjects who enroll into the study with stable brain metastasis.	This update was made to clarify the imaging interval for subjects who enter the study with stable brain metastasis.

7.1.3.1	Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)	Footnote letter e was added for WBCs.	A footnote was added to allow sites to provide WBC results (Absolute or %) per their institutional standard.
7.1.3.1	Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)	The requirement for bicarbonate was updated to permit CO2 or Bicarbonate to be assessed.	This requirement was updated to allow sites to assess Carbon Dioxide per their institutional standard.
7.1.3.1	Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)	GFR was added as an acceptable test to utilize in place of creatinine or CrCl).	This update was made to allow for GRF to be utilized in place of creatinine or CrCl).
7.1.3.1	Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)	Footnote letter d was added.	Footnote d was added to give the option to assess Urea in place of Blood Urea Nitrogen.
7.1.3.1	Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)	The requirement for all test results to be reviewed by an investigator or qualified designee and found to be acceptable prior to each dose of trial treatment was updated to exclude thyroid function tests.	The turnaround time for the results of thyroid tests is longer in comparison to other required laboratory tests. To avoid dose delays, the requirement to review the results of the of thyroid tests prior to dosing has been omitted.
7.1.3.2	Pharmacokinetic/Pharmacodynamic Evaluations	PK and ADA samples are required for all subjects randomized to pembrolizumab (MK-3475).	Per agency feedback, all subjects randomized to pembrolizumab (MK-3475) will have PK and ADA samples obtained.

7.1.5.1	Screening	Informed Consent Form for Future Biomedical Research, an archival FFPE tumor sample or Newly Obtained Tissue Collection for biomarker analysis and initial Tumor Imaging were added.	This information was added to reflect the assessments in Section 6.0- Trial Flow Chart.
7.1.5.3.2	Follow-up Visits	Text was updated to reflect that the investigator/site radiologist will assess disease progression.	Text was corrected to clarify that disease progression during the following-up period is to be assessed by the Investigator/site radiologist.
7.2 7.2.3.1 7.2.3.2 7.2.2	Assessing and Recording Adverse Events Serious Adverse Events Events of Clinical Interest Reporting of Pregnancy and Lactation to the Sponsor	Updates were made in regards to the timing of reporting reportable events.	The change was made to align with current Pembrolizumab (MK-3475) program standards.
7.2; 7.2.3.3	Assessing and Recording Adverse Events Protocol-Specific Exceptions to Serious Adverse Event Reporting	Updates to disease progression reporting were made to clarify the reporting of events associated with disease progression.	The change was made to align with current Pembrolizumab (MK-3475) program standards.
8.0	Statistical Analysis Plan	Text was updated with the new protocol SAP template language. Refer to the supplemental SAP (sSAP).	The change was made to align with current protocol SAP standard.

8.1	Statistical Analysis Plan Summary	Texts were updated throughout this section to reflect the incorporation of primary hypotheses on PD-L1 positive and strongly positive subjects.	These changes were made to align with the primary objectives on PD-L1 in this amendment.
8.1.3	Power and Sample Size	Removed 24 months of follow-up as the condition for the timing of final OS analysis.	This condition was removed per agency feedback.
8.1.3	Power and Sample Size	Power and sample size considerations were added for PD-L1 positive and PD-L1 strongly positive subjects; conditions for first PFS analysis were updated. Some repetitive texts were removed.	This change was made to align with the primary objectives on PD-L1 in this amendment. Some repetive texts were removed because details were given in later sections.
8.1.4	Interim Analysis	Table 14 was deleted from this section.	The table was deleted to avoid repetitive decryptions to later section (Section 8.2.9).
8.2.1	Responsibility for Analyses/In-House Blinding	The language on the blinding of open label trial was updated. The term “executive committee” was further specified as “executive oversight committee”.	The change was made to align with the new template language on the blinding of the open label trial. The term was updated to be consistent with the study DMC charter.

8.2.5.1.1	Progression-Free Survival (PFS)	Table 15 (now Table 12) of censoring rules is updated with more details specified. One additional sensitivity analysis with respect to special clinical scenarios was added.	These updates were based on FDA feedback on the review of protocol and sSAP.
8.2.5.2	Statistical Methods for Safety Analysis	Safety analysis methods are updated.	These updates were based on the new program-wise standard.
8.2.6	Multiplicity	Multiplicity strategy was updated with respect to the addition of new primary hypotheses for PD-L1 positive and strongly positive subjects. ORR in all subjects is included in the multiplicity control.	This change was made to align with the primary objectives on PD-L1 in this amendment.
8.2.6	Multiplicity	The strategy of multiplicity control on secondary hypotheses was further specified and updated. A new reference was added.	These updates were based on agency feedback on the review of protocol and sSAP.
8.2.7	Power and Sample Size	Power and sample size considerations were updated with respect to the addition of PD-L1 positive and PD-L1 strongly positive subjects; conditions for the first PFS analysis were updated.	These changes were made to align with the primary objectives on PD-L1 in this amendment.

8.2.9.1	PFS Analysis and Interim OS Analysis	Table 18 (now Table 15) content, format and footnote were updated. New table 16 and 17 were added.	This change was made to align with the primary objectives on PD-L1 in this amendment.
10.4	Compliance with Trial Registration and Results Posting Requirements	The Compliance with Trial Registration and Results Posting Requirements was updated.	This update was made to incorporate trial registration and results posting obligations to the EMA
11.0	List of References	Reference 67 and Reference 68 were added.	These references were added to support data provided in Section 8.1.1 Efficacy Analyses and Section 8.2.6-Multiplicity of the protocol.
12.2	Collection and Management of Specimens for Future Biomedical Research	The specimens collected for Future Biomedical Research was updated.	Additional samples were added for Future Biomedical Research.

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
8.0	Statistical Analysis Plan	The second interim analysis and/or the final analysis may be postponed for up to 4 additional months to accrue additional OS events in the PD-L1 positive subjects after the planned number of OS events in all subjects is achieved.	Because most of the alpha for testing OS is allocated to the PD-L1 positive biomarker subgroup, conduct of the interim and final analyses must consider the number of events in the PD-L1 positive subgroup.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.3	Trial Blinding/Masking	Minor wording edits	To improve readability and clarity.
6.1 6.2 7.1.5.3.3	Initial Treatment Phase Second Course Phase (Retreatment) for Pembrolizumab (MK-3475) Arm Only Survival Follow-up	The timing for additional survival status data was added.	To allow additional survival status data to be collected at time points outside of the 12 week time point.
8.2.1	Responsibility for analyses / In-House Blinding	Minor wording edits	To improve readability and clarity.

8.2.5.1.1	Progression-Free Survival (PFS)	Further clarified the sensitivity analysis rules for PFS analysis	To incorporate updated program template language.
8.2.5.1.5	Exploratory Analyses	Removed the description of the statistical methods on exploratory analysis.	To incorporate updated program template. Methodology details of exploratory analyses are included in the supplemental SAP (sSAP).

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

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

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

TITLE:

A Phase III Randomized Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel, Docetaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer

IND NUMBER: 122753
EudraCT NUMBER: 2014-002009-40

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
3.1	Primary Objective(s) & Hypothesis(es)	PD-L1 positive and strongly positive definitions have been determined. Alpha allocation among the primary hypotheses for interim and final analyses has been revised.	Clarified that the basis for PD-L1 positive and strongly positive categories using CPS cutpoints has been determined outside this study (i.e., from protocols Keynote 012, Keynote 052, and epidemiologic studies).
4.2.1	Rationale for the Trial and Selected Subject Population		
4.2.3.1.1	Primary		
8.1.3	Power and Sample Size		
8.1.4	Interim Analysis		
8.2.6	Multiplicity		
8.2.7	Sample Size and Power Calculation		
8.2.9	Interim Analyses		
8.2.9.1	PFS and Interim OS Analyses		
8.2.9.2	Final OS Analysis		

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.5.3.3	Survival Follow-up	External data monitoring committee (eDMC)	Defined in Section 7.1.5.3.3
12.4	List of Abbreviations	Added HSD (Hwang-Shih-DeCani), external data monitoring committee (eDMC), and FWER (family-wise type I error rate)	Defined in Section 8.2.6

1.0 TRIAL SUMMARY

Abbreviated Title	Ph 3 trial of Pembrolizumab (MK-3475) vs paclitaxel, docetaxel or vinflunine in recurrent/progressive metastatic urothelial cancer
Trial Phase	Phase III
Clinical Indication	Metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy
Trial Type	Interventional
Type of control	Active control without placebo
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	A) Pembrolizumab (MK-3475) 200 mg every 3 weeks B) Investigator's choice of: -Paclitaxel 175 mg/m^2 every 3 weeks; -Docetaxel 75 mg/m^2 every 3 weeks OR -Vinflunine 320 mg/m^2 every 3 weeks
Number of trial subjects	Approximately 470 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 30 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 42 days, each subject will receive treatment based on the arm to which they have been randomized. Treatment on trial 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 withdrawals consent, pregnancy of the subject, noncompliance with trial treatment or procedures requirements, subject receives 24 months of trial treatment (pembrolizumab (MK-3475) arm only), or administrative reasons. Subjects on the pembrolizumab (MK-3475) arm who attain a complete response may consider stopping trial treatment if they meet criteria for holding therapy. Subjects receiving pembrolizumab (MK-3475) 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 they meet 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 (serious adverse events and events of clinical interest will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up every 6 weeks for disease status until disease progression is confirmed by the investigator/site radiologist, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival every 12 weeks until death, withdrawal of consent, or the end of the trial.

Randomization Ratio	1:1

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

2.0 TRIAL DESIGN

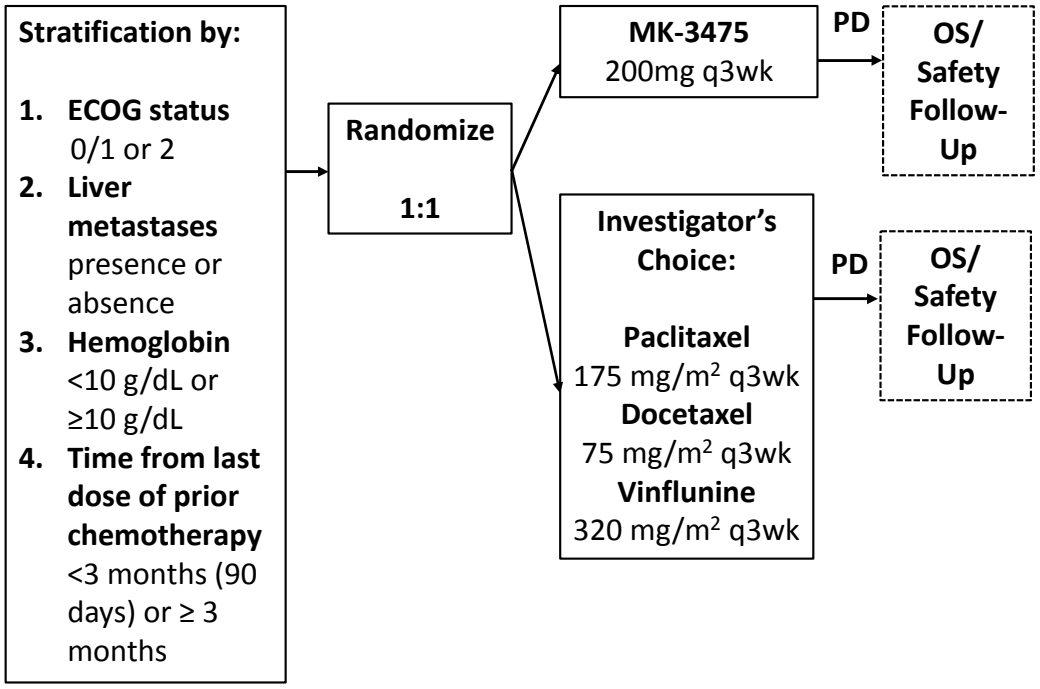
2.1 Trial Design

This is a randomized, active-controlled, multi-site, open-label trial of pembrolizumab (MK-3475) in subjects with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy, to be conducted in conformance with Good Clinical Practices.

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.



Note: The overall proportion of subjects receiving vinflunine in the control arm is capped at approximately 35%. Vinflunine will only be a comparator option in countries where vinflunine is approved for the treatment of metastatic urothelial cancer. Docetaxel will only be a comparator option for subjects with a total bilirubin ≤1x ULN, and an AST and/or ALT ≤ 1.5x ULN if alkaline phosphatase is also >2.5x ULN.

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To evaluate progression-free survival (PFS) per RECIST 1.1 by blinded independent radiologists' review of **all subjects** with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

Hypotheses (H1): Pembrolizumab (MK-3475) prolongs PFS per RECIST 1.1 by blinded independent radiologists' review in **all subjects** with recurrent/progressive metastatic urothelial cancer compared to paclitaxel, docetaxel or vinflunine.

(2) **Objective:** To evaluate the overall survival (OS) of **all subjects** with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy (recurrent/progressive metastatic urothelial cancer), when treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

Hypothesis (H2): Pembrolizumab (MK-3475) prolongs OS in **all subjects** with recurrent/progressive metastatic urothelial cancer compared to paclitaxel, docetaxel or vinflunine.

(3) **Objective:** To evaluate the PFS per RECIST 1.1 by blinded independent radiologists' review of subjects with platinum-refractory recurrent/progressive metastatic **PD-L1 positive** urothelial cancer treated with pembrolizumab compared to paclitaxel, docetaxel or vinflunine.

Hypotheses (H3): Pembrolizumab prolongs PFS per RECIST 1.1 by blinded independent radiologists' review in subjects with platinum-refractory recurrent/progressive metastatic **PD-L1 positive** urothelial cancer compared to paclitaxel, docetaxel or vinflunine.

(4) **Objective:** To evaluate the OS of subjects with platinum-refractory metastatic or locally advanced/unresectable **PD-L1 positive** urothelial cancer, when treated with pembrolizumab compared to paclitaxel, docetaxel or vinflunine.

Hypothesis (H4): Pembrolizumab prolongs OS in subjects with platinum-refractory recurrent/progressive metastatic **PD-L1 positive** urothelial cancer compared to paclitaxel, docetaxel or vinflunine.

(5) **Objective:** To evaluate the PFS per RECIST 1.1 by blinded independent radiologists' review of subjects with platinum-refractory recurrent/progressive metastatic **PD-L1 strongly positive** urothelial cancer treated with pembrolizumab compared to paclitaxel, docetaxel or vinflunine.

Hypotheses (H5): Pembrolizumab prolongs PFS per RECIST 1.1 by blinded independent radiologists' review in subjects with platinum-refractory recurrent/progressive metastatic **PD-L1 strongly positive** urothelial cancer compared to paclitaxel, docetaxel or vinflunine.

(6) **Objective:** To evaluate the OS of subjects with platinum-refractory metastatic or locally advanced/unresectable **PD-L1 strongly positive** urothelial cancer, when treated with pembrolizumab compared to paclitaxel, docetaxel or vinflunine.

Hypothesis (H6): Pembrolizumab prolongs OS in subjects with platinum-refractory recurrent/progressive metastatic **PD-L1 strongly positive** urothelial cancer compared to paclitaxel, docetaxel or vinflunine.

The study is considered to have met its primary objective if the pembrolizumab arm is superior to paclitaxel, docetaxel or vinflunine at an interim or final analysis in any of the following:

H1: PFS in all subjects (regardless of PD-L1 expression)

H2: OS in all subjects (regardless of PD-L1 expression)

H3: PFS in subjects with PD-L1 Positive expression

H4: OS in subjects with PD-L1 Positive expression

H5: PFS in subjects with PD-L1 Strongly Positive expression

H6: OS in subjects with PD-L1 Strongly Positive expression

PD-L1 positive is defined as combined proportion score (CPS) of ≥1%. The specific cutoff of **PD-L1 strongly positive** has been independently determined by data outside of the current study to be CPS ≧ 10%.

Data from KN052 demonstrated a clinically meaningful response rate and durable responses in all subjects, including those who were considered to be PD-L1 negative (CPS <1%). Response rates were also meaningfully increased when a CPS cutpoint of 10% was applied. In contrast, the magnitude of enrichment using a 1% CPS cutpoint in this population was not clinically meaningful. Based on these observations from KN052, a single CPS cutpoint of 10% has been identified for urothelial cancer. Therefore, in the second interim analysis (IA2) and final analysis, only primary hypotheses of PD-L strongly positive subjects and all subjects will be included in the multiplicity controlled statistical testing.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To evaluate the **safety and tolerability** profile of pembrolizumab (MK-3475) in subjects with recurrent/progressive metastatic urothelial cancer.

(2) **Objective:** To evaluate the objective response rate **(ORR) per RECIST 1.1**. by independent radiologists' review in **PD-L1 strongly positive, PD-L1 positive and all subjects** with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

Hypothesis: Pembrolizumab (MK-3475) improves **ORR per RECIST 1.1**. by independent radiologists' review in **PD-L1 strongly positive, PD-L1 positive and all subjects** with recurrent/progressive metastatic urothelial cancer compared to paclitaxel, docetaxel or vinflunine.

(3) **Objective**: To evaluate **PFS per modified RECIST** by independent radiologists' review of **PD-L1 strongly positive, PD-L1 positive, and all subjects** with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

Hypothesis: pembrolizumab (MK-3475) prolongs **PFS per modified RECIST** by blinded central radiology review in **PD-L1 strongly positive, PD-L1 positive and all** subjects with recurrent/progressive metastatic urothelial cancer compared to paclitaxel, docetaxel or vinflunine.

(4) **Objective:** To evaluate the objective response rate **(ORR) per modified RECIST** by independent radiologists' review in **PD-L1 strongly positive, PD-L1 positive and all subjects** with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

Hypothesis: Pembrolizumab (MK-3475) improves **ORR per modified RECIST** by independent radiologists' review in **PD-L1 strongly positive, PD-L1 positive and all subjects** with recurrent/progressive metastatic urothelial cancer compared to paclitaxel, docetaxel or vinflunine.

(5) **Objective:** To evaluate **response duration per RECIST 1.1** by independent radiologists' review in **PD-L1 strongly positive, PD-L1 positive and all subjects** with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

(6) **Objective:** To evaluate **PFS** per RECIST 1.1 from randomization to specific time points (**6 months, 12 months**) by independent radiologists' review in **PD-L1 strongly positive, PD-L1 positive and all subjects** with recurrent/progressive metastatic urothelial cancer treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

3.3 Exploratory Objectives

(1) **Objective:** To evaluate changes in health-related quality-of-life assessments from baseline in subjects with recurrent/progressive metastatic urothelial cancer using the EORTC QLQ-C30.

(2) **Objective:** To characterize utilities in previously-treated subjects with recurrent/progressive metastatic urothelial cancer using the EuroQol EQ-5D.

(3) **Objective:** To investigate the relationship between PD-L1 expression and response to pembrolizumab (MK-3475) treatment utilizing newly obtained or archival FFPE tumor tissue.

(4) **Objective:** To investigate the relationship between pembrolizumab (MK-3475) treatment and biomarkers predicting response (e.g., immunohistochemistry, proteomic signatures, genetic variation, and gene expression signatures) utilizing newly obtained or archival FFPE tumor tissue and blood.

(5) **Objective**: To evaluate progression free survival as assessed by RECIST 1.1 by investigator review in the next line of therapy (PFS2) in subjects treated with pembrolizumab (MK-3475) compared to paclitaxel, docetaxel or vinflunine.

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

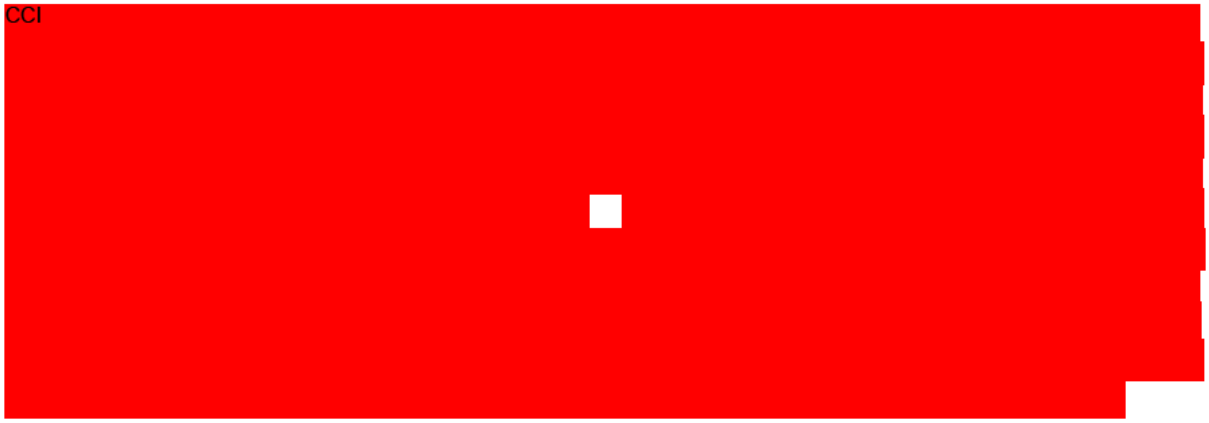
Pembrolizumab (MK-3475) (previously known as SCH 9000475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

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 CD3ζ, PKCθ 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



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 including bladder cancer, and hematologic malignancies. For study details please refer to the Investigator's Brochure.

The safety, tolerability, and antitumor activity of pembrolizumab were assessed in patients with recurrent or metastatic urothelial cancer in the KEYNOTE-012 study. Archival or newly obtained tumor samples from pts with advanced carcinoma of the renal pelvis, ureter, bladder, or urethra were screened for PD-L1 expression using a prototype immunohistochemistry assay. PD-L1 expression in stroma or ≥1% of tumor cells was required for study entry. Pts received pembrolizumab 10 mg/kg every 2 wk until complete response, progression, or unacceptable toxicity. Pts deriving benefit could remain on pembrolizumab beyond initial progression. Response was assessed every 8 wk per RECIST v1.1 by independent central review (primary efficacy end point).

