Official Protocol Title:	A Phase III Randomized, Controlled Clinical Trial of Pembrolizumab with or without Platinum-Based Combination Chemotherapy versus Chemotherapy in Subjects with Advanced or Metastatic Urothelial Carcinoma
NCT number:	NCT02853305
Document Date:	10-Jun-2021

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TITLE:

A Phase III Randomized, Controlled Clinical Trial of Pembrolizumab with or without Platinum-Based Combination Chemotherapy versus Chemotherapy in Subjects with Advanced or Metastatic Urothelial Carcinoma

IND NUMBER: 122,753

EudraCT NUMBER: 2015-005731-41

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
3475-361-10	10-JUN-2021	Global: To update the dose modification and toxicity management guidelines for immune-related adverse events (irAEs).
3475-361-09	10-APR-2020	France: Due to a significant drop off in the accrual of progression-free survival (PFS) events, the requirement for the final analysis of approximately 532 PFS events in the combo and chemo arms in all subjects has been removed. The other requirements for the final analysis remain in place.
3475-361-08	10-APR-2020	Global: Due to a significant drop off in the accrual of PFS events, the requirement for the final analysis of approximately 532 PFS events in the combo and chemo arms in all subjects has been removed. The other requirements for the final analysis remain in place.
3475-361-07	24-OCT-2019	France: In order to account for a potential delayed treatment effect, which was observed with immunotherapy study data external to this study, the Statistical Analysis Plan was revised.
3475-361-06	23-OCT-2019	Global: In order to account for a potential delayed treatment effect, which was observed with immunotherapy study data external to this study, the Statistical Analysis Plan was revised.
3475-361-05	8-MAR-2018	France: Based on their review of preliminary data from KEYNOTE-361, the external Data Monitoring Committee recommended accrual to the pembrolizumab monotherapy arm for subjects whose tumors are PD-L1 CPS<10% be stopped.

Document	Date of Issue	Overall Rationale
3475-361-04	8-MAR-2018	Global: Based on their review of preliminary data from KEYNOTE-361, the external Data Monitoring Committee recommended accrual to the pembrolizumab monotherapy arm for subjects whose tumors are PD-L1 CPS<10% be stopped.
3475-361-03	14-NOV-2017	France: Based on recent results from KEYNOTE-045 (KN045) and KEYNOTE-052 (KN052), the Statistical Analysis Plan was revised and simplified.
3475-361-02	14-SEP-2017	Global: Based on recent results from KEYNOTE-045 (KN045) and KEYNOTE-052 (KN052), the Statistical Analysis Plan was revised and simplified.
3475-361-01	12-OCT-2016	To update entrance criteria, particularly in regard to estimated creatinine clearance as an assessment of renal function and to require audiograms since subjects with Grade ≥2 audiometric hearing loss are not eligible for cisplatin.
3475-361-00	20-JUN-2016	Original

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

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

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
Appendix 12.5 Appendix 12.5.1	Country-specific Requirements France-specific Requirements	Country-specific requirements for France were added to a country-specific appendix.	A country-specific amendment is being rolled into the global amendment and placed within a country-specific appendix.
Whole document		Correction of minor administrative and typographical errors.	Corrections.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase III Randomized Controlled Trial of Pembrolizumab With or Without Chemo vs Chemo in Advanced Urothelial Carcinoma
Sponsor Product Identifiers	Pembrolizumab
Trial Phase	Phase III
Clinical Indication	Treatment of subjects with advanced or metastatic urothelial carcinoma
Trial Type	Interventional
Type of control	Active control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	1. Pembrolizumab (MK-3475) 2. Pembrolizumab with chemotherapy (cisplatin or carboplatin with gemcitabine) 3. Chemotherapy (cisplatin or carboplatin with gemcitabine).
Number of trial subjects	Approximately 990 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 3 years from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specific contact. After a screening period of 42 days, subjects will be randomized to one of the 3 treatment arms: pembrolizumab monotherapy (pembro only), pembrolizumab+chemotherapy+standard of care (SOC) (combo), and chemotherapy+SOC (chemo only). The safety and feasibility of combo therapy will be assessed by means of a safety interim analysis after the last of the first 10 subjects enrolled in the combo treatment arm completes 2 cycles of treatment. Treatment on trial will continue until verification of disease progression is confirmed by blinded independent central review (BICR), unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdrawal of consent, pregnancy of the subject, noncompliance with trial treatment or procedures requirements, or subject receives 35 administrations of pembrolizumab (approximately 2 years) (pembro only and combo treatment arms only). Investigators may consider stopping trial treatment (pembrolizumab) for subjects on the pembrolizumab arms (pembro only and combo) who attain a complete response (CR) if they meet criteria for holding therapy. Subjects who stop treatment and subsequently have progressive disease may be eligible for up to 17 administrations (1 year) of pembrolizumab re-treatment if they 1) have received 35 doses of pembrolizumab and stop trial treatment for reasons other than disease progression or intolerability or 2) attained a confirmed CR after being treated with pembrolizumab for at least 8 administrations, and had at least 2 treatments with