A total of 33 patients were enrolled, including 30 with transitional cell histology and 3 with nontransitional cell or mixed histology. Median age was 70 y (range 44-85), 70% had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 1, 52% received ≥2 prior therapies for advanced disease, and 21% had liver metastases. A total of 22 patients (67%) received ≥3 pembrolizumab doses. A total of 64% of patients reported ≥1 drug-related AE, most commonly fatigue (n = 6), peripheral edema (n = 4), and nausea (n = 3); 5 patients (15%) reported grade 3-4 drug-related AEs, with only rash seen in >1 patient (n = 2). 29 patients received ≥1 dose of pembrolizumab and had a baseline scan with measurable disease and were evaluable for response. Objective response rate (ORR) by central review was 27.6% (95% CI 12.7%-47.2%), with 3 (11%) complete responses. Response duration is 16-40+ wk (median not reached), with 6 of 7 responses ongoing.

4.1.4 Information on Other Trial-Related Therapy

The proposed choice of single agent paclitaxel, docetaxel or vinflunine for the control arm is based on common usage, in the second-line setting, input from key opinion leaders, and prior precedence in 2nd line (2L) clinical trials. Therefore, these three agents will be used as standard treatment options in the comparator arm of this trial. This allows the investigator to select either 1 of the 3 options for subjects randomized to the standard therapy arm. See Section 4.2.2.1 for additional details.

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.

Subjects with metastatic urothelial cancer that has recurred or progressed following platinum-based chemotherapy present a challenge. Although a variety of chemotherapeutic agents are used in this setting, the prognosis of subjects with recurrent/progressive urothelial cancer is generally poor despite these therapies. The median survival in most series is 7 to 9 months, and the median PFS is 3 to 5 months, with limited treatment options and substantial morbidity. Single agent or combination therapy using conventional cytotoxic chemotherapy, combined with best supportive care, is palliative for subjects with recurrent/ progressive urothelial cancer. The most widely used agents include taxanes (paclitaxel, docetaxel), pemetrexed, and, in the EU, vinflunine. There are no approved therapies for recurrent/progressive urothelial cancer in the US, while vinflunine is approved in the EU for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

After failure of first-line platinum-containing chemotherapy, objective responses to second-line cytotoxic chemotherapy are uncommon, particularly when contemporary response criteria are applied. Objective response rates of 5% to 28% have been reported with agents such as paclitaxel, docetaxel, pemetrexed and ifosfamide [29, 30, 31, 32], but few randomized, controlled studies have been conducted in the second-line setting. In single-arm studies, PFS and OS have been reported as 4 months and 9 months, respectively, with docetaxel; and 2-3 months and 7 months, respectively with paclitaxel [29, 30, 33]. In a Phase III trial, 370 previously treated patients were randomly assigned to either vinflunine or best supportive care [34]. Compared to best supportive care, treatment with vinflunine resulted in a 9% objective response rate and a trend towards increased overall survival that did not reach statistical significance in the ITT population (6.9 versus 4.6 months, hazard ratio 0.88, 95% CI 0.69-1.12).

Given the poor outcome of subsequent chemotherapy in bladder cancer patients after failure of a platinum-based regimen, the study will enroll all comers, independent of PD-L1 status. There is, however, emerging evidence of the correlation of PD-L1 expression and clinical outcomes of patients with epithelial malignancies (bladder cancer included) treated with PD-1/PD-L1 agents. Therefore, the study population will be analyzed as a whole, and also taking into account PD-L1 positive and PD-L1 strongly positive status.

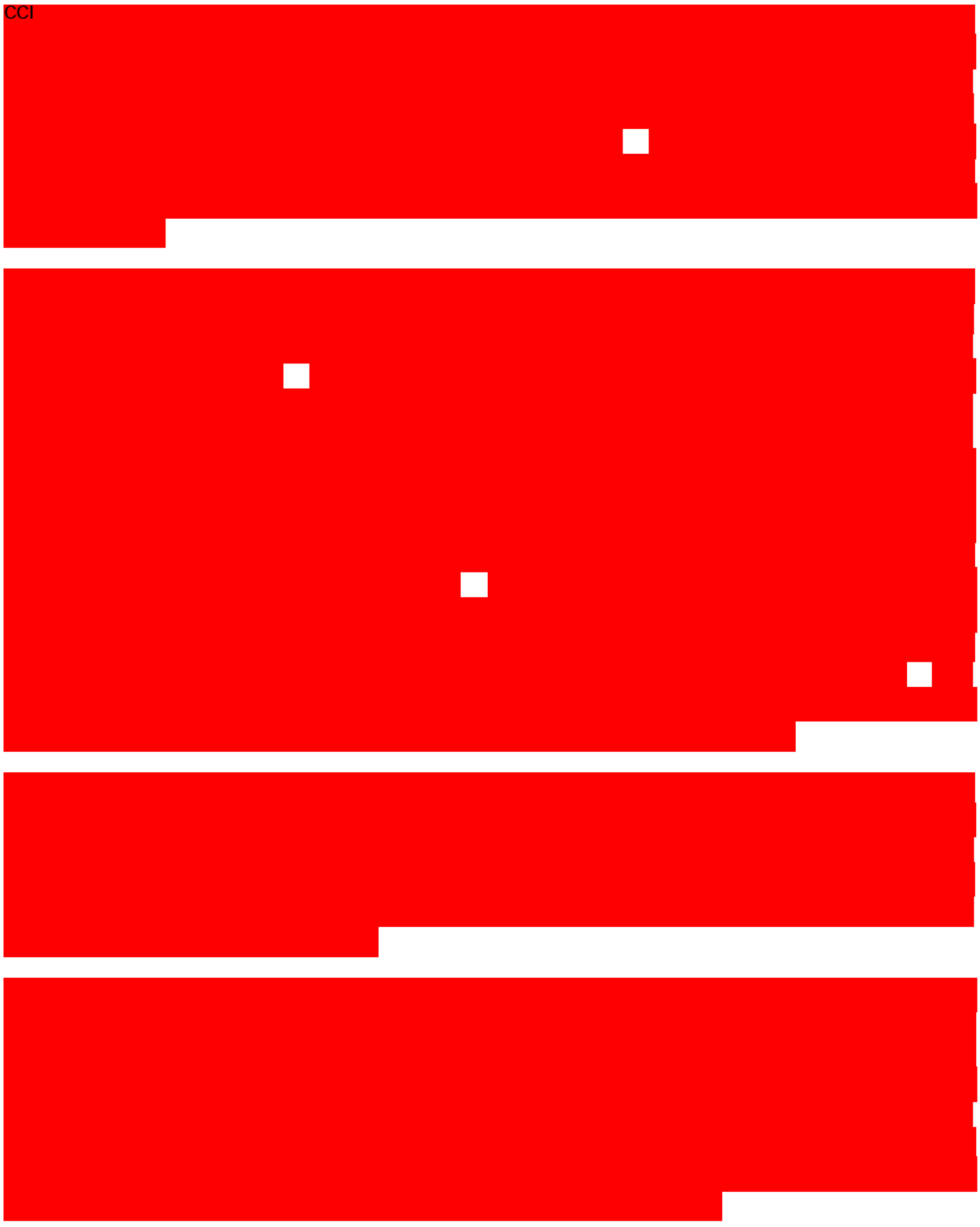
Of note, PD-L1 positive is defined as combined proportion score (CPS) of $\geq$1%. The specific cutoff of PD-L1 strongly positive has been independently determined, taking into account data outside of the current study (i.e., from protocols Keynote 012, Keynote 052 and epidemiologic studies) to be CPS $\geq$10%.

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.

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

4.2.2 Rationale for Dose Selection/Regimen/Modification

CCI



CCI

[redacted]

4.2.2.1 Rationale for the Use of Comparator

While there is no accepted standard of care for recurrent/progressive metastatic urothelial cancer, taxanes, including paclitaxel and docetaxel, are widely utilized in this setting [35]. National Comprehensive Cancer Care guidelines state that, while no standard therapy exists for the second-line therapy of urothelial cancer, taxanes are preferred agents for palliation [36]. Data from single-arm, open label studies support the use of taxanes in subjects with progressive/recurrent urothelial cancer, but demonstrate the limited benefit of these chemotherapeutic regimens. A small, open-label study of docetaxel in this patient population demonstrated an ORR of 13.3%; (95% CI 3.8%; 30.7%), a median PFS of 4 months, and a median overall survival of 9 months (95% CI 6 to 12 months) [30]. An open-label study of paclitaxel in subjects with progressive/recurrent urothelial cancer demonstrated an ORR of 10% (95% CI 0%; 20%), a median PFS of 2.2 months and a median overall survival of 7.2 months [29]. Although no labeled dosing guidelines for these agents are available for subjects with urothelial cancer, docetaxel is typically administered at 75 mg/m^2 Q3W, consistent with the dose for labeled indications. Paclitaxel has frequently been administered at Q3W doses of 175-250 mg/m^2 or equivalent weekly dosing to subjects with metastatic urothelial cancer, including in recent large Phase II and III clinical studies [37, 38].

In a Phase III trial, 370 previously treated urothelial cancer patients were randomly assigned to either vinflunine at 280-320mg/m^2 Q3W or best supportive care [34]. Compared to best supportive care, treatment with vinflunine resulted in a 9% objective response rate and a trend towards increased overall survival that did not reach statistical significance in the ITT population (6.9 versus 4.6 months, hazard ratio 0.88, 95% CI 0.69-1.12). PFS was 3 months in the vinflunine arm and 1.5 months in the arm that received best supportive care alone. In a multivariate Cox analysis, the addition of vinflunine was independently correlated with improved survival. On the basis of these data, vinflunine is has been approved in the EU as monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary

Overall survival (OS) is the gold standard endpoint to demonstrate superiority of antineoplastic therapy. Progression free survival (PFS) may be an acceptable scientific endpoint for a randomized Phase III trial to support accelerated approval in a population with a high unmet medical need and poor response to currently available therapies, such as in subjects with recurrent/progressive urothelial cancer. RECIST 1.1 will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. Because the treatment assignment is unblinded, images will be read by independent radiologists blinded to treatment assignment to minimize bias in the response assessments. The first on-study radiographic imaging assessment will be performed at 9 weeks (±7 days) from randomization and then every 6 weeks (±7 days) thereafter or more frequently if clinically indicated.

Given emerging evidence of the correlation of PD-L1 expression and clinical outcomes of patients with epithelial malignancies (bladder cancer included) treated with PD-1/PD-L1 agents, the study population will be analyzed as a whole, and also taking into account PD-L1 positive and PD-L1 strongly positive status.

Of note, PD-L1 positive is defined as combined proportion score (CPS) of ≥1%. The specific cutoff of PD-L1 strongly positive has been independently determined to be CPS ≥10%, taking into account data outside of the current study.

Data from KN052 demonstrated a clinically meaningful response rate and durable responses in all subjects, including those who were considered to be PD-L1 negative (CPS <1%). Response rates were also meaningfully increased when a CPS cutpoint of 10% was applied. In contrast, the magnitude of enrichment using a 1% CPS cutpoint in this population was not clinically meaningful. Based on these observations from KN052, a single CPS cutpoint of 10% for urothelial cancer has been identified. Therefore, in the second interim analysis (IA2) and final analysis, only primary hypotheses of PD-L strongly positive subjects and all subjects will be included in the multiplicity controlled statistical testing.

4.2.3.1.2 Secondary

4.2.3.1.2.1 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 EQ-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 [41]. 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 patient 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 patient by qualified site personnel. The objective of the HEA form is for the site personnel to collect information from patients 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 recurrent/progressive 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. The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-neoplastic 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-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-neoplastic treatment should also be followed and recorded.

4.2.3.3 Planned Exploratory Biomarker Research

Additional biomarker research to identify factors important for pembrolizumab (MK-3475) therapy may also be pursued. For example, tumor and blood (including serum and plasma) samples from this study 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.

CCI

[redacted]

CCI

[redacted]

4.2.3.4 Future Biomedical Research

CCI

[redacted]

CCI [redacted]

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 and Female subjects of at least 18 years of age with recurrent/progressive metastatic urothelial cancer 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 urothelial cancer of the renal pelvis, ureter, bladder, or urethra. Both transitional cell and mixed transitional/non-transitional cell histologies are allowed, but transitional cell carcinoma must be the predominant histology. Subjects with non-urothelial cancer of the urinary tract are not allowed.

4. Have had progression or recurrence of urothelial cancer following receipt of a first-line platinum-containing regimen (e.g. cisplatin , carboplatin):

    a. Received a first-line platinum-containing regimen in the metastatic setting or for inoperable locally advanced disease;

    or

    b. Received adjuvant platinum-containing therapy following cystectomy for localized muscle-invasive urothelial cancer, with recurrence/progression ≤12 months following completion of therapy.

    or

    c. Received neoadjuvant platinum-containing therapy prior to cystectomy for localized muscle-invasive urothelial cancer, with recurrence ≤12 months following completion of therapy.

    Note: Primary chemoradiation given for subjects who are not considered surgical candidates is not considered a line of therapy for the purpose of this study.

    Note: Subjects with locally advanced unresectable disease who subsequently become eligible for surgery after platinum-containing therapy are not eligible for this study, unless they subsequently have disease recurrence in the metastatic setting.

5. Have received no more than two prior lines of systemic chemotherapy for metastatic urothelial cancer. Subjects for whom the most recent therapy has been a non-platinum-based regimen following progression/recurrence on platinum-based therapy (i.e. third-line subjects) are eligible if they have progressed/recurred on their most recent therapy.

    Note: primary chemoradiation for unresectable muscle-invasive bladder cancer with the aim of bladder preservation will not be considered a prior line of systemic therapy for the purposes of determining study eligibility.

6. Have provided tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. A newly-obtained biopsy is strongly preferred but not required if archival tissue is adequate for analysis. Adequacy of the archived or freshly-obtained biopsy specimen must be confirmed by the central laboratory during the screening period prior to enrollment.

7. Have measureable disease based on RECIST 1.1 as assessed by the investigator/site radiologist. Tumor lesions situated in a previously irradiated area are considered measureable 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. Subjects with an ECOG performance status of 2 must have a hemoglobin ≥10 g/dL, must not have liver metastases, and must have received the last dose of their last prior chemotherapy regimen ≥3 months (90 days) prior to enrollment.

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[b] **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤2.5xULN[b] **OR** ≤5xULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) 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 ≤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.

[b] Docetaxel will only be a comparator option for subjects with a total bilirubin ≤1x ULN, and an AST and/or ALT ≤ 1.5x ULN if alkaline phosphatase is also >2.5x ULN.

10. Female subjects 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 pembrolizumab or 180 days after the last dose of paclitaxel, docetaxel or vinflunine (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 pembrolizumab (MK-3475) or 180 days after the last dose of paclitaxel, docetaxel or vinflunine.

    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 in or has participated in a study of an investigational agent or using an investigational device within 4 weeks prior to the first dose of trial treatment.

3. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

4. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

5. 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., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    Note: Subjects with ≤ Grade 2 neuropathy or ≤ 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.

6. 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; Gleason score ≤ 6, PSA undetectable.

7. 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 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.

8. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic or immunosuppressive agents. Subjects with vitiligo, diabetes Type I, or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjøgren's syndrome will not be excluded from the study.

9. Has active cardiac disease, defined as:

    a. Myocardial infarction or unstable angina pectoris within 6 months of the first date of study therapy.

    b. History of serious ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation), high-grade atrioventricular block, or other cardiac arrhythmias requiring anti-arrhythmic medications (except for atrial fibrillation that is well controlled with antiarrhythmic medication); history of QT interval prolongation.

    c. New York Heart Association (NYHA) Class III or greater congestive heart failure, or left ventricular ejection fraction of < 40%.

10. Has evidence of interstitial lung disease or active non-infectious pneumonitis.

11. Has an active infection requiring systemic therapy.

12. Has a history of severe hypersensitivity reaction (e.g. generalized rash/erythema, hypotension, bronchospasm, angioedema or anaphylaxis) to paclitaxel or to other drugs formulated with polyoxyethylated castor oil, to docetaxel or other drugs formulated with polysorbate 80, or to vinflunine or other vinca alkaloids.

13. Requires ongoing therapy with a medication that is a strong inhibitor or inducer of the CYP3A4 enzymes (a common list of such agents may be found in Section 12.9).

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

15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

17. Has received prior therapy with an anti-PD-1 or anti-PD-L1 agent, or with an agent directed to another co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137).

18. Has received prior chemotherapy for urothelial cancer with all available study therapies in the control arm (i.e. both prior paclitaxel and docetaxel in regions where vinflunine is not an approved therapy, or prior paclitaxel, docetaxel and vinflunine in regions where vinflunine is an approved therapy).

19. Has a known history of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies).

20. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

21. Has received a live virus vaccine within 30 days of planned start of trial treatment.

22. 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(s) to be used in this trial are outlined below in Table 2.

Table 2 Trial Treatment

Drug	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 cycle	Experimental
Paclitaxel*	175 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	Active comparator
Docetaxel*	75 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	Active comparator
Vinflunine**	320 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	Active comparator

* In case of mild hepatic impairment (total bilirubin ≥1.25 ULN), paclitaxel should be started at a dose of 135 mg/m^2. Docetaxel will only be a comparator option for subjects with a total bilirubin ≤1x ULN, and an AST and/or ALT ≤ 1.5x ULN if alkaline phosphatase is also >2.5x ULN.

** In case of WHO/ECOG performance status (PS) of ≥1 or PS of 0 and prior pelvic irradiation, vinflunine should be started at the dose of 280 mg/m². In the absence of any hematological toxicity during the first cycle causing treatment delay or dose reduction, the dose will be increased to 320 mg/m² every 3 weeks for the subsequent cycles. See Section 5.2.1.2.1 for additional guidelines on dose modification for vinflunine, including starting doses in the setting of mild renal and hepatic impairment and in the elderly.

Note: The overall proportion of subjects receiving vinflunine in the control arm is capped at approximately 35%. Vinflunine will only be a comparator option in countries where vinflunine is approved for the treatment of metastatic urothelial cancer.

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

All supplies indicated in Table 2 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

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

5.2.1 Dose Selection/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. There are no specific calculations or evaluation required to be performed in order to administer the proper dose to each subject.

Treatment on the standard treatment arm will be prepared and administered as per the approved product label. The body surface area (BSA) in m^2 should be calculated per local guidance.

5.2.1.2 Dose Modification for Pembrolizumab (MK-3475)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6 .1 for supportive care guidelines, including use of corticosteroids.

Table 3 Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs, or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Table 8 – Infusion Treatment Guidelines for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.2.1.2.1 Dose Modification for Standard Treatment with Paclitaxel, Docetaxel or Vinflunine

In general, treatment with paclitaxel, docetaxel or vinflunine will be withheld for drug-related Grade 4 hematologic toxicities and for non-hematologic toxicity ≥ Grade 3 and subsequent doses modified as per Table 4 below. Dose modifications will be applied for all subsequent doses. Specific dose modification guidance for paclitaxel, docetaxel and vinflunine is found below in Sections 5.2.1.2.2.1, 5.2.1.2.2.2 and 5.2.1.2.2.3. Dose modifications for intolerable Grade 2 drug-related adverse events may be considered after consultation with the Sponsor. Dose modifications for paclitaxel, docetaxel or vinflunine should also be considered according to local product labels.

Table 4 Dose Modification Guidelines for Drug-Related Adverse Events on the Active Comparator Arm

Toxicity*	Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
Neutropenia	Grade 1, 2, 3 or Grade 4 lasting ≤7 days	All	Hold treatment until neutrophils recover to >1500 cells/mm^3	N/A	N/A
	Grade 4 lasting > 7 days	1st occurrence	Hold treatment until neutrophils recover to >1500 cells/mm^3	Restart treatment at: Paclitaxel: 135 mg/m^2 Docetaxel: 60 mg/m^2 Vinflunine: 280 mg/m^2	Treatment discontinuation should be considered
		2nd occurrence	Hold treatment until neutrophils recover to >1500 cells/mm^3	Restart treatment at: Paclitaxel: 100 mg/m^2 Docetaxel: 50 mg/m^2 Vinflunine: 250 mg/m^2	Treatment discontinuation should be considered
		3rd occurrence	Yes	N/A	Yes
Thrombocytopenia	Grade 1, 2, 3	All	Hold treatment until platelets recover to >100,000 cells/mm^3	N/A	N/A
	Grade 4	1st occurrence	Hold treatment until platelets recover to > 100,000 cells/mm^3	Restart treatment at: Paclitaxel: 135 mg/m^2 Docetaxel: 60 mg/m^2 Vinflunine: 280 mg/m^2	Treatment discontinuation should be considered
		2nd occurrence	Hold treatment until platelets recover to >100,000 cells/mm^3	Restart treatment at: Paclitaxel: 100 mg/m^2 Docetaxel: 50 mg/m^2 Vinflunine: 250 mg/m^2	Treatment discontinuation should be considered

Toxicity*	Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
		3rd occurrence	Yes	N/A	Yes
Anemia	Grade 1, 2, 3	All	Until anemia resolves to Grade 1 or baseline	N/A	N/A
	Grade 4	1st occurrence	Until anemia resolves to Grade 1 or baseline	Restart treatment at: Paclitaxel: 135 mg/m^2 Docetaxel: 60 mg/m^2 Vinflunine: 280 mg/m^2	Treatment discontinuation should be considered
		2nd occurrence	Until anemia resolves to Grade 1 or baseline	Restart treatment at: Paclitaxel: 100 mg/m^2 Docetaxel: 50 mg/m^2 Vinflunine: 250 mg/m^2	Treatment discontinuation should be considered
		3rd occurrence	Yes	N/A	Yes
Non-hematological toxicity and other hematological toxicity not described above**	Grade 1, 2	All	No	None	N/A
	Grade 3, 4	1st occurrence	Yes, until toxicity resolves to Grade 0-1 or baseline	Restart treatment at: Paclitaxel: 135 mg/m^2 Docetaxel: 60 mg/m^2 Vinflunine: 280 mg/m^2	Treatment discontinuation should be considered
		2nd occurrence	Yes, until toxicity resolves to Grade 0-1 or baseline	Restart treatment at: Paclitaxel: 100 mg/m^2 Docetaxel: 50 mg/m^2 Vinflunine: 250 mg/m^2	Treatment discontinuation should be considered
		3rd occurrence	Yes	N/A	Yes

*See Table 5, Table 6 and Table 7 for additional dose modifications for drug-related adverse events specific to vinflunine, paclitaxel and docetaxel, respectively.
**Subjects who experience suspected severe hypersensitivity reaction to paclitaxel, docetaxel or vinflunine (e.g. generalized rash/erythema, hypotension and/or bronchospasm, angioedema or anaphylaxis) should be discontinued from trial treatment. See Table 4 for guidelines on management of peripheral neuropathy.

In cases where the toxicity does not resolve to Grade 0-1 within 4 weeks after the last infusion (2 weeks for vinflunine), trial treatment should be discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 4 weeks may continue in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.6.1.

5.2.1.2.1.1 Specific Dose Modifications for Vinflunine

In case of WHO/ECOG performance status (PS) of ≥1 or PS of 0 and prior pelvic irradiation, vinflunine treatment should be started at the dose of 280 mg/m². In the absence of any hematological toxicity during the first cycle causing treatment delay or dose reduction, the dose will be increased to 320 mg/m² every 3 weeks for the subsequent cycles.

In subjects with moderate renal impairment (40 ml/min≤CrCl≤60 ml/min), the recommended dose is 280 mg/m² given once every 3 weeks. In subjects with renal impairment (30 ml/min≤CrCl<40 ml/min), the recommended dose is 250 mg/m² given once every 3 weeks.

The recommended dose of vinflunine is 250 mg/m² given once every 3 weeks in subjects with mild liver impairment (Child-Pugh grade A) or in subjects with a Prothrombin time ≥60% NV and 1.5xULN < Bilirubin ≤xULN and presenting at least one of the following criteria: transaminases > ULN and/or GGT > 5xULN .

The doses recommended in subjects ≥75 years old are as follows:

- in subjects at least 75 years old but less than 80 years, the dose of vinflunine to be given is 280 mg/m² every 3 weeks.
- in subjects 80 years old and beyond, the dose of vinflunine to be given is 250 mg/m² every 3 weeks.

In subjects who initiate vinflunine at 280 mg/m^2 and who experience an AE requiring dose modification, the dose should be reduced to 250 mg/m^2 following the 1st occurrence and resolution, and discontinued following a 2nd occurrence. In subjects who initiate vinflunine at 250 mg/m^2 and who experience an AE requiring dose modification, vinflunine should be discontinued.

Cases of Posterior Reversible Encephalopathy Syndrome (PRES) have been observed after administration of vinflunine. The typical clinical symptoms are, with various degrees: neurological (headache, confusion, seizure, visual disorders), systemic (hypertension), and gastrointestinal (nausea, vomiting). Radiological signs are white matter abnormalities in the posterior regions of the brain.

Vinflunine should be discontinued in subjects who develop neurological signs of PRES.

Specific dose modifications for subjects receiving vinflunine are detailed below in Table 5.

Table 5 Vinflunine Dose Modification for Drug-Related Adverse Events

Toxicity	Dose Adjustment				
	Initial Dose: Vinflunine 320 mg/m^2			Initial Dose: Vinflunine 280 mg/m^2	
	1st Event	2nd Consecutive Event	3rd Consecutive Event	1st Event	2nd Consecutive Event
Neutropenic fever (defined as T ≥100.5°F and ANC ≤ 1,000//L)	Vinflunine 280 mg/m^2	Vinflunine 250 mg/m^2	Discontinue treatment	Vinflunine 250 mg/m^2	Discontinue treatment
Mucositis or Constipation Grade 2 ≥5 days or Grade ≥3 any duration[1]					
Cardiac ischemia in patients with prior history of myocardial infarction or angina pectoris	Discontinue treatment	N/A	N/A	Discontinue treatment	N/A

[1]NCI CTC Grade 2 constipation is defined as requiring laxatives, Grade 3 as an obstipation requiring manual evacuation or enema, Grade 4 as an obstruction or toxic megacolon. Mucositis Grade 2 is defined as "moderate", Grade 3 as "severe" and Grade 4 as "life-threatening"

5.2.1.2.1.2 Specific Dose Modifications for Paclitaxel

Paclitaxel should not be administered to subjects with baseline neutrophil counts of less than 1500 cells/mm^3. Subjects should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1500 cells/mm^3. Severe conduction abnormalities have been documented in <1% of subjects during paclitaxel therapy and in some cases requiring pacemaker placement. If subjects develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

In case of mild hepatic impairment (total bilirubin ≥1.25 ULN), paclitaxel should be started at a dose of 135 mg/m^2.

Dose modifications for subjects receiving paclitaxel are detailed below in Table 6.

Table 6 Paclitaxel Dose Modification for Drug-Related Adverse Events

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
Peripheral Neuropathy	Grade 1, 2		No	135 mg/m^2	N/A
	Grade 3, 4		Yes	N/A	Discontinue upon onset
Neutropenic fever (defined as T ≥100.5°F and ANC ≤ 1,000//L)		1	Hold until ANC ≥1,500/L	135 mg/m^2	
		2	Hold until ANC ≥1,500/L	100 mg/m^2	
		3	Yes	N/A	Yes

5.2.1.2.1.3 Specific Dose Modifications for Docetaxel

Docetaxel should not be given to subjects with bilirubin > 1x ULN, or to subjects with AST and/or ALT > 1.5 x ULN with concomitant alkaline phosphatase >2.5 x ULN. Subjects with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of Grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Docetaxel should also not be given to subjects with a neutrophil count of < 1500 cells/mm^3.

Severe fluid retention has been reported following docetaxel therapy. Subjects should be premedicated with oral corticosteroids prior to each docetaxel Injection administration to reduce the incidence and severity of fluid retention (See Section 5.2.2.3). Subjects with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions. Subjects developing peripheral edema may be treated with standard measures, *e.g.*, salt restriction, oral diuretic(s).

Dose modifications for subjects receiving docetaxel are detailed below in Table 7.

Table 7 Docetaxel Dose Modification for Drug-Related Adverse Events

Toxicity	Grade	Occurrence	Hold Treatment	Dose modification	Treatment Discontinuation
Peripheral Neuropathy	Grade 1, 2		No	60 mg/m^2	N/A
	Grade 3, 4		Yes	N/A	Discontinue upon onset
Neutropenic fever (defined as T ≥100.5°F and ANC ≤ 1,000//L)		1	Hold until ANC ≥1,500/L	60 mg/m^2	
		2	Hold until ANC ≥1,500/L	50 mg/m^2	
		3	Yes	N/A	Yes

5.2.2 Timing of Dose Administration

Trial treatment of pembrolizumab (MK-3475) may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Trial treatment of paclitaxel, docetaxel or vinflunine may be administered up to 3 days before or after scheduled dosing date for administrative reasons per investigator's judgment.

All trial treatments will be administered on an outpatient basis.

5.2.2.1 Pembrolizumab (MK-3475)

Trial treatment of pembrolizumab (MK-3475) should be administered on Day 1 of each 3 week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

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 the preparation of the pembrolizumab (MK-3475) infusion fluid and administration of infusion solution.

5.2.2.2 Paclitaxel

Trial treatment of paclitaxel should be administered on Day 1 of each 3 week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

Paclitaxel 175 mg/m^2 will be administered as an IV infusion administered over 3 hours. See Section 5.2.1.2.1.2 for guidelines on adjustment of initial dose.

All subjects should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel. The appropriate premedication regimen may be determined by the investigator.

5.2.2.3 Docetaxel

Trial treatment of docetaxel should be administered on Day 1 of each 3 week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

Docetaxel 75 mg/m^2 will be administered as an IV infusion administered over 1 hour.

All subjects should be premedicated with oral corticosteroids, such as dexamethasone 16 mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. The appropriate premedication regimen may be determined by the investigator.

5.2.2.4 Vinflunine

Trial treatment of vinflunine should be administered on Day 1 of each 3 week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

Vinflunine 320 mg/m^2 will be administered as an IV infusion administered over 20 minutes. See Section 5.2.1.2.1.1 for guidelines on adjustment of initial dose.

5.2.3 Trial Blinding/Masking

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

Imaging data for the primary analysis will be centrally reviewed by independent radiologist(s) without knowledge of subject treatment assignment. The study team at the Sponsor consisting of clinical, statistical, statistical programming and data management personnel, will be blinded to subject-level PD-L1 biomarker results until the time that the cutoff value of PD-L1 expression level for PD-L1 strongly positive is established and formally documented exclusively based on data outside of this study. Access to the allocation schedule for summaries or analyses will be restricted to an unblinded external statistician, and, as needed, an external scientific programmer performing the analysis, who will have no other responsibilities associated with the study.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are two treatment arms. Subjects will be assigned randomly in a 1:1 ratio to pembrolizumab (MK-3475) OR investigator's choice of paclitaxel, docetaxel or vinflunine. Within the control arm, the overall proportion of subjects receiving vinflunine will be capped at approximately 35%. Investigators must select one treatment among the control arm options before randomization occurs, to use in the event that the subject is randomized to the control arm.

5.4 Stratification

Randomization will be stratified according to the following factors:

1. Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1vs. 2)
2. Presence or absence of liver metastases
3. Hemoglobin (≥ 10 g/dL vs. <10 g/dL)
4. Time from completion of most recent chemotherapy (<3 months or ≥3 months)*.

   Note: Subjects with ECOG 2 may only be enrolled if liver metastases are absent, hemoglobin is ≥10 g/dL, and time from completion (last dose) of most recent chemotherapy is ≥ 3 months (90 days).

* 90 days.

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 considered on an exceptional case by case basis 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.
    - Note: It is acceptable for subjects receiving paclitaxel, docetaxel or vinflunine to receive live vaccines while participating in the trial.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
    - Note: For subjects randomized to the paclitaxel, docetaxel or vinflunine arm, the use of glucocorticoids on trial treatment is acceptable and is required for premedication.
    - Note: 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.
- Strong inhibitors or inducers of the CYP3A4 enzymes (a common list of such agents may be found in Section 12.8).
- QT/QTc-prolonging drugs for subjects receiving vinflunine (a common list of such agents may be found in Section 12.9).

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 for Pembrolizumab (MK-3475)

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 below. 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, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1 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.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis**:

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - All subjects who experience 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. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.

- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table 8 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 8 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6.2 Supportive Care Guidelines for Paclitaxel, Docetaxel and Vinflunine

Pre-medication(s) for paclitaxel and docetaxel will be given as per standard of care (See Sections 5.2.2.2 and 5.2.2.3). Corticosteroid pre-treatment or post-treatment of paclitaxel and docetaxel is acceptable in concordance with the local label or standard of care.

Injection site reactions, including reactions secondary to extravasation, have been reported with paclitaxel. These reactions were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. More severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been reported. A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Severe conduction abnormalities have been documented in <1% of subjects during paclitaxel therapy and in some cases requiring pacemaker placement. If subjects develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

Severe fluid retention has been reported following docetaxel therapy. Subjects should be premedicated with oral corticosteroids prior to each docetaxel Injection administration to reduce the incidence and severity of fluid retention (See Section 5.2.2.3). Subjects with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions. Subjects developing peripheral edema may be treated with standard measures, *e.g.*, salt restriction, oral diuretic(s).

In order to prevent constipation, laxatives and dietary measures including oral hydration are recommended from day 1 to day 5 or 7 after each vinflunine administration. Subjects at high risk of constipation (concomitant treatment with opiates, peritoneal carcinomas, abdominal masses, prior major abdominal surgery) should be medicated with an osmotic laxative from day 1 to day 7 administered once a day in the morning before breakfast.

Refer to the approved product label for additional supportive care guidance.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

MK 3475, paclitaxel, docetaxel and vinflunine may also have adverse effects on a fetus in utero. Furthermore, it is not known if these agents have transient adverse effects on the composition of sperm. Therefore, non-pregnant, non-breast-feeding women may only 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 be either 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 pembrolizumab (MK-3475) or up to 180 days after the last dose of paclitaxel, docetaxel or vinflunine.

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.

Male subjects randomized to receive paclitaxel, docetaxel or vinflunine should seek medical advice regarding cryopreservation of sperm prior to receiving treatment, due to the possibility of infertility.

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 MK-3475 or paclitaxel, docetaxel or vinflunine, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the

fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether MK-3475, paclitaxel, docetaxel or vinflunine are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

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
- Radiographic disease progression as determined by local/site assessment
    - Note: For unconfirmed radiographic disease progression, or confirmed progression with reduction in disease burden from baseline please see Section 5.8.1
- 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 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 Radiologic Progression

Immunotherapeutic agents such as pembrolizumab (MK-3475) may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

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 (≥ 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 9 below. Confirmatory imaging maybe performed as early as 28 days later; alternatively, the scan performed at the next scheduled time point (every 42 days ±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 Sections 5.2.1.2 and 7.2 may NOT continue to receive trial therapy.

Table 9 Imaging and Treatment After 1st Radiologic Evidence of PD

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at ≥ 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 ≥ 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 and site radiologist), an exception may be considered to continue treatment upon consultation with the Sponsor.

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 and PFS of the primary endpoint in this trial.

5.8.3 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days (± 3 days) after the last dose of study medication or before the initiation of a new antineoplastic treatment. Procedures and assessments performed at the Safety Follow-Up Visit and beyond should follow guidelines described in the Trial Flow Chart (Section 6.0). All AEs that occur within the 30-day safety follow-up visit should be recorded. Subjects with an AE >Grade 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new antineoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded. In subjects who start another cancer therapy before 30 days after discontinuation of study therapy, the Safety Follow-Up Visit should occur prior to the subject receiving another cancer therapy.

5.8.4 Duration of Follow-up

All subjects will be followed for at least 30 days after their last dose of trial treatment or until initiation of a new anti-cancer treatment, whichever occurs first. Subjects who are discontinued from the trial due to an unacceptable drug-related AE will be followed until the resolution of the AE to Grade 0-1 or stabilization or until initiation of a new therapy for their cancer, whichever occurs first. Subjects who discontinued study therapy without documented disease progression, should continue to be monitored for disease status by radiologic imaging according to the guidelines described in the Trial Flow Chart (Section 6.0) for post-treatment follow-up. Disease monitoring should continue to be assessed every 6 weeks (±7 days) (every 12 weeks following the 1st 12 months of trial treatment) until, 1) for approximately

two years after the last dose of trial treatment, 2) start of a new antineoplastic therapy, 3) documented disease progression, or 4) until death, whichever occurs first.

5.8.5 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 the 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 (±7 days) or every 12 weeks (±7 days) after year 1 (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 (± 7 days) to assess for survival status, until death, withdrawal of consent, or end of the study, whichever occurs first.

The Sponsor may request survival status data more frequently than every 12 weeks at specific time points during the study. Refer to section 7.1.5.3.3 Survival Follow-up for additional information.

Post-study treatments and the subject's response to them will also be collected.

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. The trial may be stopped early for futility or safety at the recommendation of the Data Monitoring Committee (DMC).
2. Quality or quantity of data recording is inaccurate or incomplete
3. Poor adherence to protocol and regulatory requirements
4. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
5. Plans to modify or discontinue the development of the study drug

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	Screening Phase	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 5	6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]	-42 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	Every 6 weeks post discon ±7	Every 12 weeks ±7
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		
Trial Treatment Administration				X[d]	X	X	X	X	X				
Post-study Anticancer Therapy Status												X	X
Survival Status													X
Clinical Procedures/Assessments													
Review Adverse Events[h, i]		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	
ECOG Performance Status[l]			X	X	X	X	X	X	X	X	X	X	
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]		

Trial Period:	Screening Phase	Screening Phase	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 5	6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]	-42 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	Every 6 weeks post discon ±7	Every 12 weeks ±7
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory													
Pharmacokinetics (pembrolizumab (MK-3475) arm only)[r]				X[r, s]	X[r]		X[r]				X[r]	X[r]	
Anti-MK-3475 Antibodies [pembrolizumab (MK-3475) arm only][r]				X[r]	X[r]		X[r]				X[r]	X[r]	
Blood for serum and plasma for Correlative Studies[t]				X									
Blood samples for RNA and DNA for Correlative Studies[u]				X	X	X				X			
Blood for Genetics[v]				X									
Efficacy Measurements													
Tumor Imaging		X[w,z]					X[x]		X[x]	X[y]		X[b]	
Tumor Tissue Collection													
Archival or Newly Obtained Tissue Collection for biomarker analysis[aa]	X												
Patient Reported Outcomes													
EuroQol EQ-5D				X[bb]	X[bb]	X[bb]	X[bb]		X[bb]	X[bb]	X[bb]		
EORTC QLQ-C30				X[bb]	X[bb]	X[bb]	X[bb]		X[bb]	X[bb]	X[bb]		
Health Economic Assessment (HEA)					X[bb]	X[bb]	X[bb]		X[bb]	X[bb]	X[bb]		

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 (for pembrolizumab (MK-3475) arm only) 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 days ± 7) from randomization and every 6 weeks thereafter (42 days ± 7 days) regardless of any treatment delays.
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 ± 7days) after year 1 until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by investigator/site radiologist (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression by the central imaging vendor, the subject should be contacted by telephone every 12 weeks to assess for survival status. Survival data may be requested more frequently than 12 weeks as per Section 7.1.5.3.3.
d. In general, the window for each visit is ± 3 days unless otherwise noted. Cycle 1 treatment must be given within 3 days of randomization.
e. Written consent must be obtained prior to performing any protocol specified procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 42 days prior to the first dose of trial treatment). Screening number will be assigned when the trial informed consent is signed.
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.
g. Prior medications – Record all medications taken within 30 days of the first dose of trial treatment. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for AEs as defined in Section 7.2.
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 Screening Visit; 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.
l. ECOG PS at Screening to be performed ≤ 10 days prior to Day 1 of trial treatment visit.
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.
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.
o. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
p. For the paclitaxel/docetaxel/vinflunine arm, CBC and Chemistry tests should be collected on Day 1 of each 3 week cycle. For Cycles 1 and 2, CBC and Chemistry tests should also be collected on Days 8 and 15 of each cycle. In subsequent cycles, CBC and Chemistry tests on Day 8 and Day 15 may be performed at the Investigator's discretion. Thyroid Function Tests should be collected every 6 weeks. For the pembrolizumab (MK-3475) arm, CBC and Chemistry tests should be collected on Day 1 of each 3 week cycle. Thyroid Function Tests should be collected every 6 weeks. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests. For Cycle 1, the Screening samples are sufficient if performed within 10 days. For subjects with a baseline estimated creatinine clearance below the normal institutional laboratory range, a baseline measured creatinine clearance should be performed.
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.
r. Pembrolizumab (MK-3475) arm only. Pre-dose trough PK and anti- pembrolizumab (MK-3475) antibody samples will be collected at Cycles 1, 2, 4, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug, and 3 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab (MK-3475). Additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab (MK-3475) infusion at Cycles 1 and 8.
s. An additional single PK sample should be drawn between 72 and 168 hours after Cycle 1 dosing.
t. 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
u. Blood samples 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.
v. 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.
w. The initial tumor imaging will be performed within 28 days prior to randomization. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to randomization. Measureable disease based on RECIST 1.1 must be confirmed by investigator/site radiologist before enrollment. All subjects will have a baseline bone scan performed at screening. Subjects with positive bone scans at baseline will be followed with additional scans performed at 9 weeks (± 7 days)from randomization 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.
x. The first on-study imaging time point will be performed at 9 weeks (±7 days) from randomization 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.

y. 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 is not mandatory.

z. All subjects will have a baseline bone scan performed at screening. Subjects with positive bone scans at baseline will be followed with additional scans performed at 9 weeks (±7 days) from randomization and then every 6 weeks (±7 days) thereafter or more frequently if clinically indicated. Subjects with new symptoms concerning osseous metastasis will be evaluated with a bone scan. Refer to Section 7.1.2.6.3 of the protocol.

aa. Baseline tumor tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy (FNA not adequate) must be provided to the central vendor prior to randomization.. Adequacy of the biopsy specimen for 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.

bb. It is most relevant and strongly recommended that Electronic patient outcomes (ePROs) are administered prior to drug administration, adverse event evaluation and disease status notification 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.

6.2 Second Course Phase (Retreatment) for Pembrolizumab (MK-3475) Arm Only

Trial Period:	Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	1	2	3	4	To be repeated beyond 6 cycles: 5	To be repeated beyond 6 cycles: 6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose ±3	Every 6 weeks post discon ±7	Every 12 weeks ±7
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
Survival Status										X
Clinical Procedures/Assessments										
Review Adverse Events[h]	X	X	X	X	X	X	X	X[i]	X[i]	
Full Physical Examination[j]	X[j]									
Directed Physical Examination[j]		X	X	X	X	X	X			
Vital Signs, Weight and Height[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[s]		
Chemistry Panel[o]	X[n]	X	X	X	X	X	X	X[s]		
Urinalysis	X									
T3, FT4 and TSH[o]	X[n]		X		X			X[s]		
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory										
Pharmacokinetics[p]	X	X			X			X[p]	X[p]	
Anti-MK-3475 Antibodies[p]	X	X			X			X[p]	X[p]	
Efficacy Measurements										
Tumor Imaging[q]	X		X		X		X[r]		X	

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.
b. In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (±7 days) until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression by the investigator/site radiologist, the subject should be contacted by telephone every 12 weeks to assess for survival status. Survival data may be requested more frequently than 12 weeks as per Section 7.1.5.3.3.
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 intolerability 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 AEs 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 Screening Visit; 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.
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, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
p. Pembrolizumab (MK-3475) only. Pre-dose trough PK and anti- pembrolizumab (MK-3475) antibody samples will be collected at Cycles 1, 2, 4 and every 4 cycles thereafter, 30 days after discontinuation of study drug, and 3 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab (MK-3475).
q. 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 dose of trial treatment 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 pembrolizumab (MK-3475) cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. The Sponsor will collect radiological assessments for analysis by a central imaging vendor. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual.
r. 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.
s. Unresolved labs that are drug-related AEs should be followed until resolution. Labs do not need to be repeated after 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. 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.

7.1.1.5 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 and record in the trial database.

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

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

Investigators must choose a standard treatment (paclitaxel, docetaxel or vinflunine) prior to randomization and document the selection in the trial database (See Data Entry Guidelines).

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

Interruptions from the protocol specified treatment for greater than 12 weeks between pembrolizumab (MK-3475) doses on the pembrolizumab (MK-3475) treatment arm 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) or comparator infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab (MK-3475) or comparator administered.

The instructions for preparing and administering pembrolizumab (MK-3475) will be provided in the Pharmacy Manual. Treatment with paclitaxel, docetaxel or vinflunine will be prepared and administered as per the approved product label.

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 clinical indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.6). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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). Refer to the separate 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 12-Lead Electrocardiogram

A standard 12-lead ECG will be performed using local standard procedures once at screening visit as described in Section 6 – Trial Flow Chart. Clinically significant abnormal findings should be recorded as medical history.

7.1.2.3 Physical Exam

7.1.2.3.1 Full Physical Exam

The investigator or clinical designee will perform a complete physical exam during the screening period (See Trial Flow Chart Section 6.0). Clinically significant abnormal findings should be recorded as medical history. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3.2 Directed Physical Exam

The investigator or qualified designee will perform a directed physical exam as clinically indicated prior to Day 1 of each treatment cycle starting with Cycle 2. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.4 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.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.5) at screening (within ≤10 days prior the dosing on Day 1 Cycle 1) and prior to the dosing on Day 1 of each treatment cycle and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Process for image collection and transmission to the central vendor can be found in the Site Imaging Manual. CT scan is the preferred imaging modality for this study. Tumor imaging may be performed by computed tomography (CT) 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.

Local site investigator/radiology assessment based on RECIST 1.1 will be used to determine subject eligibility. All scheduled images for all study subjects from the sites will be submitted to the central imaging vendor. 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 investigator/site radiologist must review pre-trial images to confirm the subject has measurable disease per RECIST 1.1. The baseline imaging scan should also be submitted to the central imaging vendor. Bone scans will be performed at baseline for all subjects.

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. The same imaging technique should be used in a subject throughout the trial. 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 ±7 days) from randomization. Subsequent imaging should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After the first 12 months on trial therapy, the imaging interval should be decreased to every 12 weeks (±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, whichever is clinically indicated.

Imaging should continue to be performed until disease progression is assessed by the investigator, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, 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. Subjects with positive bone scans at baseline will be followed with additional scans performed at 9 weeks (Day 63 ±7 days) from randomization. Subsequent scans should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After the first 12 months on trial therapy, the scanning interval should be decreased to every 12 weeks (±7 days). Subjects with new symptoms concerning osseous metastasis (e.g., new persistently elevated alkaline phosphatase) will be evaluated with a bone scan. Additionally, plain X-ray evaluation should be obtained for symptomatic sites with negative bone scan evaluations. New osseous uptake, upon confirmation with CT, 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 12.7) will be applied by the central imaging vendor as the primary measure for assessment of tumor response and date of disease progression. Subjects in the pembrolizumab (MK-3475) arm 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 to subjects in the control arm as well. All scans, including confirmatory scans, should be submitted to the central imaging vendor for retrospective evaluation.

Imaging during the follow-up period is to be repeated every 6 weeks (42 ±7 days), or every 12 weeks 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.

Local reading (investigator assessment with site radiology reading) 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. The central imaging vendor will receive all images from the sites, and a retrospective analysis of subject eligibility and treatment response by modified RECIST, will also be performed by a central vendor.

7.1.2.7 Tumor Tissue Collection and Correlative Blood Sampling

Either an archival FFPE tumor sample or 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 prospectively in this trial. The tumor tissue must be received by the central vendor and be deemed adequate for evaluation prior to subject randomization. If new scientific data emerge that indicate that an existing biopsy or surgical specimen is suboptimal for identification of subjects, only new biopsies will be acceptable for determination of 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.

Blood for correlative biomarker studies should be collected prior to Cycle 1, Cycle 2, Cycle 3 and at treatment discontinuation.

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. It is most relevant and strongly recommended that ePROs are administered prior to drug administration, adverse event evaluation and disease status notification.in the following order: EuroQol EQ-5D first then EORTC QLQ-C30 at the time points specified in the Trial Flow Chart.

The Health Economic Assessment (HEA) form will be completed via an interview with the patient 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 10.

Table 10 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)[e]	Aspartate aminotransferase (AST)	Specific gravity	Total thriiodothyronine (T3) (or Free T3)[b]
Red Blood Cell Count	Carbon dioxide (CO_2 or bicarbonate)[b]	Microscopic exam, if abnormal results are noted	Free thyroxine (free T4)
Absolute Neutrophil Count	Calcium	Urine pregnancy test[a]	Thyroid Stimulating Hormone (TSH)
Absolute Lymphocyte Count	Chloride		PK [for subjects on the pembrolizumab (MK-3475) arm only]
	Creatinine[c] (GFR can also be used in place of creatinine or CrCl)		[Anti- pembrolizumab (MK-3475) Antibodies (for subjects on the pembrolizumab (MK-3475) arm only]
	Glucose		Blood for correlative studies
	Phosphorus		Blood for FBR
	Potassium		Blood for Genetics

Hematology	Chemistry	Urinalysis	Other
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen [d]		
	Uric acid		

[a] Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
[b] Carbon dioxide and/or bicarbonate do not need to be performed if these tests are not done as part the of standard of care in the region
[c] For subjects with a baseline calculated creatinine clearance below the normal institutional laboratory range, a baseline measured creatinine clearance should be performed.
[d] Blood Urea Nitrogen is preferred; if not available urea may be tested
[e] Absolute or % acceptable per institutional standard.

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 are not required to be available nor reviewed prior to each dose of trial treatment.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

To further evaluate pembrolizumab (MK-3475) immunogenicity and pembrolizumab (MK-3475) exposure in this indication, and also to evaluate exposure of the 200 mg fixed dosing regimen, sample collections for analysis of anti-drug antibodies (ADA) and PK are currently planned as shown in the Trial Flowchart (Sections 6.1. and 6.2).

7.1.3.2.1 Blood Collection for Serum Pembrolizumab (MK-3475)

Sample collection, storage and shipment instructions for serum PK samples will be provided in the Procedures Manual. PK samples should only be drawn for subjects in the pembrolizumab (MK-3475) arm.

7.1.3.2.2 Blood Collection for Anti- pembrolizumab (MK-3475) Antibodies

Sample collection, storage and shipment instructions for anti- pembrolizumab (MK-3475) antibody samples will be provided in the Procedures Manual. Anti- pembrolizumab (MK-3475) antibody samples should only be drawn for subjects in the pembrolizumab (MK-3475) arm.

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 RNA
- Leftover biomarker samples (serum and plasma)

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 on the pembrolizumab (MK-3475) arm 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 (PPD), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

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

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 42 days prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

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 within 42 days. ICF must be signed prior to completing any protocol specified procedure.

- Informed Consent Form for Future Biomedical Research (optional) signed within 42 days of randomization.
- Archival or Newly Obtained Tissue Collection for biomarker analysis to be obtained within 42 days prior to randomization.
- Initial Tumor Imaging should be performed within 28 day of randomization.
- 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).

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

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 on the pembrolizumab (MK-3475) arm 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 MK-3745. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
  - Stopped initial treatment with pembrolizumab (MK-3475) after attaining an investigator-determined confirmed CR according to RECIST 1.1
    - Was treated for at least 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 not 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-Treatment Visits

7.1.5.3.1 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days (±3) 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 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 (±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 at the 3-month Follow-up visits, and any subsequent visits for imaging that may occur-until PD is confirmed. Once the subject stops the imaging assessments for this protocol every 6 weeks or every 12 weeks after year 1 (e.g. for PD or starting a new antineoplastic therapy), the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks (± 7 days) to assess for survival status. Post-study treatments and the subject's response to them will also be collected.

The Sponsor may request survival status be assessed at additional time points during the course of the study. For example, these additional time points may be requested prior to; an external data monitoring committee (eDMC) safety review, efficacy interim analysis, and/or final analysis. All subjects who are not known to have died prior to the request for these additional survival status time points will be contacted at that time.

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 any dose of 1,000 mg or greater (≥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. An overdose for all other trial treatments will be defined as any dose exceeding the prescribed dose by 20%. 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. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 11 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." This document can be found in the administrative binder and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

   ECIs 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 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 11 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**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.

7.3.2 Executive Oversight Committee

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

7.3.3 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.1.4 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

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 hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to 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).

Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥ 10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months) will be the stratification variables in all stratified analyses.

8.1.1 Efficacy Analyses

The intention-to-treat (ITT) population will serve as the primary analysis population in this study. The primary efficacy endpoints are progression-free-survival (PFS) (i.e., time from randomization to documented progressive disease or death due to any cause, whichever occurs first) and overall survival (OS) (i.e., time from randomization to death due to any cause) in PD-L1 strongly positive, PD-L1 positive, and all subjects. The primary analyses of PFS will be based on blinded independent radiologists' review using RECIST 1.1. Supportive analyses based on investigator's assessments using RECIST 1.1 will also be performed. The secondary endpoints include PFS per modified RECIST (see Section 8.2.3.1 for definition) and objective response rate (ORR) per RECIST 1.1 and modified RECIST based on blinded independent radiologists' review. All the stratified analyses will be based on the stratification factors implemented for enrollment. In addition, a supportive stratified analyses will also be conducted for the primary efficacy endpoints based on the four strata defined by the number of risk factors (0, 1, 2 or 3 to 4) of the following [67]: Eastern Cooperative Oncology Group (ECOG) Performance Scale >0, presence of liver metastases, hemoglobin <10 g/dL), and time from completion of most recent chemotherapy <3 months. An outline of the efficacy analysis strategy is presented in Table 13 in Section 8.2.5.1. The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple comparisons, multiple populations and interim analyses is described in Section 8.2.9 Interim Analyses and in Section 8.2.6 Multiplicity.

8.1.2 Safety Analyses

The All-Patients-as-Treated (APaT) population will be employed for safety analyses. The analysis of safety results will follow a tiered approach. Please see Section 8.2.5.2 for details.

8.1.3 Power and Sample Size

The study will randomize approximately 470 patients with a 1:1 ratio between the pembrolizumab (MK-3475) arm and the standard treatment arm. The study is event-driven and the sample size calculation is driven by survival events. Assuming the prevalence rates of PD-L1 positive subjects and PD-L1 strongly positive subjects among the overall population are 55% and 33%, respectively, a sample size of 470 all subjects will provide approximately 260 PD-L1 positive subjects and 156 PD-L1 strongly positive subjects.

The sample size and power calculation of PFS is based on the following assumptions: 1) progression-free survival follows an exponential distribution with a median of 4 months in the standard treatment arm, 2) true hazard ratios between pembrolizumab (MK-3475) and standard therapy of 0.45, 0.5 and 0.5 for PD-L1 strongly positive, PD-L1 positive and all subjects, respectively, 3) an enrollment period of 12 months, and 4) a yearly dropout rate of 5%. The estimated numbers of PFS events in PD-L1 strongly positive subjects and all subjects at the final PFS evaluation are estimated to be 137 and 420, respectively. The study provides 97% power for the PFS hypothesis in PD-L1 strongly positive subjects and >99% power for the PFS hypothesis in all subjects.

The final OS analysis will be carried out after approximately 370 deaths in all subjects and 110 deaths in PD-L1 strongly positive subjects have occurred between the pembrolizumab (MK-3475) arm and the paclitaxel, docetaxel or vinflunine arm for all subjects, barring early stopping for futility or efficacy. With the above numbers of events and before any alpha roll-over, the study provides 88% and 86% power to demonstrate superiority of OS of pembrolizumab (MK-3475) relative to standard therapy at the pre-specified initial alpha (one-sided) levels in PD-L1 strongly positive and all subjects, respectively. The sample size and power calculation of OS are based on the following assumptions: 1) overall survival follows an exponential distribution with a median of 8 months in the control arm; 2) the hazard ratio for OS between pembrolizumab (MK-3475) and control is 0.5, 0.6 and 0.7 for PD-L1 strongly positive, PD-L1 positive and all subjects, respectively. (deemed to be clinically meaningful in this population); 3) an enrollment period of 12 months and a minimum of 18 months follow-up after enrollment completion; and 4) a yearly drop-out rate of 2%.

The family-wise type I error rate for the primary hypotheses on PFS and OS as well as the secondary hypotheses on ORR is strongly controlled at 2.5% (one-sided) using the graphical method of Maurer and Bretz [68]. Additional details are provided in Section 8.2.6 Multiplicity.

8.1.4 Interim Analysis

There will be two interim analyses of PFS and OS for PD-L1 strongly positive (CPS≥10%) subjects and all subjects, respectively. For PD-L1 positive subjects, only the PFS and OS analyses at IA1 are included in the multiplicity controlled testing strategy. The timing of these interim analyses will be triggered by the pre-specified number of OS events. Results of the interim analyses will be reviewed by an external data monitoring committee (DMC). Further details of interim analyses are provided in Section 8.2.9 Interim Analysis as well as in the DMC Charter.

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.

Although the trial is open label, analyses or summaries generated by randomized treatment assignment, actual treatment received, and/or PD-L1 biomarker status will be limited and documented. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment. The study team at the Sponsor consisting of clinical, statistical, statistical programming and data management personnel, will be blinded to subject-level PD-L1 biomarker results until the time that the cutoff value of PD-L1 expression level for PD-L1 strongly positive is established and formally documented exclusively based on data outside of this study.

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

Access to the allocation schedule for this study will be restricted to an external unblinded statistician and, as needed, an external scientific programmer performing the analysis, who will have no other responsibilities associated with the study.

Treatment-level results at interim analyses of PFS and OS will be provided by an external unblinded statistician to the eDMC. Key enrollment metrics and study data will also be monitored by the external unblinded statistician to inform the timing of the interim PFS and OS analyses as needed. Limited additional SPONSOR personnel may be unblinded to the treatment level results of the interim analyses, if required, in order to act on the recommendations of the eDMC or facilitate regulatory filing after the interim analyses. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician.

The eDMC will serve as the primary reviewer of the unblinded results of the interim analyses and will make recommendations for discontinuation of the study or modification to an executive oversight committee of the SPONSOR. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive

oversight committee may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the DMC Charter.

8.2.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3. The study is considered to have met its primary objective if pembrolizumab (MK-3475) is superior to the paclitaxel, docetaxel or vinflunine arm either in PFS or in OS at an interim analysis or final analysis in the overall population, the PD-L1 positive population or the PD-L1strongly positive population.

8.2.3 Analysis Endpoints

8.2.3.1 Efficacy Endpoints

Primary

Progression-free survival - RECIST 1.1 by blinded independent radiologists' review

Progression-free-survival (PFS) is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded independent radiologists' review or death due to any cause, whichever occurs first. See Section 8.2.5.1.1 for the definition of censoring.

A supportive analysis of PFS will be conducted using site radiology review as defined in the Imaging Review Charter.

Overall Survival

Overall Survival (OS) is defined as the time from randomization to death due to any cause. Patients without documented death at the time of the final analysis will be censored at the date of the last follow-up.

Secondary

Objective Response Rate (ORR) – RECIST 1.1 by blinded independent radiologists' review

Objective response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR). Responses are based upon blinded central radiologists' review per RECIST 1.1.

A supportive analysis of ORR will be conducted using site radiology review as defined in the Imaging Review Charter.

PFS/ORR – modified RECIST by blinded independent radiologists' review

PFS and ORR per modified RECIST are defined as specified for the respective endpoints using RECIST 1.1 above, with the exception that a confirmation assessment of PD (at least 4 weeks after the initial PD assessment) is required for subjects who remain on treatment following a documented PD per RECIST 1.1. Subjects who discontinue treatment following a documented PD assessment per RECIST 1.1 will be counted as having disease progression on the date of the documented PD assessment. See Section 8.2.5.1.1 for the definition of censoring.

Supportive analyses will be conducted using site radiology review as defined in the Imaging Review Charter.

Response Duration - – RECIST 1.1 by blinded independent radiologists' review

For subjects who demonstrated CR or PR, response duration is defined as the time from first documented evidence of CR or PR until disease progression or death. Response duration for subjects who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment. Response duration will be calculated for RECIST 1.1 based on blinded independent radiologists' review and site review.

Exploratory

Exploratory endpoints of this study include but are not limited to PFS2, disease control rate, and response to treatment by biomarker subgroups. Patient-reported outcomes (PROs) while on treatment and post-discontinuation will be examined. The detailed PRO analysis plan will be included in a separate document.

An exploratory analysis of PFS2, defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever first, will be carried out. If progression after next-line therapy cannot be measured, a PFS event is defined as the end or discontinuation of next-line treatment or death from any cause, whichever occurs first. Patients alive and for whom a PFS event has not been observed will be censored at the last time known to be alive and without second disease progression.

8.2.3.2 Safety Endpoints

Safety measurements are described in Section 7.

8.2.4 Analysis Population

8.2.4.1 Efficacy Analysis Population

The analysis of primary efficacy endpoints are based on the intention-to-treat (ITT) population, i.e., subjects will be included in the treatment group to which they are randomized. Details on the approach to handling missing data are provided in Section 8.2.5 Statistical Methods.

8.2.4.2 Safety Analysis Populations

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized subjects who received at least 1 dose of study treatment. Subjects will be included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data. Subjects who take incorrect trial treatment for the entire treatment period will be included in the treatment group corresponding to the trial treatment actually received. The baseline measurement and at least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial treatment is required for inclusion in the analysis of each specific parameter.

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

8.2.5 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 8.2.5.2. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 8.2.6, Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than for formal tests of hypotheses.

8.2.5.1 Statistical Methods for Efficacy Analyses

The family-wise type I error rate for this study is strictly controlled at 2.5% (one -sided) that allows the trial to declare positive in PFS or OS in the ITT population.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints and multiple analyses is described in Section 8.2.6 and Section 8.2.9.

8.2.5.1.1 Progression-Free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The same stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model. A sensitivity analysis based on a multivariate Cox PH model with treatment, stratification factors and other factors as covariates will also be provided.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment

at which PD is objectively documented per RECIST 1.1, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by central imaging vendor, two sensitivity analyses with different sets of censoring rules will be performed. The first sensitivity analysis is the same as the primary analysis except that the data for any subject who misses two or more consecutive disease assessments (with or without a subsequent death or progression) are censored at the last disease assessment prior to missing visits. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of new anticancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for subjects without documented PD or death. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 12. In addition to the primary analysis and two sensitivity analyses listed in Table 12, another analysis, sensitivity analysis 3, will be conducted with special censorings rules for specific clinical scenarios. Sensitivity analysis 3 is the same as the primary analysis except that it censors subjects with any of the following two clinical scenarios before PD or death at the time of last disease assessment prior to the clinical scenarios: (1) use of radiotherapy before study treatment discontinuation; (2) occurrence of a skeletal-related event (e.g., fracture) in patients with bone metastases at study entry. In case there is an imbalance between the treatment groups on disease assessment schedules or censoring patterns, we will also perform the following two additional PFS sensitivity analyses: (1) a PFS analysis using time to scheduled tumor assessment visit from randomization as opposed to actual tumor assessment time; (2) Finkelstein (1986)'s likelihood-based score test for interval-censored data, which modifies the Cox proportional hazard model for interval censored data, will be used as a supportive analysis for the PFS endpoint [41]. The interval will be constructed so that the left endpoint is the date of the last disease assessment without documented PD and the right endpoint is the date of documented PD or death, whichever occurs earlier.

Table 12 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation				Analysis Approach		
Event Status	**Study Therapy Discontinued**	**New Anti-Cancer Therapy Initiated**	**# Missed Disease Assessments Before Event**	**Primary Analysis**	**Sensitivity Analysis 1**	**Sensitivity Analysis 2**
No PD and No Death	No	No	N/A	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment
No PD and No Death	Yes	No	N/A	Censored at last disease assessment	Censored at last disease assessment	progressed at treatment discontinuation
No PD and No Death	Yes or No	Yes	N/A	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
No PD and No Death	Yes or No	No	≥ 2 consecutive assessments	Censored at last disease assessment	Censored at last disease assessment prior to the ≥ 2 missed disease assessments	Censored at last disease assessment
PD or Death	Yes or No	No	≤ 1	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or Death	Yes or No	No	≥ 2 consecutive assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Progressed at date of documented PD or death

The proportional hazards assumption on PFS will be examined using both graphical and analytical methods if warranted. The log[-log] of the survival function vs. time for PFS will be plotted for the comparison between pembrolizumab (MK-3475) and the paclitaxel, docetaxel or vinflunine arm. If the curves are not parallel, indicating that hazards are not proportional, a supportive analysis will be conducted to further account for the possible nonproportional hazards effect associated with immunotherapies using Fleming and Harrington's weighted log-rank test with the class of weights ($G^{\rho, \gamma}$) [66]. The weights will be assigned under the assumption of a delayed clinical benefit so that later event times are weighted more heavily than early event times. Using this class of weights assuming parameters $\rho = 0$ and $\gamma = 1$, the weight at a given event time is 1 minus the estimated survival function.

8.2.5.1.2 Overall Survival (OS)

The Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. The same stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model. A sensitivity analysis based on a multivariate Cox PH model with treatment, stratification factors and other factors as covariates will also be provided.

Subjects in the standard treatment arm may switch to another anti PD-1 treatment following confirmation of progressive disease. Exploratory analyses to adjust for the effect of crossover (to other PD-1therapies) on OS may be performed based on recognized methods, e.g. the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1989), two stage model, etc. The choice of the method will be based on an examination of the appropriateness of the data to the assumptions required by the method. The RPSFT model provides a randomization-based estimate of treatment effect (RBEE) corrected for the bias induced by crossover. The 95% confidence intervals of the hazard ratio for OS after adjustment of the cross-over effect will be provided. The Kaplan-Meier estimates of the OS rate at 3 months, 6 months (when most cross-overs are likely to occur) and other time points of interest will also be compared between the two treatment groups to explore the confounding effect of subsequent treatments. To further account for the possible confounding effect, a sensitivity analysis of OS that censors subjects at the time of initiation of new therapy will be performed and an OS analysis that treats initiation of new therapy as a time-dependent binary covariate will also be conducted. In the case where the proportional hazards assumption doesn't hold, Fleming and Harrington's weighted log-rank test or other methods, as appropriate, will be conducted. Further details of sensitivity analyses will be described in supplemental SAP.

8.2.5.1.3 Objective Response Rate (ORR)

Stratified Miettinen and Nurminen's method with strata weighted by sample size will be used for comparison of the objective response rates between the treatment groups. The p-value and 95% confidence interval for the difference in response rates between the pembrolizumab (MK-3475) arm and the standard therapy arm will be provided. The same stratification factors used for randomization (see Section 5.4) will be applied to the analysis. Sensitivity analyses will be performed for comparison of ORR based on investigator's assessment. The ORR in overall population has also been included in the multiplicity scheme; see Section 8.2.6.

8.2.5.1.4 Response Duration

If sample size permits, response duration 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. Response duration will be assessed using RECIST 1.1 separately by independent radiologists' review and by site radiology review.

A summary of the primary analysis strategy for the primary and secondary efficacy endpoints is provided in Table 13.

8.2.5.1.5 Exploratory Analyses

Details of the statistical methods on exploratory analyses can be found in the sSAP.

Table 13 Efficacy Analysis Methods for Primary and Secondary Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Primary or Supportive Approach	Statistical Method	Analysis Population†	Missing Data Approach
Primary Endpoints:				
PFS (RECIST 1.1) by independent radiologists' review	P	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 12
PFS (RECIST 1.1) by independent radiologists' review – Sensitivity Analyses 1& 2	S	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 12
OS	P	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Model based (censored at last contact date)
OS	S	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at time of initiation of new therapy or last assessment date

Endpoint/Variable (Description, Time Point)	Primary or Supportive Approach	Statistical Method	Analysis Population†	Missing Data Approach
OS	S	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method using initiation of new therapy as time-dependent covariate	ITT	Censored at last contact date
Secondary Endpoints :				
Objective response rate (RECIST 1.1) by independent radiologists' review	P	Stratified Miettinen and Nurminen method	ITT	Patients with missing data are considered non-responders
PFS (modified RECIST) by independent radiologists' review	P	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 12
Objective response rate (modified RECIST) by independent radiologists' review	P	Stratified Miettinen and Nurminen method	ITT	Patients with missing data are considered non-responders
Response duration (RECIST 1.1) by independent radiologists' review	P	Summary statistics using Kaplan-Meier method	All responders in ITT	Non-responders are excluded from analysis
† The analysis populations for H3 and H4 are ITT in PDL1 positive subjects, and for H5 and H6 are ITT in PDL1 strongly positive subjects.				

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, vital signs, and ECG measurements.

Time to Grade 3-5 AE

Time to first Grade 3-5 AE is defined as the time from the first day of study drug to the first event of Grade 3-5 AE. For patients without a Grade 3-5 AE, the time to first Grade 3-5 AE is censored at 30 days post last study dose. The Kaplan-Meier method will be used to estimate the curve of time to first Grade 3-5 AE. The treatment difference in time to first Grade 3-5 AE will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. The same stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model.

Tiered Approach for Other Safety Analyses

The analysis of safety results will follow a tiered approach (Table 14). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

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

For this protocol, there are no Tier 1 events. In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, any drug related AE, any serious AE, any Grade 3-5 AE, an AE which is both Grade 3-5 and drug-related, an AE which is both drug-related and serious, dose modification due to AE, and who discontinued due to an AE, and death will be considered Tier 2 endpoints. 95% confidence intervals (Tier 2) will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the stratified Miettinen and Nurminen method.

To properly account for the potential difference in follow-up time between the study arms, which is expected to be longer in the pembrolizumab (MK-3475) arm, AE incidence density adjusted for treatment exposure analyses may be performed as appropriate. Based on emerging external data, the supportive analysis strategy for safety parameters may be modified to improve the integrity and efficiency of the design. Should this happen, the change will be documented in the sSAP, if not in a protocol amendment, at the earliest time before any unblinding of the data.

Table 14 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE		X	X
	Any Grade 3-5 AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Any Grade3-5 and Drug-Related AE		X	X
	Dose Modification due to AE		X	X
	Discontinuation due to AE		X	X
	Death		X	X
	Specific AEs, SOCs (including ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs (incidence <4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects randomized, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables. The reasons for exclusion from the ITT population (if any) will be summarized.

8.2.6 Multiplicity

Based on emerging biomarker data external to this study, the initial alpha allocation among the primary hypotheses is revised in Amendment 13 onward to reflect the change in biomarker strategy (Section 4.2.3.1.1). The reallocation of alpha occurs after the conduct of IA1, and proper adjustment is made to maintain the control of family-wise type I error rate (FWER) with the implementation of this change. The type I error actually spent at IA1 will be kept intact and the re-allocation will only be applied to the remaining unspent alpha. The family-wise type I error rate for this study is strongly controlled at 2.5% (one-sided) across all six primary hypotheses on PFS and OS and the secondary hypothesis on ORR, with the following alpha allocation before any alpha roll-over or adjustment for actual information fraction:

- 0.1% allocated to the PFS hypothesis in all subjects (H1), with 0.02% planned at IA1;
- 1.0% allocated to the OS hypothesis in all subjects (H2), with 0.02% planned at IA1;
- 0.02% allocated to the PFS hypothesis in PD-L1 positive subjects (H3) at IA1 only;
- 0.18% allocated to the OS hypothesis in PD-L1 positive subjects (H4) at IA1 only;
- 0.38% allocated to the PFS hypothesis in PD-L1 strongly positive subjects (H5), with 0.07% planned at IA1;
- 0.82% allocated to the OS hypothesis in PD-L1 strongly positive subjects (H6), with 0.04% planned at IA1;

where the alpha spent at IA1 is based on the assumption of the planned information fractions along with the original pre-specified alpha allocation prior to Amendment 13 by the pre-specified alpha spending function of Hwang-Shih-DeCani (HSD) with gamma parameter (-4).

Under the revised alpha allocation, the alpha spending at IA2 and final analysis are determined by first applying the same HSD gamma (-4) spending function to distribute unspent alpha to IA2 and final analysis, respectively, and then incorporating them with the alpha that has already been spent at IA1 to form an interpolated alpha spending among the three analyses. For example, if the information fraction of OS at IA2 for all subjects (H2) is 75%, then the alpha spending function of HSD gamma (-4) will distribute the total of 0.98% un-spent alpha for this hypothesis under the revised strategy with cumulative alpha spending of 0.35% and 0.98% at IA2 and FA, respectively. Incorporating the planned alpha spend of 0.02% at IA1, the new cumulative alpha spending for the three analyses for all subjects becomes 0.02%, 0.37% (0.35%+0.02%) and 1.00% (0.98% + 0.02%). The corresponding stopping bounds in p-values at IA2 and FA can then be calculated. Please note the alpha spent at IA1, IA2 and final analysis will all be updated for the final report based on the actual numbers of events at each analysis and the corresponding boundaries will be adjusted

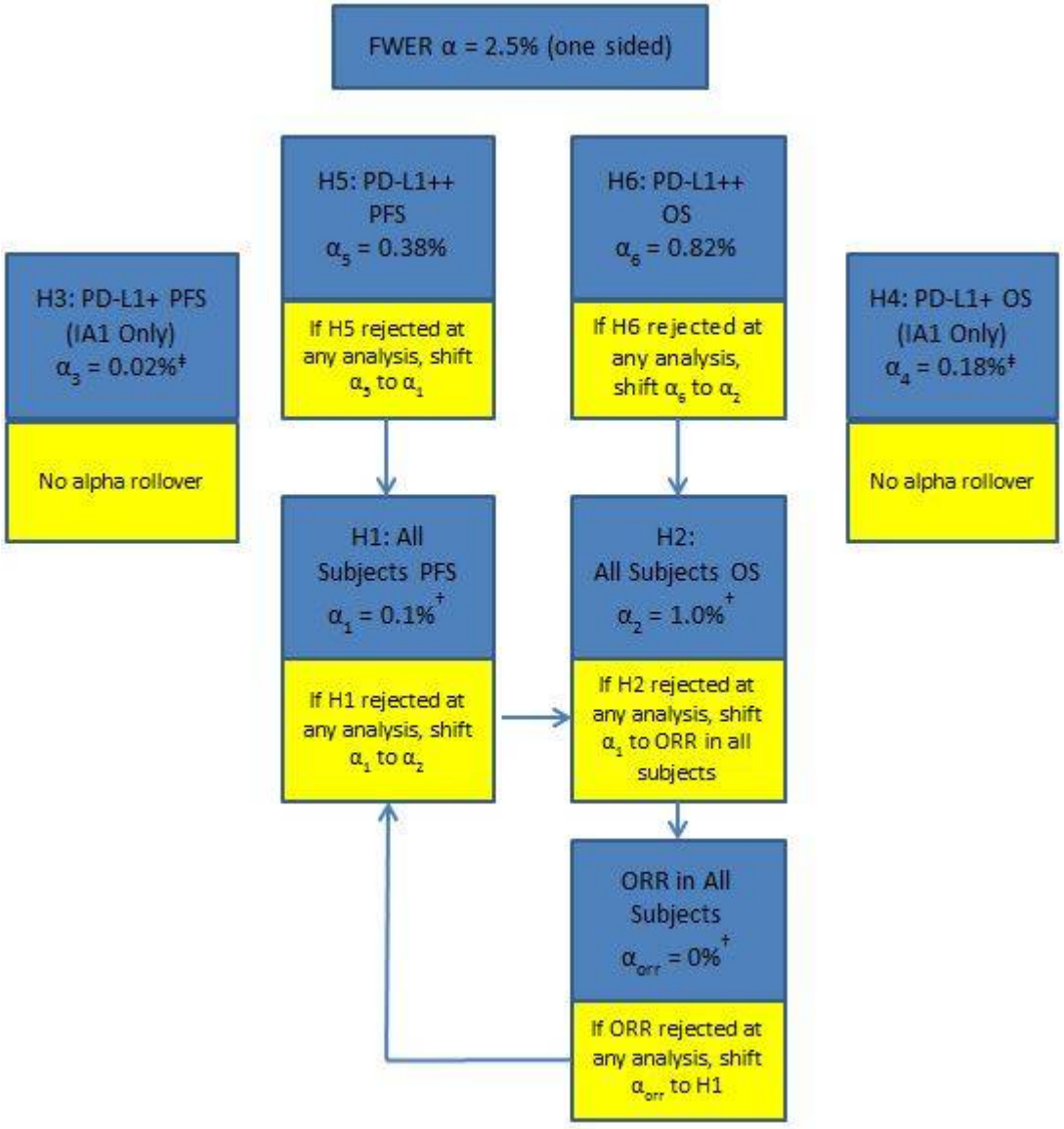
accordingly. Table 15 summarizes cumulative alpha spending at each analysis under the current alpha allocation and planned events for each analysis.

Table 15 Cumulative Alpha Spending

Hypothesis	Analysis (Planned # of events; Information Fraction)	Cumulative Alpha Spending Based on Alpha Allocation[†]
PFS		
H1 All Subjects	IA1 (273; 65%)	0.000233
	IA2 (357; 85%)	0.000540
	FA (420; 100%)	0.001000
H3 PD-L1 Positive	IA1 (151; 65%)	0.000233
	IA2 (197; 85%)	n/a
	FA (232; 100%)	n/a
H5 PD-L1 Strongly Positive	IA1 (89; 65%)	0.000698
	IA2 (116; 85%)	0.002356
	FA (137; 100%)	0.003767
OS		
H2 All Subjects	IA1 (185; 50%)	0.000238
	IA2 (277; 75%)	0.003714
	FA (370; 100%)	0.010000
H4 PD-L1 Positive	IA1 (99; 50%)	0.001788
	IA2 (149; 75%)	n/a
	FA (198; 100%)	n/a
H6 PD-L1 Strongly Positive	IA1 (55; 50%)	0.000358
	IA2 (82; 75%)	0.003155
	FA (110; 100%)	0.008212
[†]Before any alpha roll-over according to the method of Maurer and Bretz (2013).		

If the pembrolizumab (MK-3475) arm is demonstrated to have a superior PFS or OS to the control arm at any analysis, then the initially allocated alpha will be rolled from that specific hypothesis into another hypothesis following the pre-specified rules in Figure 2 using the graphical approach of Maurer and Bretz (2013) [68]. Actual alpha allocation after the roll-over will be updated based on the spending function used.

The ORR hypothesis (RECIST 1.1 per independent radiologist's review) in all subjects will be tested following a group sequential approach. The ORR hypothesis is initially assigned a type I error rate of 0% and thus, cannot be tested unless the null hypothesis of H2 (OS in all subjects) is successfully rejected. Depending on the results from the primary hypotheses testing, the ORR hypothesis can be tested at different type I error levels. The nominal type I error rates for the interim analyses and final analysis that will allow tight control of the overall type I error will be distributed by an alpha spending function of Hwang-Shih-DeCani based with gamma parameter (-4) based on the information fraction. The information fraction for ORR analysis is determined by the proportion of subjects who have "mature ORR information", defined as subjects who enrolled at least 27 weeks prior to the interim data cutoff date and thus had an opportunity to have at least 4 scheduled scans if not discontinued. Only subjects with "mature ORR information" will be included into the ORR analysis.



† Initially assigned alpha before any alpha rollover; final alpha level is subject to change with respect to actual alpha rollover.
‡ Based on assumed information fractions for demonstration purpose only and will be updated accordingly with respect to actual information.

Figure 2 Type I Error Reallocation Strategy Following Closed Testing Principle

8.2.7 Sample Size and Power Calculation

The study is event-driven and plans to randomize approximately 470 subjects with 1:1 ratio into the pembrolizumab (MK-3475) arm and the paclitaxel, docetaxel or vinflunine arm.

PFS analysis: The first PFS analysis will be conducted at the time of the first interim analysis for OS when the enrollment is completed and approximately 185 total OS events are observed for all subjects. All subjects enrolled at the time of the database lock will be included. Assuming the prevalence rates of PD-L1 positive and PD-L1 strongly positive subjects among the overall population are 55% and 33%, respectively, a sample size of 470 all subjects may provide approximately 260 PD-L1 positive subjects and 156 PD-L1 strongly positive subjects. At the time of the first PFS analysis for PD-L1 positive and all subjects, approximately 151 and 273 PFS events (per primary censoring rules), respectively, may have occurred. At this analysis the study has approximately 77% and 99% powers to demonstrate superiority in PFS of pembrolizumab (MK-3475) relative to the paclitaxel, docetaxel or vinflunine arm for PD-L1 positive and all subjects, respectively, at the pre-specified initial alpha (one-sided) level as specified in Section 8.2.6. With the assumed sample size of ~156 PD-L1 strongly positive subjects and the projected ~89 PFS events available at this time, this analysis would have ~72% power to reject the null hypothesis of PFS in PD-L1 strongly positive subjects (H5). The sample size and power calculation is based on the following assumptions: 1) progression-free survival follows an exponential distribution with a median of 4 months in the standard therapy arm, 2) the true hazard ratio between pembrolizumab (MK-3475) and standard therapy are 0.45, 0.5 and 0.5 for PD-L1 strongly positive, PD-L1 positive and all subjects, respectively, 3) an enrollment period of 12 months, and 4) a yearly dropout rate of 5%. Any change to the timing, along with its rationale, will be documented in a memo to the study file before the database lock.

The second analysis of PFS per RECIST 1.1 by independent radiology review will be performed for PD-L1 strongly positive and all subjects at the time of the second interim OS analysis when approximately 277 OS events are observed for all subjects and 82 OS events are observed for PD-L1 strongly positive subjects. The final PFS analysis will be conducted at the time of the final OS analysis when approximately 370 OS events are observed for all subjects and 110 OS events are observed for PD-L1 strongly positive subjects. It is expected that at this time approximately 137 and 420 PFS events would have been observed between the two arms for PD-L1 strongly positive and all subjects, respectively. With the above assumed PFS events, overall power of the PFS analyses for the two populations are approximately 97% and >99%, respectively. On the other hand, these numbers of events can also test the following hazard ratios with 90% power: 0.50, 0.56 and 0.65 for strongly positive, positive and all subjects, respectively.

OS analyses: The first interim analysis for OS will be conducted after the full enrollment and approximately 185 OS events are observed for all subjects. The purpose of the OS interim analysis is to determine if the risk/benefit ratio to the trial population as a whole is unacceptable and subsequently whether the trial may be stopped early at the recommendation of the DMC. Further details of the interim analysis strategy, including efficacy and futility rules, are given in Section 8.2.9.

The final OS analysis will be conducted after approximately 370 deaths in all subjects and 110 deaths in PD-L1 strongly positive subjects have occurred between the pembrolizumab (MK-3475) arm and the paclitaxel, docetaxel or vinflunine arm, if the trial is not stopped early for efficacy or futility. The timing of the final OS analysis is expected to be about 18 months after enrollment completion. With 370 events at the final analysis, the study provides 88%and 86% powers to demonstrate superiority in OS of pembrolizumab (MK-3475) relative to standard therapy at the initially allocated alpha levels before any alpha roll-over in PD-L1 strongly positive and all subjects, respectively. Conditional on different scenarios of alpha roll-overs, the overall power of OS in all subjects can be up to 92%.

The sample size and power calculation is based on the following assumptions: 1) OS follows an exponential distribution with a median of 8 months in the standard therapy arm, 2) hazard ratio between pembrolizumab (MK-3475) and standard therapy is 0.5, 0.6 and 0.7 for PD-L1 strongly positive, PD-L1 positive and all subjects, respectively, 3) an enrollment period of 12 months and a minimum of 18 months follow-up after enrollment completion; and 4) a yearly drop-out rate of 2%.

ORR analysis: As described in Section 8.2.6, the ORR hypothesis in all subjects is initially assigned a type I error rate of 0%. Conditional on the success of OS hypothesis in all subjects (H2), the ORR analysis can be tested following a group sequential approach with overall alpha rolled over from H2. The information fraction of ORR analysis will be calculated at the time of the interim analyses of OS and used by the pre-specified alpha spending function to determine nominal type I error rates at interim analyses that will allow tight control of the overall type I error rate. It is projected that the information fractions of the ORR analysis is about 60% at the time of the first OS interim analysis and 100% at the time of the second OS interim analysis. Depending on the results from the primary hypotheses on OS and PFS, the possible overall type I error rate available for the ORR analysis is ranged from 0% to 2.3% under the revised alpha allocation in this amendment. Under one specific scenario with type I error rates of 1.8%, this study can rule out a between-group ORR difference of 11.6% with ~90% power and a group sequential design of two analyses (information fractions of 60% and 100%), assuming the underlying ORR for the control group is 11.6%. If the type I error rate is only 1.0% in the above example, then the between-group ORR difference of 11.6% can be ruled out with 84% power.

The assumptions for the median PFS of 4 months, the median OS of 8 months and the ORR of 11.6% in the standard therapy arm are based on a weighted average of median PFS, median OS and ORR estimates from 2L trials of single agents [29, 30, 32, 33, 34, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62].

The sample size and power calculations were performed using the software EAST and R (package “gsDesign”).

8.2.8 Subgroup Analyses and Effect of Baseline Factors

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

- Age category (≤65 vs. >65 years)
- PD-L1 subgroup (strongly positive vs. not strongly positive)
- 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)
- Prior platinum therapy (carboplatin vs. cisplatin)
- Setting of most recent prior therapy (neoadjuvant vs. adjuvant vs. 1L metastatic vs. 2L metastatic)
- Presence or absence of liver metastases at baseline
- Baseline hemoglobin (≥ 10 g/dL vs. <10 g/dL)
- Time from completion/discontinuation of most recent prior therapy to baseline (<3months vs. ≥3 months)
- Histology (transitional cell vs. mixed transitional/non-transitional histology)
- Smoking status (never vs. former vs. current)
- Brain metastasis status (prior brain metastasis vs. no prior brain metastasis)
- Investigators' choice of paclitaxel, docetaxel or vinflunine
- Burden of disease in terms of baseline tumor volume

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 Analysis

There are two planned interim analyses for PD-L1 strongly positive and all subjects, respectively. For PD-L1 positive subjects, the hypotheses of PFS and OS will only be tested at IA1. The futility bounds of this study are non-binding and the bounds are considered guidance rather than strict bounds. Results of the interim analysis will be reviewed by an eDMC. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission if any of the six primary objectives are met at interim analysis. Further details of interim analyses are provided below and will be incorporated into the DMC Charter.

8.2.9.1 PFS and Interim OS Analysis

The first PFS and OS analysis will take place when enrollment is complete and approximately 185 OS events have been observed between the pembrolizumab (MK-3475) and standard therapy for all subjects. The first interim analysis is expected to occur ~15 months after study start.

As specified in Section 8.2.6, an interpolated alpha spending function based on HSD gamma (-4) and the revised alpha allocation is constructed to implement group sequential boundaries that control the type I error rates for PFS hypotheses H1 and H5. The pembrolizumab (MK-3475) arm will be compared to the paclitaxel, docetaxel or vinflunine arm. At the first interim analysis, an approximate observed HR of ~0.655 or less would demonstrate PFS superiority for all subjects at $\alpha = 0.02\%$ (one-sided). This hazard ratio corresponds to approximately 2.1-month improvement over the median PFS of 4 months in the paclitaxel, docetaxel or vinflunine arm. However, because immunotherapies have been shown to impact PFS curves at later time points (i.e., the tail of the curve), the observed difference in medians may be an underrepresentation of the treatment effect. If there are fewer than or more than the projected number of PFS events at the time of the first interim analysis, the alpha functions will be adjusted to accommodate the revised interim analysis timing using the fraction of the estimated total PFS events.

Similarly, for both OS hypotheses (H2 and H6), an interpolated alpha spending function based on HSD gamma (-4) and the revised alpha allocation is constructed to implement group sequential boundaries that control the type I error rate. Please see Section 8.2.6 for details. The non-binding futility analyses are also planned with a beta spending function of HSD gamma (-20). Table 16 and Table 17 summarize the efficacy and futility rules for the OS analyses.

Approximately 185 OS events will be observed for all subjects at the time of the first interim analysis and an interim OS analysis will be conducted at the level determined by the spending function boundaries and the actual number of OS events. As shown in Table 16 an approximate observed hazard ratio < ~0.598, i.e., at least 5.4-month improvement in median OS, would demonstrate OS superiority at the interim analysis for all subjects (H2). A futility analysis will be conducted at the same time and an observed hazard ratio > 1.30 will approximately meet the criterion for futility. The boundaries for OS hypothesis testing will be re-calculated if the actual monitoring schedule is altered. If there are more than 185 OS events for all subjects at the time of the first interim analysis, the alpha and beta spending functions will be adjusted to accommodate the revised interim analysis timing using the fraction of planned total OS events in the overall population that drives timing of analyses.

Table 16 summarizes the timing, sample size and decision guidance for the planned PFS and OS analyses (IA1, IA2 and Final Analysis) for PD-L1 strongly positive, positive and all subjects under one hypothetical scenario with initially assigned type I rates only. Table 17 summarizes the futility boundaries of the OS hypotheses at the interim analysis. The actual boundaries will be determined from the actual number of PFS or OS events at the time of the specified IA using the alpha- and beta-spending functions.

Table 16 Summary of Timing, Sample Size and Decision Guidance at the Planned PFS and OS Analyses

Analysis	Criteria for Conduct of Analysis (Projected timing)	Value	Approx. Number of Events	Efficacy Boundary†		
				Z Statistic	p-value (1-sided) at Boundary	Approx. Observed HR at Boundary
IA 1: PFS (H1, H3, H5) OS (H2, H4, H6)	Full enrollment ~ 185 OS events (50% information) for all subjects	H1 PFS All Subjects	273	3.500	0.0002	0.655
		H2 OS All Subjects	185	3.494	0.0002	0.598
		H3 PFS PDL1 Positive	151	3.500	0.0002	0.566
		H4 OS PDL1 Positive	99	2.913	0.0018	0.557
		H5 PFS PDL1 Strongly Positive	89	3.196	0.0007	0.508
		H6 OS PDL1 Strongly Positive	55	3.384	0.0004	0.402
IA 2: PFS (H1 and H5) OS (H2 and H6)	~277 OS events (75% information) for all subjects and ~ 82 OS events (75% information) for PDL1 Strongly Positive Subjects	H1 PFS All Subjects	357	3.345	0.0004	0.702
		H2 OS All Subjects	277	2.683	0.0036	0.725
		H5 PFS PDL1 Strongly Positive	116	2.865	0.0021	0.588
		H6 OS PDL1 Strongly Positive	82	2.745	0.0030	0.546
Final Analysis: PFS (H1and H5) OS (H2 and H6)	~ 370 OS events for all subjects and ~110 OS events for PDL1 Strongly Positive Subjects	H1 PFS All Subjects	420	3.182	0.0007	0.733
		H2 OS All Subjects	370	2.381	0.0086	0.781
		H5 PFS PDL1 Strongly Positive	137	2.782	0.0027	0.622
		H6 OS PDL1 Strongly Positive	110	2.459	0.0070	0.625

† Based on initially assigned type I error rate before any alpha roll-over and projected number of events at study mile stones. Actual efficacy boundaries will be based on actual numbers of events available at study milestones.

Table 17 Summary of Futility Boundary at the Planned Interim Analyses on OS

Analysis	Value	Approx. Number of Events	Non-binding Futility Boundary		
			Z Statistic	p-value (1-sided) at Boundary	Approx. Observed HR at Boundary
IA 1	H2 OS All Subjects	185	-1.767	0.961	1.297
	H4 OS PDL1 Positive	99	-1.938	0.974	1.476
	H6 OS PDL1 Strongly Positive	55	-1.715	0.957	1.587
IA 2	H2 OS All Subjects	277	0.100	0.460	0.988
	H6 OS PDL1 Strongly Positive	82	0.148	0.441	0.968
For demonstration purpose, the beta in this table is based on initially assigned alpha only; actual futility bounds will be updated if overall beta is changed with respect to alpha roll-over.					

If a null hypothesis is rejected, the alpha can be rolled over to another hypothesis following the pre-specified rules in Section 8.2.6. The revised decision guidance for PFS and OS with respect to the rolled-over alpha from the rejection of other hypothesis(es) is summarized in Table 18 below. Please note that the actual boundaries for the alpha spending function will be adjusted based on the actual number of events and/or ORR information fractions observed at the time of the corresponding analysis.

Table 18 Summary of Revised Efficacy Decision Guidance (Selected Scenarios)

Analysis	Value	Updated Efficacy Boundary (after alpha roll-over†)		
		Z Statistic	p-value (1-sided) at Boundary	Approx. Observed HR or ORR-Difference‡ at Boundary
If Null Hypotheses of H5 and H6 are Rejected				
IA 1	H1 PFS All Subjects	3.060	0.0011	0.691
	H2 OS All Subjects	3.331	0.0004	0.613
IA 2	H1 PFS All Subjects	2.870	0.0021	0.738
	H2 OS All Subjects	2.475	0.0067	0.743
Final Analysis	H1 PFS All Subjects	2.677	0.0037	0.770
	H2 OS All Subjects	2.143	0.0161	0.800
If Null Hypotheses of H1, H5 and H6 are Rejected				
IA 1	H2 OS All Subjects	3.265	0.0005	0.619
IA 2	H2 OS All Subjects	2.390	0.0084	0.751
Final Analysis	H2 OS All Subjects	2.045	0.0204	0.809
If Null Hypothesis of H2 is Rejected				
IA 1	ORR All Subjects	2.899	0.0019	12.9%
IA 2	ORR All Subjects	2.358	0.0092	8.2%
Final Analysis	ORR All Subjects	2.358	0.0092	8.2%
If Null Hypothesis of H2 and H6 are Rejected				
IA 1	ORR All Subjects	2.254	0.0121	8.2%
IA 2	ORR All Subjects	2.164	0.0152	7.5%
Final Analysis	ORR All Subjects	2.164	0.0152	7.5%
†Only selective scenarios are demonstrated in this table. ‡Assume the underlying ORRs in the control and pembrolizumab groups are 11.6% and 23.2%, respectively.				

8.2.9.2 Final OS Analysis

The final analysis will take place when approximately 370 deaths in all subjects and 110 deaths in PD-L1 strongly positive subjects have occurred between the pembrolizumab (MK-3475) arm and the paclitaxel, docetaxel or vinflunine arm in all subjects which is expected to occur ~30 months after study start. If the timing of events occurs faster than anticipated, the test boundary at the final analysis will be adjusted to use the remaining Type I error not spent at earlier analyses. A 95% confidence interval will be provided for the hazard ratio to characterize the OS effect in case the superiority is not demonstrated.

8.2.10 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the study. Compliance with trial treatment administration will be measured by subjects: 1) receiving unscheduled study agent infusions/injections; 2) missing an infusion/injection. Numbers and percentages of subjects and infusion/injection visits with any deviation in these measures will be reported for the ITT population.

8.2.11 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles. Dose intensity will also be summarized as appropriate.

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 19.

Table 19 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab (MK-3475) 100 mg/ 4 mL	Solution for Infusion
Vinflunine 250 mg/ 10 mL	Solution for Infusion
Docetaxel 80 mg/4 mL	Solution for Infusion
Paclitaxel 100 mg/ 16.7 mL	Solution for Infusion

The paclitaxel, vinflunine and docetaxel will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements. All other products will be provided locally by the trial site, subsidiary or designee.

Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible to record the lot number, manufacturer and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

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

Subjects will receive open label pembrolizumab (MK-3475) vials, vinflunine kits, docetaxel kits and paclitaxel kits. Each kit of vinflunine, docetaxel and paclitaxel will contain one vial.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return.

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.

11.0 LIST OF REFERENCES

1. Disis ML. Immune regulation of cancer. J Clin Oncol 2010; 28(29):4531-8.

2. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8):793-800.

3. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nature 2002;2:116-26.

4. Brown JA, Dorfman DM, Ma F-R, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 2003;170:1257-66.

5. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

6. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Caner Res 2007;13(6):1757-61.

7. Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007;26:373-400.

8. Usubütün A, Ayhan A, Uygur MC, Ozen H, Toklu C, Ruacan S. Prognostic factors in renal cell carcinoma. J Exp Clin Cancer Res 1998;17(1):77-81.

9. Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund L-T. Prognostic effect of epithelial and stromal symphocyte infiltration in non-small cell lung cancer. Clin Cancer Res 2008;14(16):5220-7.

10. Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen p, Lardon F, et al. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol 2010;11:19.

11. Diez M, Pollán M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, et al. Histopathologic prognostic score in colorectal adenocarcinomas. Anticancer Res 1998;18:689-94.

12. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313:1960-4.

13. Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol 2010;15:544-51.

14. Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, et al. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori 2008;94:426-30.

15. Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. J Cutan Pathol 2010;37(Suppl 1):48-53.

16. Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. Lancet 2009;10:840-841.

17. Hillen F, Baeten CIM, van de Winkel A, Creytens D, van der Schaft DWJ, Winnepenninckx V, et al. Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. Cancer Immunol Immunother 2008;57:97-106.

18. Lee HE, Chae SW, Lee YJ, Kim MA, Lee HS, Lee BL, et al. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. Br J Cancer 2008;99(10):1704-11.

19. Leffers N, Gooden MJM, de Jong RA, Hoogeboom B-N, ten Hoor KA, Hollema H, et al. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother 2009;58:449-59.

20. Nishimura H, Honjo T, Minato N. Facilitation of β selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med 2000;191(5):891-7.

21. Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, et al. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Intern 2010;107:1500-6.

22. Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma V-M. Prognostic value of tumour-infiltrating lynmphocytes (TILs) in colorectal cancer. J Pathol 1997;182:318-24.

23. Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.

24. Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.

25. Ölcher M, Braun M, Friedrichs N, Rudlowski C, Bercht E, Fimmers R, et al. Foxp3+ cell infiltration and granzyme B+/Foxp3+ cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59:909-19.

26. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. PNAS 2001;98(24):13866-71.

27. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisted. Annu Rev Immunol 2005;23:515-48.

28. Jemal A, Bray F, Center MM, Ferlay J, Ward E, and Forman D. Global Cancer Statistics. CA Cancer J Clin 2011;61:69-90.

29. Vaughn DJ, Broome CM, Hussain M, Gutheil JC and Markowitz AB. Phase II Trial of Weekly Paclitaxel in Patients With Previously Treated Advanced Urothelial Cancer. Journal of Clinical Oncology. 2002;20(4):937-940.

30. McCaffrey JA, Hilton S, Mazumdar M, Sadan S, Kelly WK, Scher HI and Bajorin DF. Phase II Trial of Docetaxel in Patients With Advanced or Metastatic Transitional-Cell Carcinoma. Journal of Clinical Oncology. 1997;15(5):1853-1857.

31. Witte RS, Elson P, Bono B, Knop R, Richardson RR, Dreicer R, and Loehrer Sr. PJ. Journal of Clinical Oncology. 1997;15(2):589-593.

32. Sweeney CJ, Roth BJ, Kabbinavar FF, Vaughn DJ, Arning M, Curiel RE, Obasaju CK, et al. Phase II Study of Pemetrexed for Second-Line Treatment of Transitional Cell Cancer of the Urothelium. Journal of Clinical Oncology. 2006;24:3451-3457.

33. Joly F, Houede N, Noal S, Chevreau C, Priou F, Chinet-Charrot P, Rolland F, Flechon A, et al. Clinical Genitourinary Cancer. 2009;7(2):E28-E33.

34. Bellmunt J, Theodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, Caty A, Carles J, et al. Journal of Clinical Oncology. 2009;27(27):4454-4461.

35. Sonpavde G, Sternberg CN, Rosenberg JE, Hahn NM, Galsky MD, and Vogelzang NJ. Second-line systemic therapy and emerging drugs for metastatic transitional-cell carcinoma of the urothelium. Lancet Oncol. 2010;11(9):861-870.

36. NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 2.2014, NCCN.org

37. Bellmunt J, von der Maase H, Mead GM, Skoneczna I, De Santis M, Daugaard G, Boehle A, Chevreau C, et al. Randomized Phase III Study Comparing Paclitaxel/Cisplatin/Gemcitabine and Gemcitabine/Cisplatin in Patients With Locally Advanced or Metastatic Urothelial Cancer Without Prior Systemic Therapy: EORTC Intergroup Study 30987. Journal of Clinical Oncology. 2012;30:1107-1113.

38. Wong Y-N, Litwin S, Vaughn D, Cohen S, Plimack ER, Lee J, Song W, Dabrow M, et al. Phase II Trial of Cetuximab With or Without Paclitaxel in Patients With Advanced Urothelial Tract Carcinoma. Journal of Clinical Oncology. 2012;30(28):3545-3551.

39. Rabin R and de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-343.

40. Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985; 4: 213–226.

41. Finkelstein DM (1986). A proportional hazards model for interval-censored failure time data. *Biometrics* **42,** 845-54.

42. Akaza H, Naito S, Usami M, Miki T, Miyanaga N, Taniai H and the Japanese Gemcitabine Study Group. Efficacy and Safety of Gemcitabine Monotherapy in Patients with Transitional Cell Carcinoma after Cisplatin-Containing Therapy: A Japanese Experience. Jpn J Clan Oncol 2007;37(3)201-206.

43. Albers P Onkologie 2002 Albers P, Siener R, Haertlein M, Fallahi M, Haeutle D, Perabo FGE, Steiner G, Blatter J and Mueller SC. Gemcitabine Monotherapy as Second-Line Treatment in Cisplatin-Refractory Transitional Cell Carcinoma – Prognostic Factors for Response and Improvement of Quality of Life. Onkologie 2002;25:47-52.

44. Bellmunt J Cancer Invest 2002 Bellmunt J, Cos J, Cleries R, Perez M, Ribas A, Eres N, Murio JE, Margarit C, and Baselga J. Feasibility trial of methotrexate-paclitaxel as a second line therapy in advance urothelial cancer. Cancer Invest 2002;20(5-6):673-685.

45. Culine S, Theodore C, De Santis M, Bui B, Demkow T, Lorenz J, Rolland F, Delgado F-M, et al. A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. British Journal of Cancer 2006;94:1395-1401.

46. Dreicer R, Li S, Manola J, Haas N, Roth B, and Wilding G. Phase 2 Trial of Epothilone B Analog BMS-247550 (Ixabepilone) in Advanced Carcinoma of the Urothelium (E3800): A Trial of the Eastern Cooperative Oncology Group. Cancer 2007; 100:759-63.

47. Fechner G, Siener R, Reimann M, Kobalz L, Albers P, and Members of the German Association of Urologic Oncology (AUO) Bladder Cancer Study Group. Randomised phase II trial of gemcitabine and paclitaxel second-line chemotherapy in patients with transitional cell carcinoma (AUO Trial AB 20/99). J Clin Pract 2006;60(1):27-31.

48. Gallagher DJ, Milowsky MI, Gerst SR, Ishill N, Riches J, Regazzi A, Boyle MG, Trout A, et al. Phase II Study of Sunitinib in Patients With Metastatic Urothelial Cancer. Journal of Clinical Oncology 2010;28(8):1373-1379.

49. Kanai K, Kikuchi E, Ohigashi T, Miyajima A, Nakagawa K, Nakashima J, and Oya M. Gemcitabine and paclitaxel chemotherapy for advanced urothelial carcinoma in patients who have received prior cisplatin-based chemotherapy. Int J Clin Oncol 2008;(13):510-514.

50. Ko Y-J, Canil CM, Mukherjee SD, Winquist E, Elser C, Eisen A, Reaume MN, Zhang L, et al. Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicenter, phase 2 study. Lancet Oncology 2013;14(8):769-776.

51. Krege S, Rembrink V, Borgermann CH, Otto T, and Rubben H. Docetaxel and Ifosfamide as Second Line Treatment for Patients with Advanced or Metastatic Urothelial Cancer After Failure of Platinum Chemotherapy: A Phase 2 Study. The Journal of Urology 2001;165:67-71.

52. Lin C-C, Hsu C-H, Huang C-Y, Keng J-Y, Tsai Y-C, Huang K-H, Cheng A-L and Pu Y-S. Gemcitabine and ifosfamide as a second-line treatment for cisplatin-refractory metastatic urothelial carcinoma: a phase II study. Anti-Cancer Drugs 2007;18:487-491.

53. Lorusso V, Pollera CF, Antimi M, Luporini G, Gridelli C, Frassineti GL, Oliva C, Pacini M, et al. A Phase II Study of Gemcitabine in Patients with Transitional Cell Carcinoma of the Urinary Tract Previously Treated with Platinum. Eu J Can 1998;34(8):1208-1212.

54. Milowsky MI, Iyer G, Regazzi AM, Al-Ahmade H, Gerst SR, Ostrovnaya I, Gellert LL, Kaplan R, et al. Phase II study of everolimus in metastatic urothelial cancer. BJU 2013;112:462-470.

55. Prozanto P, Vigani A, Pensa F, Vanoli M, Tani F, and Vaira F. Second Line Chemotherapy with Ifosfamide as Outpatient Treatment for Advanced Bladder Cancer. Am J of Clin Oncol 1997; 20(5):519-521.

56. Sternberg CN, de Mulder PHM, Theodore C, Fossa SD, Van Oosterom AT, Witjes F, Spina M, van Groeningen CJ, et al. Randomized Phase III Trial of High-Dose-Intensity Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (MVAC) Chemotherapy and Recombinant Human Granulocyte Colony-Stimulating Factor Versus Classic MVAC in Advanced Urothelial Tract Tumors: European Organization for Research and Treatment of Cancer Protocol No. 30924. Journal of Clinical Oncology. 2001;19:2638-2646.

57. Suyama T, Ueda T, Fukasawa S, Imamura Y, Nakamura K, Miyasaka K, Sazuka T, Egoshi K-I, et al. Combination of Gemcitabine and Paclitaxel as Second-line Chemotherapy for Advanced Urothelial Carcinoma. Jpn J Clin Oncol 2009;39(4):244-250.

58. Sweeney CJ, Williams SD, Finch DE, Bihrle R, Foster RS, Collins M, Fox S, Roth BJ. A Phase II Study of Paclitaxel and Ifosfamide for Patients with Advanced Refractory Carcinoma of the Urothelium. Cancer 1999;86:514-518.

59. Takahashi T, Higashi S, Nishiyama H, Segawa T, Nakamura E, Kinoshita H, Itoh N, Yamamoto S, et al. Biweekly Paclitaxel and Gemcitabine for Patients with Advanced Urothelial Cancer Ineligible for Cisplatin-Based Regimen. Jpn J Clin Oncol 2006;36(2):104-108.

60. Vaishampayan UN, Faulkner JR, Small EJ, Redman BG, Keiser WL, Petrylak DP, Crawford ED. Phase II Trial of Carboplatin and Paclitaxel in Cisplatin-Pretreated Advanced Transitional Cell Carcinoma. Cancer 2005;104:1627-1632.

61. Vaughn DJ, Srinivas S, Stadler WM, Pili R, Petrylak D, Sternberg CN, Smith, DC, Ringulette S, et al. Vinflunine in Platinum-Pretreated Patients With Locally Advanced or Metastatic Urothelial Carcinoma. Cancer 2009;115:4110-7.

62. Witte RS, Manola J, Burch PA, Kuzel T, Weinshel EL, and Loeher, Sr. PJ. Topotecan in previously treated advanced urothelial carcinoma: an ECOG phase II trial. Investigational New Drugs 1998;16:191-195.

63. Chen C, Beckman RA. Hypothesis testing in a confirmatory phase III trial with a possible subset effect. Stat Biopharm Res 2009;1(4):431-40.

64. Wang S-J, O'Neil RT, Hung HMJ. Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset. Pharmaceut Statist 2007;6:227-44.

65. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 2004;291(3):335-42.

66. Harrington DP, Fleming TR. A class of rank test procedures for censored survival data. Biometrika, 1982; 69 (3): 553-566.

67. Sonpavde, G., Pond, G. R., Fougeray, R., Choueiri, T. K., Qu, A. Q., Vaughn, D. J., et al. Time from prior chemotherapy enhances prognostic risk grouping in the second-line setting of advanced urothelial carcinoma: a retrospective analysis of pooled, prospective phase 2 trials. *European urology* 2013; *63*(4): 717-723.

68. Maurer, W., and Bretz, F. Multiple testing in group sequential trials using graphical approaches. Statistics in Biopharmaceutical Research 2013; 5.4 :311-320.

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, RNA, serum, plasma, and tumor 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, RNA, serum, plasma, and tumor 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 (PPD) 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

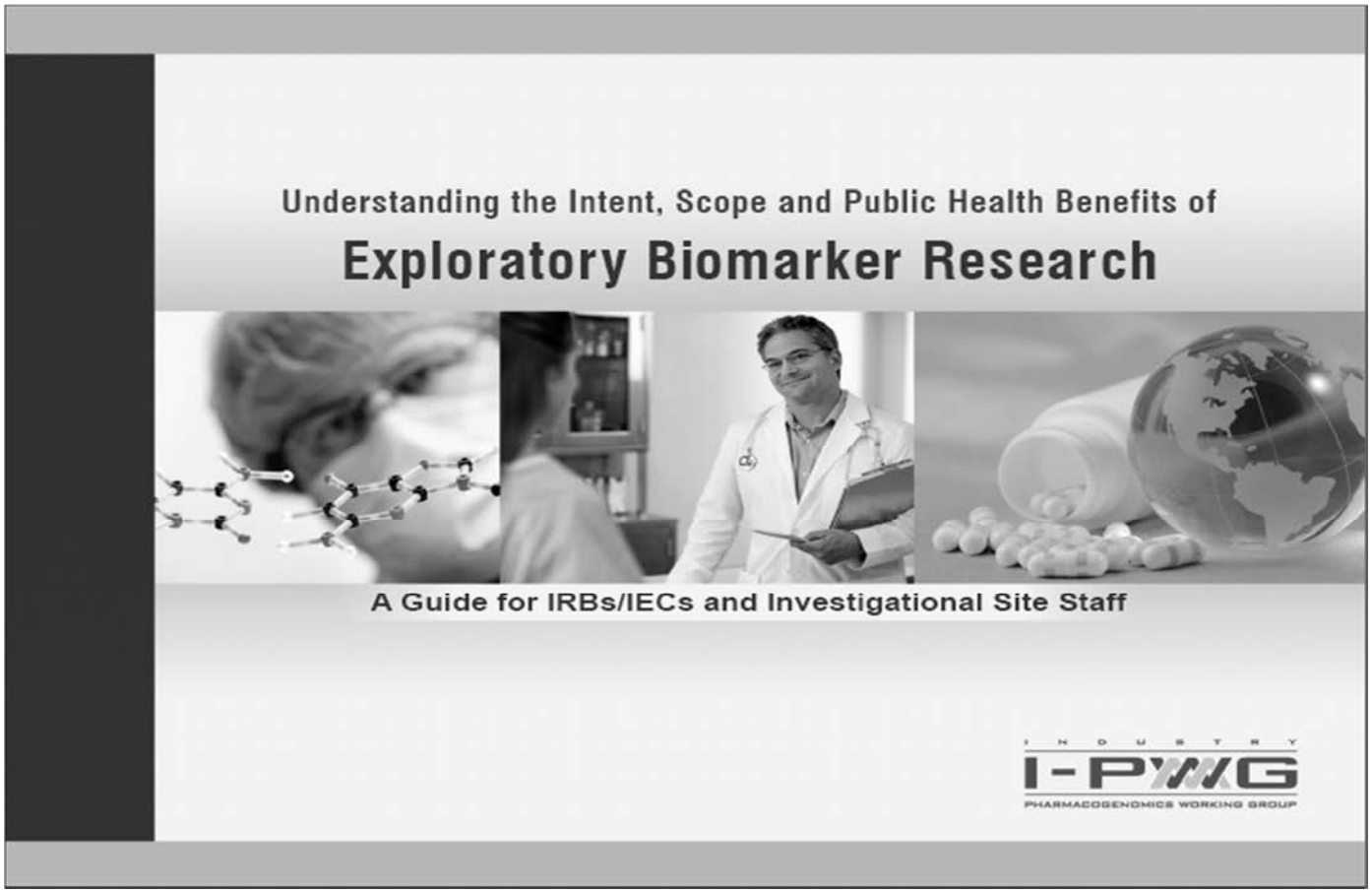
Any questions related to the future biomedical research should be e-mailed directly to PPD.

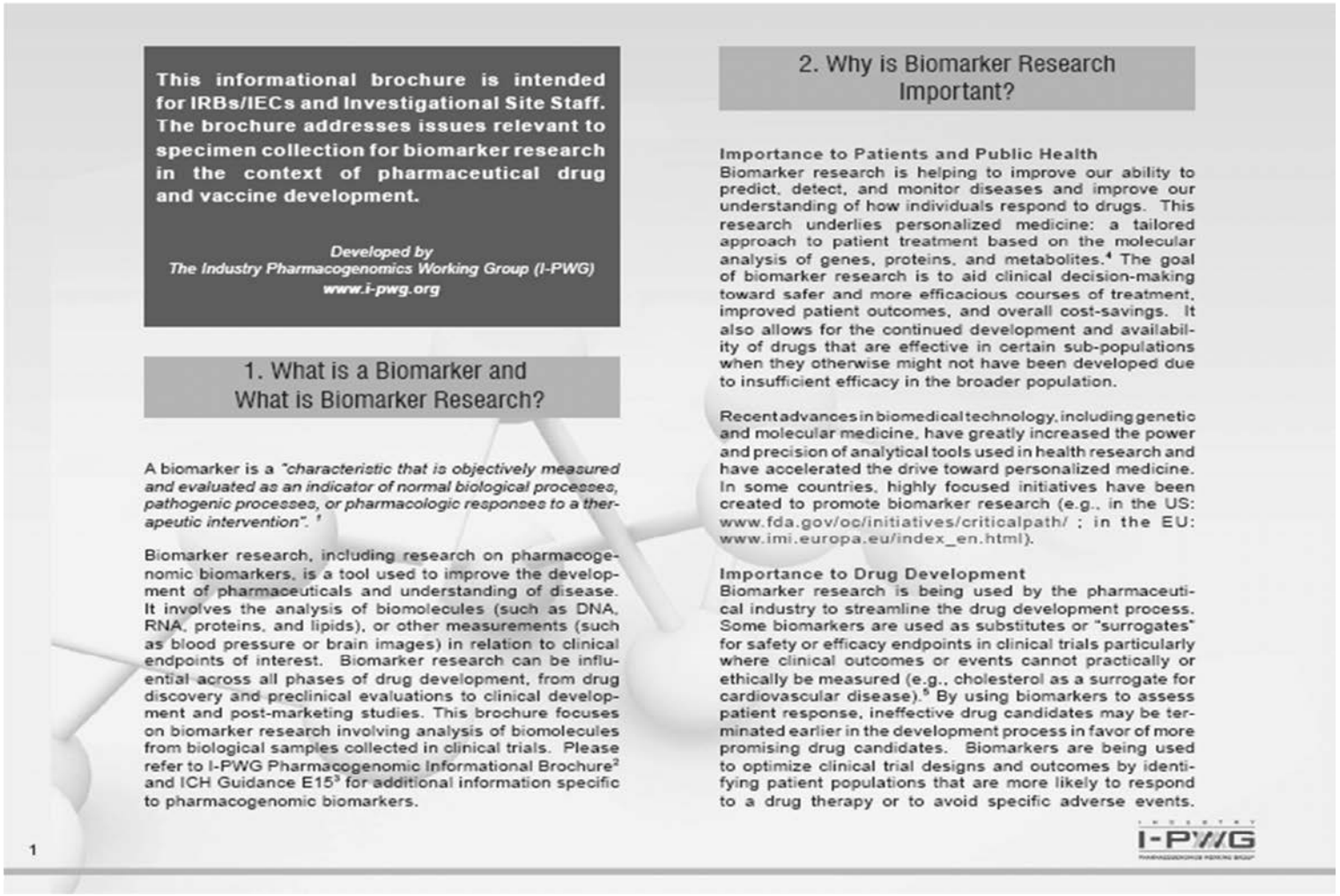
14. References

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

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

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





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

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

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

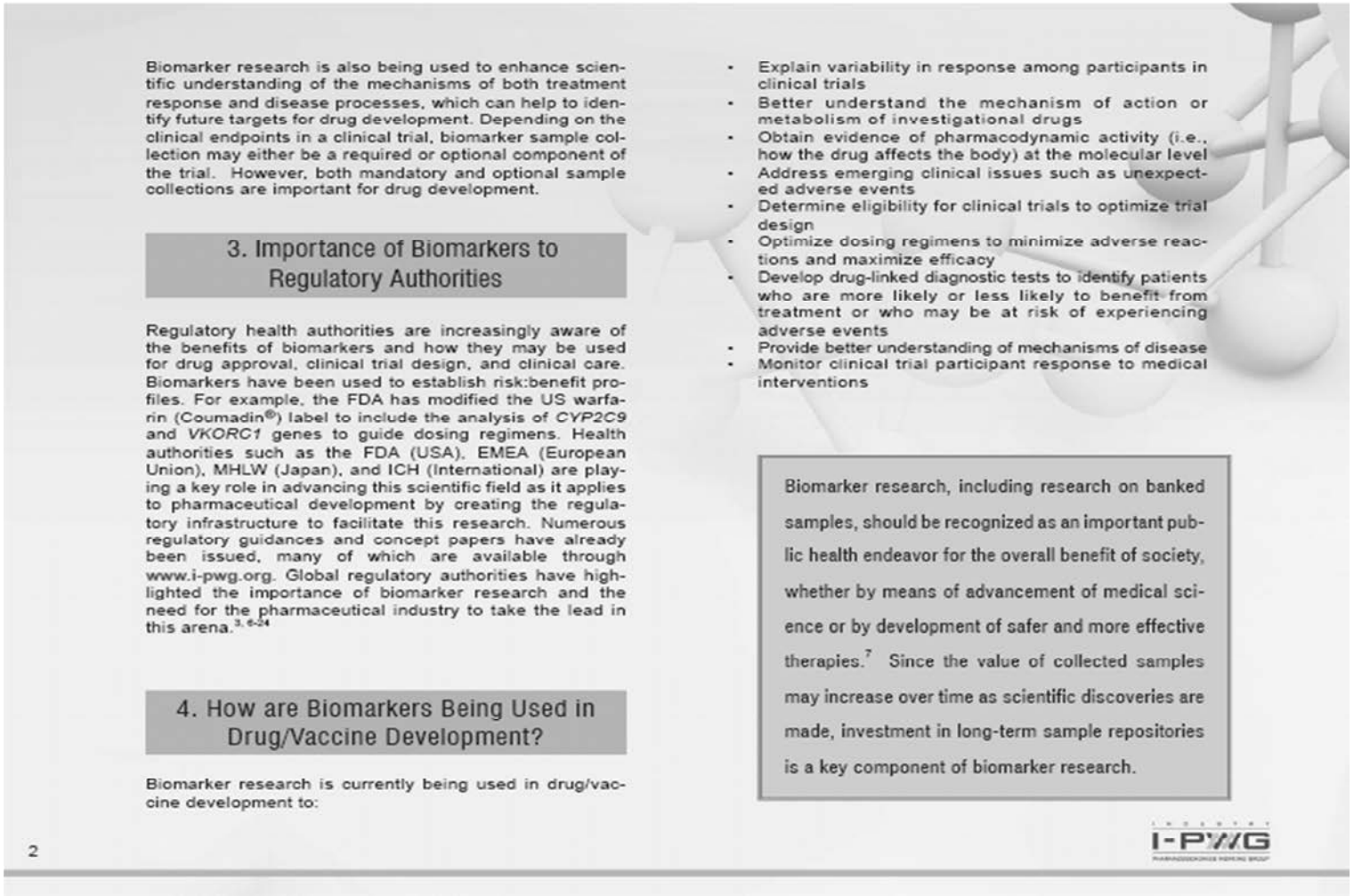
Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to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

Importance to Drug Development

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

I-PWG

1



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?

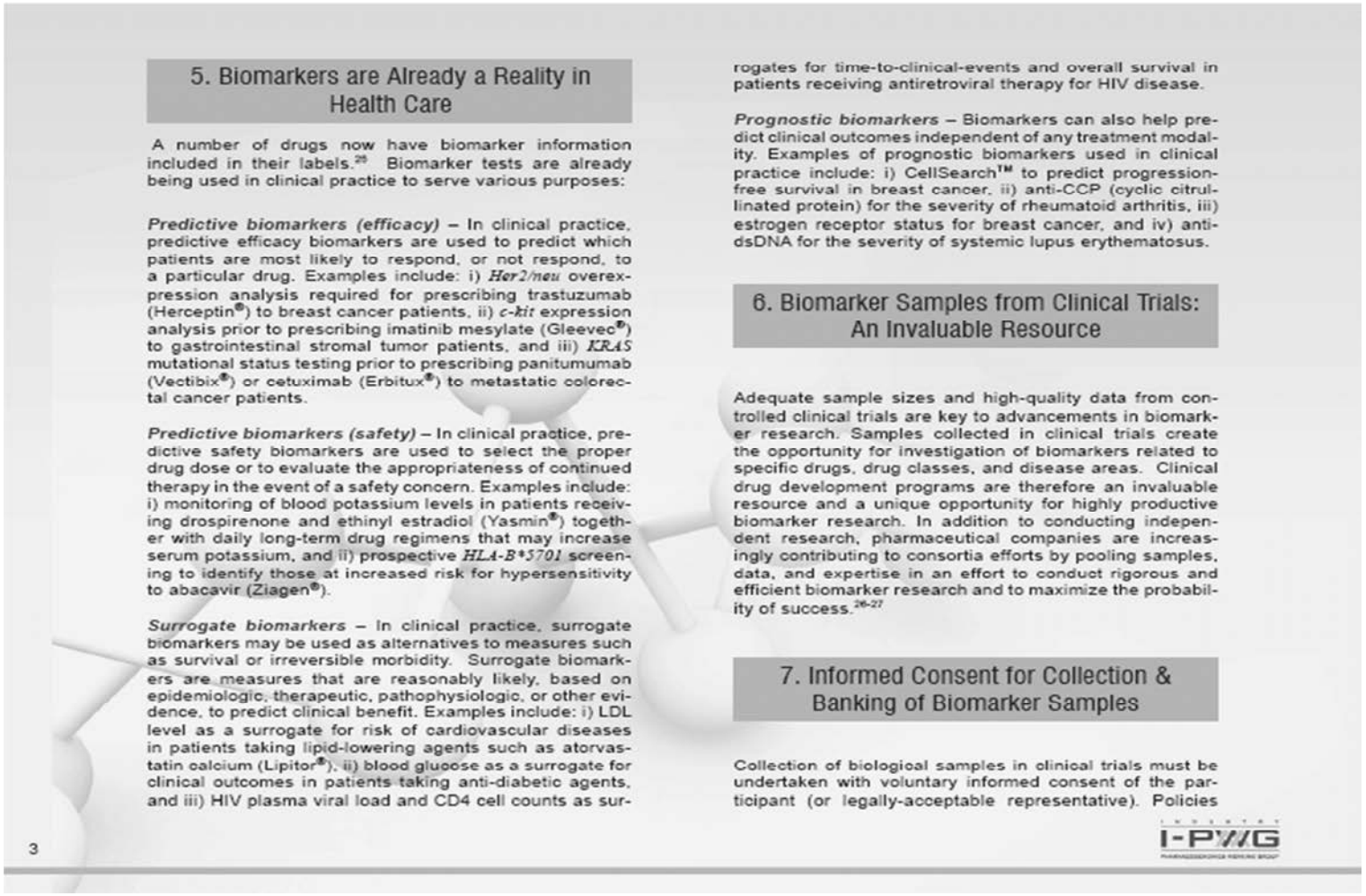
Biomarker research is currently being used in drug/vaccine development to:

- 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.

I-PWG

2



5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

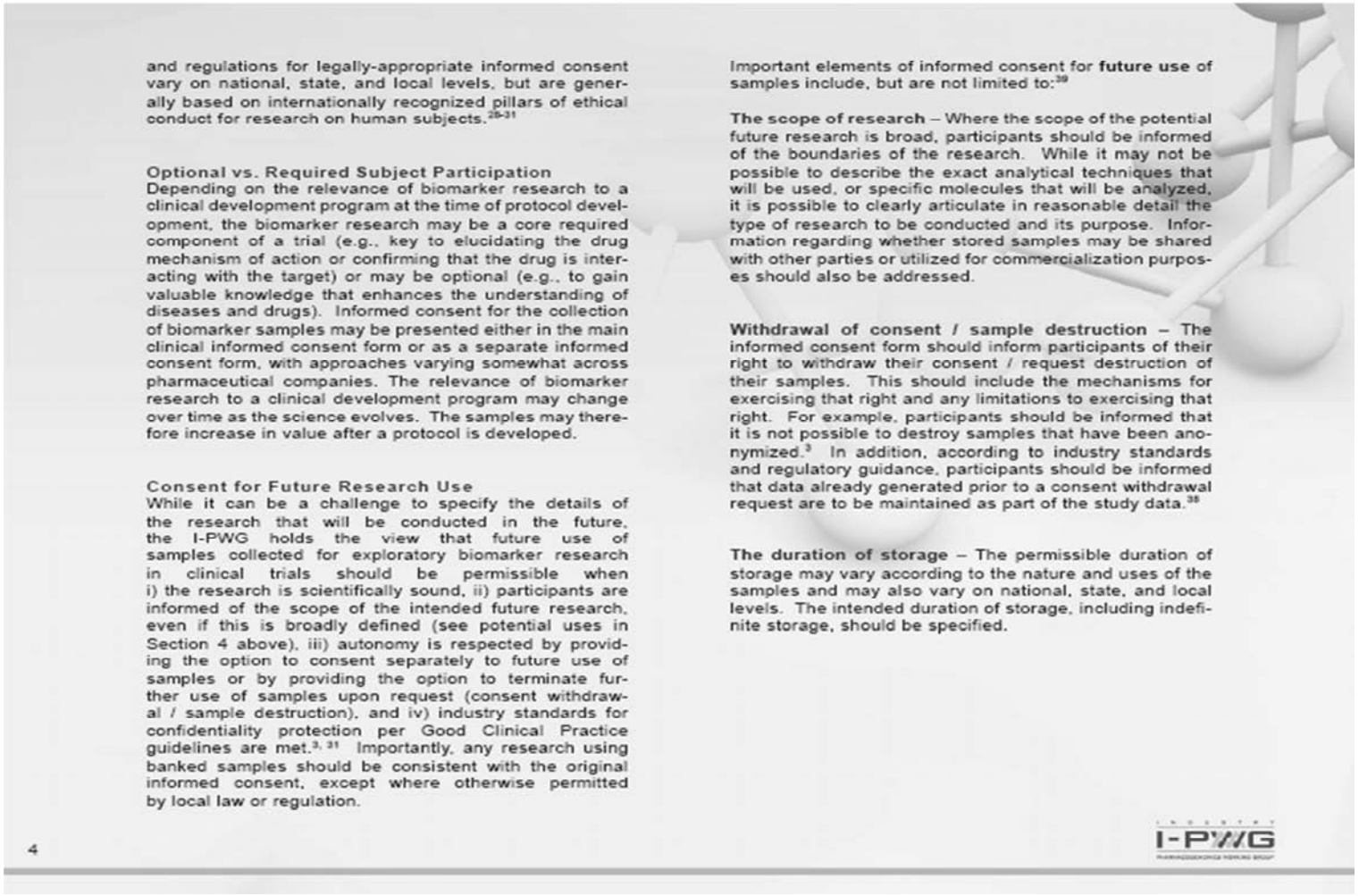
Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

3

I-PWG



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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

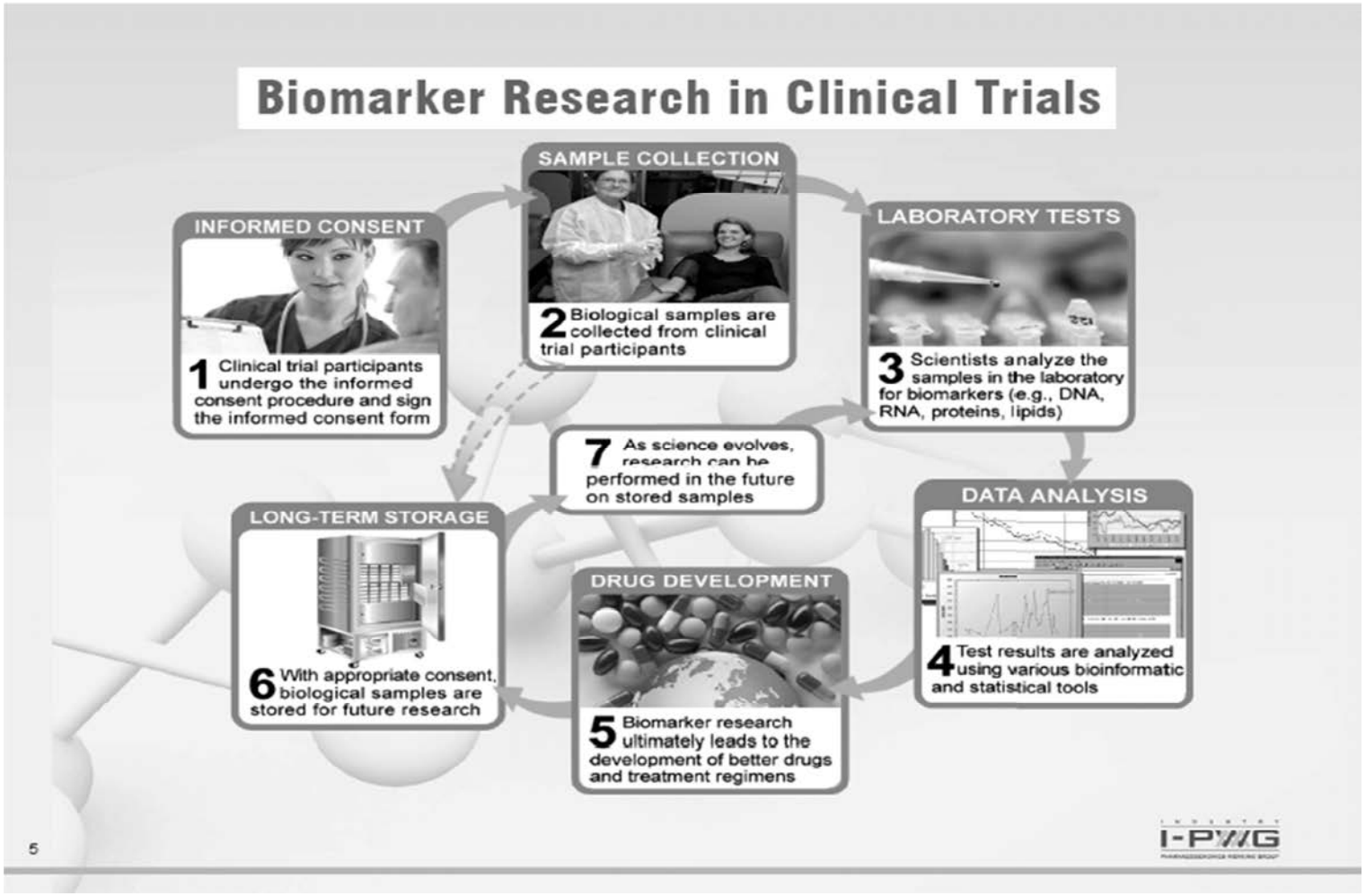
The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible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

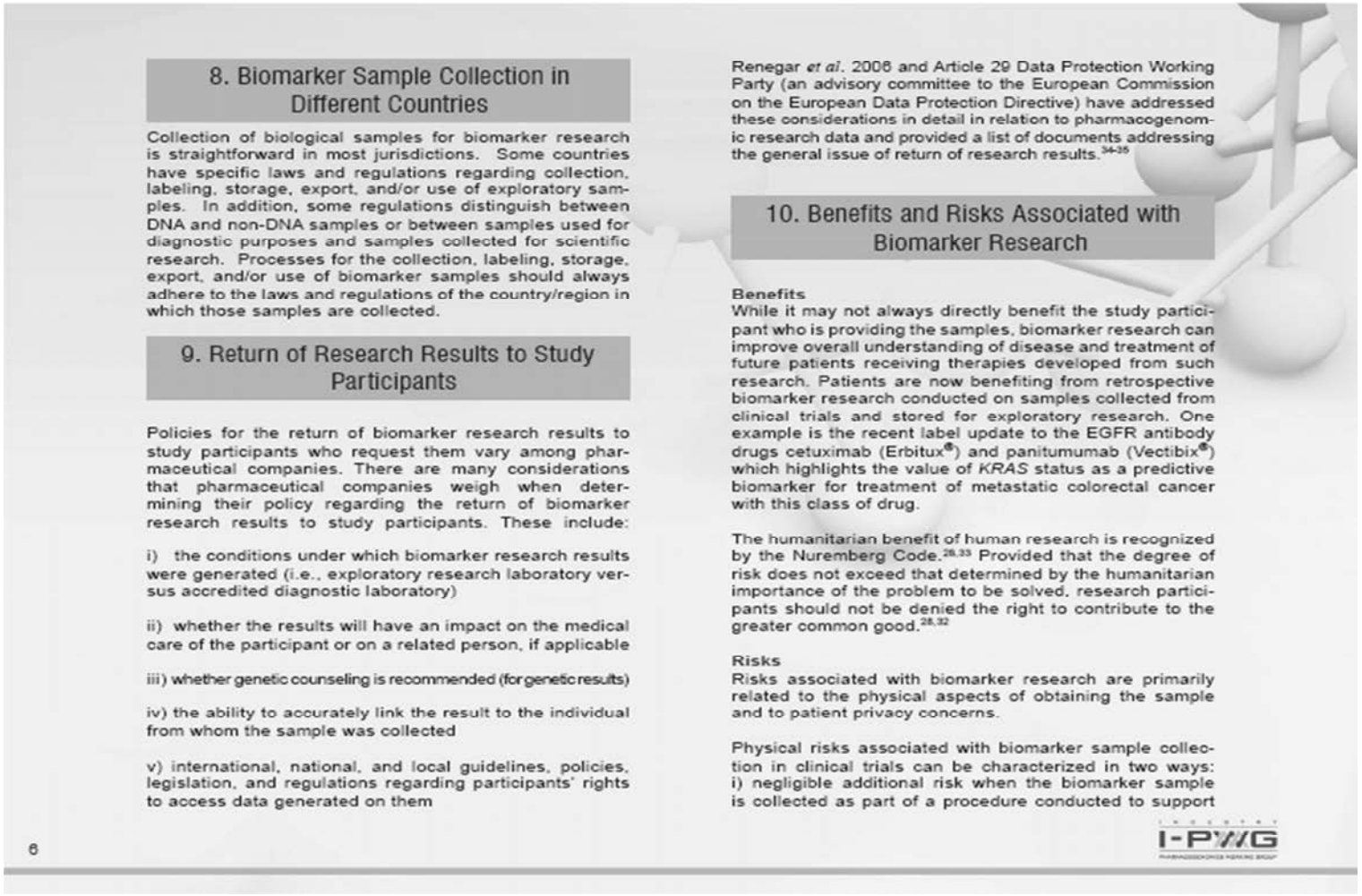
Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants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

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

4

I-PWG


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



8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

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

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

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

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

6

I-PWG

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

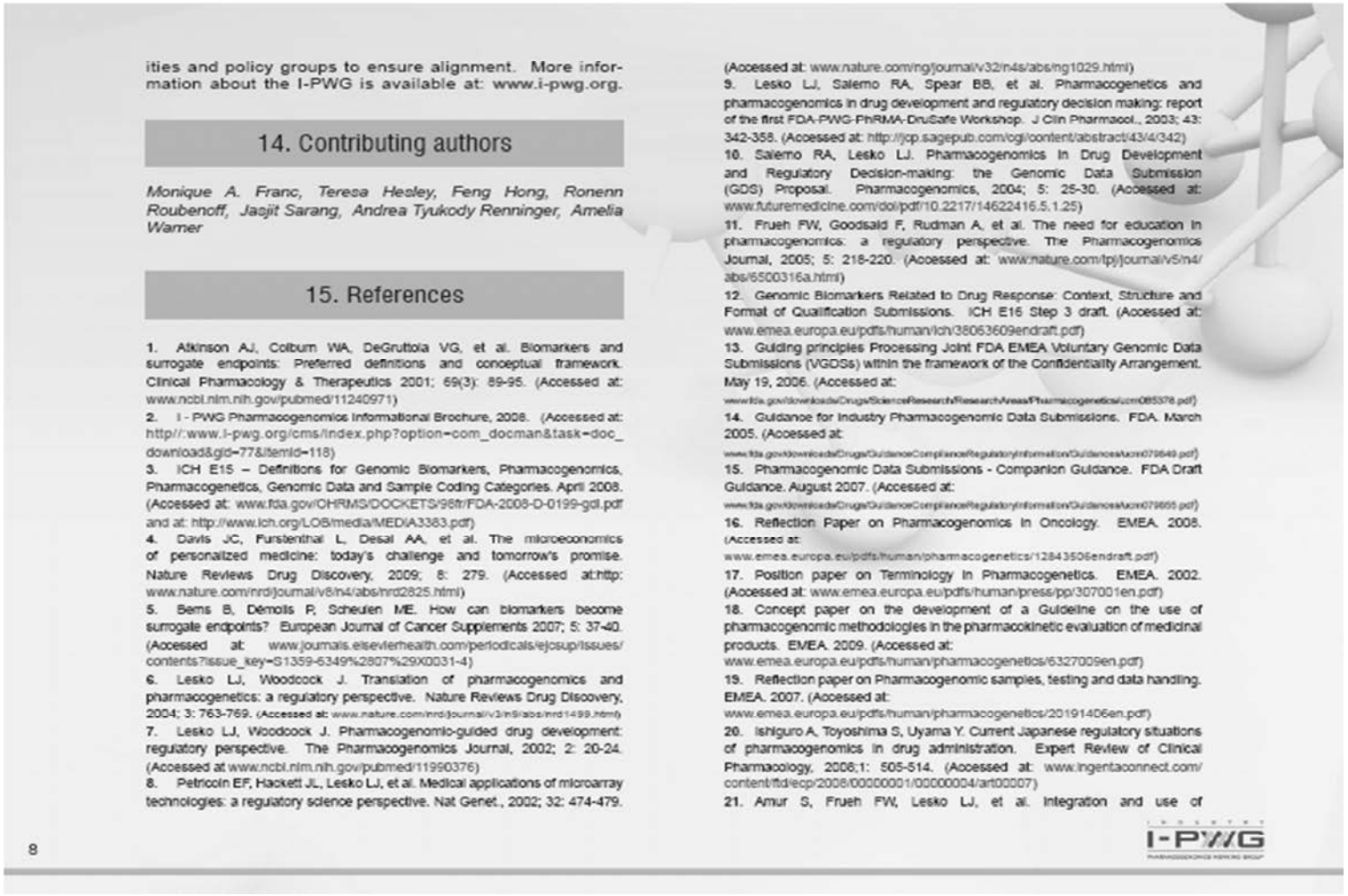
Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

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-

7

I-PWG



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

14. Contributing authors

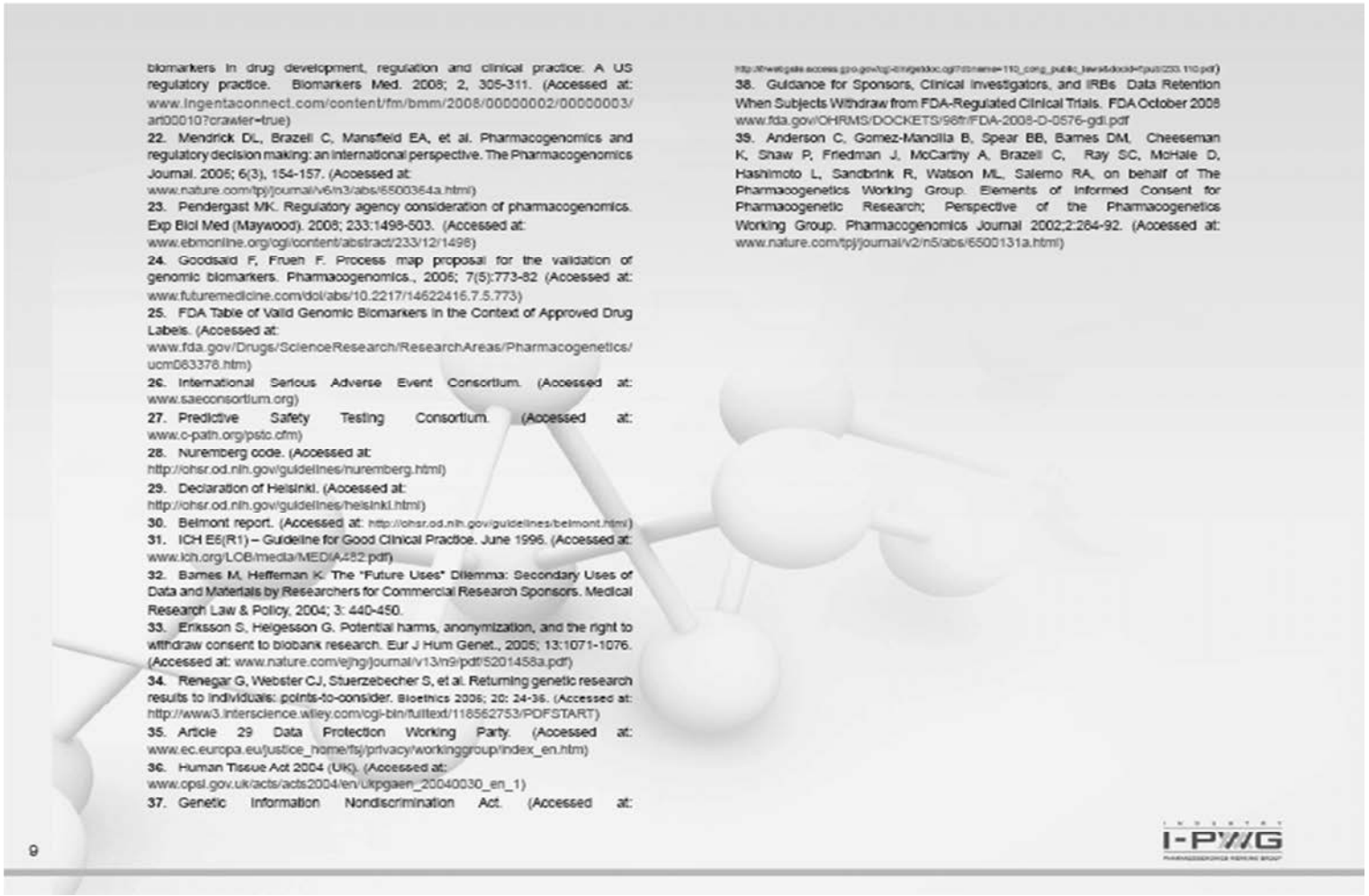
Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jasjit Sarang, Andrea Tyukody Renninger, Amelia Warner

15. References

1. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics 2001; 69(3): 89-95. (Accessed at: www.ncbi.nlm.nih.gov/pubmed/11240971)
2. I - PWG Pharmacogenomics Informational Brochure, 2008. (Accessed at: http//:www.i-pwg.org/cms/index.php?option=com_docman&task=doc_download&gid=77&Itemid=118)
3. ICH E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)
4. Davis JC, Furstenthal L, Desai AA, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nature Reviews Drug Discovery, 2009; 8: 279. (Accessed at:http: www.nature.com/nrd/journal/v8/n4/abs/nrd2825.html)
5. Berns B, Démolis P, Scheulen ME. How can biomarkers become surrogate endpoints? European Journal of Cancer Supplements 2007; 5: 37-40. (Accessed at: www.journals.elsevierhealth.com/periodicals/ejosup/issues/contents?issue_key=S1359-6349%2807%29X0031-4)
6. Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews Drug Discovery, 2004; 3: 763-769. (Accessed at: www.nature.com/nrd/journal/v3/n9/abs/nrd1499.html)
7. Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. The Pharmacogenomics Journal, 2002; 2: 20-24. (Accessed at www.ncbi.nlm.nih.gov/pubmed/11990376)
8. Petricoin EF, Hackett JL, Lesko LJ, et al. Medical applications of microarray technologies: a regulatory science perspective. Nat Genet., 2002; 32: 474-479. (Accessed at: www.nature.com/ng/journal/v32/n4s/abs/ng1029.html)
9. Lesko LJ, Salerno RA, Spear BB, et al. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PhRMA-DruSafe Workshop. J Clin Pharmacol., 2003; 43: 342-358. (Accessed at: http://jcp.sagepub.com/cgi/content/abstract/43/4/342)
10. Salerno RA, Lesko LJ. Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal. Pharmacogenomics, 2004; 5: 25-30. (Accessed at: www.futuremedicine.com/doi/pdf/10.2217/14622416.5.1.25)
11. Frueh FW, Goodsaid F, Rudman A, et al. The need for education in pharmacogenomics: a regulatory perspective. The Pharmacogenomics Journal, 2005; 5: 218-220. (Accessed at: www.nature.com/tpj/journal/v5/n4/abs/6500316a.html)
12. Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions. ICH E16 Step 3 draft. (Accessed at: www.emea.europa.eu/pdfs/human/ich/38063609endraft.pdf)
13. Guiding principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement. May 19, 2006. (Accessed at: www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085378.pdf)
14. Guidance for Industry Pharmacogenomic Data Submissions. FDA. March 2005. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079849.pdf)
15. Pharmacogenomic Data Submissions - Companion Guidance. FDA Draft Guidance. August 2007. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079865.pdf)
16. Reflection Paper on Pharmacogenomics in Oncology. EMEA. 2008. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf)
17. Position paper on Terminology in Pharmacogenetics. EMEA. 2002. (Accessed at: www.emea.europa.eu/pdfs/human/press/pp/307001en.pdf)
18. Concept paper on the development of a Guideline on the use of pharmacogenomic methodologies in the pharmacokinetic evaluation of medicinal products. EMEA. 2009. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/6327009en.pdf)
19. Reflection paper on Pharmacogenomic samples, testing and data handling. EMEA. 2007. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/2019146en.pdf)
20. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. Expert Review of Clinical Pharmacology, 2008;1: 505-514. (Accessed at: www.ingentaconnect.com/content/ftd/ecp/2008/00000001/00000004/art00007)
21. Amur S, Frueh FW, Lesko LJ, et al. Integration and use of

8

I-PWG



biomarkers in drug development, regulation and clinical practice: A US regulatory practice. Biomarkers Med. 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/bmm/2008/00000002/00000003/art00010?crawler=true)

22. Mendrick DL, Brazell C, Mansfield EA, et al. Pharmacogenomics and regulatory decision making: an international perspective. The Pharmacogenomics Journal. 2006; 6(3), 154-157. (Accessed at: www.nature.com/tpj/journal/v6/n3/abs/6500364a.html)

23. Pendergast MK. Regulatory agency consideration of pharmacogenomics. Exp Biol Med (Maywood). 2008; 233:1498-503. (Accessed at: www.ebmonline.org/cgi/content/abstract/233/12/1498)

24. Goodsaid F, Frueh F. Process map proposal for the validation of genomic biomarkers. Pharmacogenomics., 2006; 7(5):773-82 (Accessed at: www.futuremedicine.com/doi/abs/10.2217/14622416.7.5.773)

25. FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. (Accessed at: www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)

26. International Serious Adverse Event Consortium. (Accessed at: www.saeconsortium.org)

27. Predictive Safety Testing Consortium. (Accessed at: www.c-path.org/pstc.cfm)

28. Nuremberg code. (Accessed at: http://ohsr.od.nih.gov/guidelines/nuremberg.html)

29. Declaration of Helsinki. (Accessed at: http://ohsr.od.nih.gov/guidelines/helsinki.html)

30. Belmont report. (Accessed at: http://ohsr.od.nih.gov/guidelines/belmont.html)

31. ICH E6(R1) – Guideline for Good Clinical Practice. June 1996. (Accessed at: www.ich.org/LOB/media/MED/A482.pdf)

32. Barnes M, Heffernan K. The "Future Uses" Dilemma: Secondary Uses of Data and Materials by Researchers for Commercial Research Sponsors. Medical Research Law & Policy, 2004; 3: 440-450.

33. Eriksson S, Helgesson G. Potential harms, anonymization, and the right to withdraw consent to biobank research. Eur J Hum Genet., 2005; 13:1071-1076. (Accessed at: www.nature.com/ejhg/journal/v13/n9/pdf/5201458a.pdf)

34. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2006; 20: 24-36. (Accessed at: http://www3.interscience.wiley.com/cgi-bin/fulltext/118562753/PDFSTART)

35. Article 29 Data Protection Working Party. (Accessed at: www.ec.europa.eu/justice_home/fsj/privacy/workinggroup/index_en.htm)

36. Human Tissue Act 2004 (UK). (Accessed at: www.opsi.gov.uk/acts/acts2004/en/ukpgaen_20040030_en_1)

37. Genetic Information Nondiscrimination Act. (Accessed at: http://thomas.loc.gov/cgi-bin/query/z?c110:S.358.ENR:)

38. Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials. FDA October 2008 www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0576-gdl.pdf

39. Anderson C, Gomez-Mancilla B, Spear BB, Barnes DM, Cheeseman K, Shaw P, Friedman J, McCarthy A, Brazell C, Ray SC, McHale D, Hashimoto L, Sandbrink R, Watson ML, Salerno RA, on behalf of The Pharmacogenetics Working Group. Elements of Informed Consent for Pharmacogenetic Research; Perspective of the Pharmacogenetics Working Group. Pharmacogenomics Journal 2002;2:264-92. (Accessed at: www.nature.com/tpj/journal/v2/n5/abs/6500131a.html)


www.i-pwg.org

12.4 Abbreviations

Abbreviation/Term	Definition
2L	Second Line
AE	Adverse Event
ADA	Anti-Drug Antibodies
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ß-HCG	Beta Human Chorionic Gonadotropin
BSA	Body Surface Area
CBC	Complete Blood Count
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
DNA	Deoxyribonucleic acid
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDMC	External Data Monitoring Committee
EOC	Executive Oversight Committee
ePRO	Electronic Patient Reported Outcomes
ERC	Ethics Review Committee
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FWER	Family-wise type I error rate
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
HSD	Hwang-Shih-DeCani
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
ISS	International Staging System
ITIM	Immunoreceptor Tyrosine-based Switch Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITT	Intent-to-Treat
IV	Intravenous
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System

Abbreviation/Term	Definition
Kg	kilogram
mAb	Monoclonal Antibody
mcL	Millimeters
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.
NA or N/A	Not Applicable
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PFS	Progression Free Survival
PGt	Pharmacogenetic
PK	Pharmacokinetic
PK/PD	Pharmacokinetic-Pharmacodynamic
PO	Oral Administration
PR	Partial Response
PSA	Prostate Specific Antigen
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
TIL	Tumor-Infiltrating Lymphocytes
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WHO	World Health Organization

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.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

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

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

12.7 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.

12.8 Strong Inhibitors and Strong Inducer of CYP3A4

Strong inhibitors of CYP3A4 include:

- Clarithromycin
- Indinavir
- Itraconazole
- Ketoconazole
- Nefazodone
- Nelfinavir
- Ritonavir
- Saquinavir

This appendix is not intended to be a comprehensive list of strong CYP3A4 inhibitors, but to provide a practical list of commonly prescribed medications that should be avoided in subjects participating in this study. Additional guidance for investigators on potential strong CYP3A4 inhibitors of clinical significance may be found at http://medicine.iupui.edu/flockhart/.

The web-based resources are intended as guidance for the investigators and not necessarily as a list of prohibited medications.

Strong inducers of CYP3A4 include:

- Carbamazepine
- Phenytoin
- Phenobarbital
- Rifampin
- Hypericum perforatum (St John's Wort)

12.9 QT Prolongation Medications

FDA DRUG PRODUCT LABELS QT PROLONGATION				
Boxed Warnings	**Warnings & Precautions**	**Adverse Reactions**	**Clinical Pharmacology**	**Clinical Studies**
Arsenic Trioxide	Amiodarone	Citalopram	Ambrisentan	Citalopram
Droperidol	Arsenic Trioxide	Clarithromycin	Azilsartan Medoxomil	Dofetilide
Ibutilide	Azithromycin	Dronedarone	Azithromycin	
Itraconazole	Bisacodyl	Droperidol	Citalopram	
Ketoconazole	Ciprofloxacin	Erythromycin	Crizotinib	
Nilotinib	Citalopram	Fesoterodine	Darifenacin	
Vandetanib	Clarithromycin	Fluoxetine	Desvenlafaxine	
	Clozapine	Granisetron	Dexlansoprazole	
	Cyclophosphamide	Ketoconazole	Dolasetron	
	Dasatinib	Mirtazapine	Eltrombopag Olamine	
	Dofetilide	Ondansetron	Etravirine	
	Dolasetron	Oxybutynin	Everolimus	
	Droperidol	Risperidone	Ezogabine	
	Erythromycin	Sertraline	Fexofenadine	
	Ezogabine	Sotalol	Ibutilide	
	Famotidine	Vandetanib	Ixabepilone	
	Fluconazole	Venlafaxine	Ketoconazole	
	Fluoxetine		Levetiracetam	
	Gemifloxacin		Mexiletine	
	Granisetron		Moxifloxacin	
	Haloperidol		Nilotinib	
	Ibutilide		Olopatadine	
	Iloperidone		Plerixafor	
	Itraconazole		Pseudoephedrine	
	Ketoconazole		Quinidine	
	Levofloxacin		Ranolazine	
	Lopinavir/Ritonavir		Telbivudine	
	Methadone		Teriflunomide	
	Nabilone		Tolterodine	
	Nilotinib		Vandetanib	
	Ofloxacin		Voriconazole	
	Ondansetron			
	Paroxetine			
	Pimozide			
	Posaconazole			
	Propafenone			
	Quinine Sulfate			
	Ranolazine			
	Romidepsin			

FDA DRUG PRODUCT LABELS QT PROLONGATION				
Boxed Warnings	**Warnings & Precautions**	**Adverse Reactions**	**Clinical Pharmacology**	**Clinical Studies**
	Sevoflurane			
	Solifenacin			
	Sorafenib			
	Sotalol			
	Sunitinib			
	Tacrolimus			
	Tolterodine			
	Vandetanib			
	Vardenafil			
	Vemurafenib			
	Voriconazole			
	Ziprasidone			

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	