	pembrolizumab after CR was declared (Section 7.1.5.2.1). The decision to re-treat will be at the discretion of the investigator; re-treatment will occur only if the subject meets the criteria for re-treatment and the trial is ongoing. After the last dose of trial treatment, each subject will be followed for 30 days for AE monitoring. Serious AEs (SAEs) will be collected for 90 days after the last dose of trial treatment or 30 days after the end of treatment if the subject initiates new anti-cancer therapy, whichever is earlier. All drug-related SAEs and events of clinical interest (ECIs) will be reported regardless of time frame. Subjects who discontinue trial treatment without disease progression will have post-treatment follow-up for disease status, including radiographic imaging, until disease progression initiating a nontrial cancer treatment, withdrawing consent, or becoming lost to follow-up. Subjects who discontinue treatment due to disease progression will also continue to be followed for survival status. All subjects will be followed for overall survival approximately every 12 weeks until death, withdrawal of consent, or the end of the trial. To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. Once the participant has achieved the study objective or the study has ended, the participant is discontinued from this study and will be enrolled in an extension study to continue protocol-defined assessments.

Randomization Ratio	1:1:1 (all arms) for all subjects from trial initiation until 21-FEB-2018. After 21-FEB-2018, 1:1:1 (all arms) for subjects whose tumors are PD-L1 CPS ≥10% and 1:1 (combo arm and chemo only arm) for subjects whose tumors are PD-L1 CPS <10%.

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a Phase III randomized, active-controlled, parallel-group, multisite, open-label trial to determine the efficacy and safety of pembrolizumab with or without chemotherapy versus chemotherapy alone in subjects with advanced or metastatic urothelial carcinoma (bladder cancer). Subjects will be enrolled regardless of programmed death-ligand 1 (PD-L1) status (Combined Positive Score [CPS] ≥10% or CPS <10%). Approximately 1,300 subjects will be screened. Approximately 990 subjects will be randomized. The population will comprise of subjects with advanced or metastatic urothelial carcinoma whose disease is not subject to curative surgery. Subjects must have measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as determined by investigator/site radiologist. During the 42-day screening period, each subject must provide a newly obtained or archival formalin-fixed paraffin-embedded (FFPE) tumor biopsy for PD-L1 determination by immunohistochemistry (IHC) by a central laboratory. The biopsy should be from a muscle-invasive urothelial carcinoma or a metastatic biopsy, originating from the original tumor.

Note: PD-L1 CPS ≥10% and CPS <10% are replacing the designation of PD-L1 positive and negative, respectively, that were referenced in the overall trial design used in the base protocol (KN361-00).

Subjects will be stratified based on PD-L1 results, and therefore adequacy of tissue specimen for PD-L1 determination is required.

In the pembro only arm and combo arm, each subject will receive the following dose of pembrolizumab:

- Pembrolizumab 200 mg every 3 weeks (Q3W) (Day 1 of each 3-week cycle) for a maximum of 35 doses.

In the combo and chemo only arms, each subject will receive 6 cycles of platinum-based combination chemotherapy as per investigator's choice (based on clinical factors; refer to Section 4.2.1 for cisplatin ineligibility guidelines) of either:

- Cisplatin intravenous (IV) infusion 70 mg/m^2 on Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle + gemcitabine IV infusion 1,000 mg/m^2 Day 1 and Day 8 of each 3-week cycle

  OR (only if ineligible for cisplatin; refer to Section 4.2.1 for cisplatin ineligibility guidelines)

- Carboplatin IV infusion area under the curve 5 (AUC 5) (or AUC 4.5 if required per local guidelines) Day 1 (or Day 2 if required per local guidelines) of each 3-week cycle + gemcitabine IV infusion 1,000 mg/m^2 Day 1 and Day 8 of each 3-week cycle.

To ensure that random distribution is maintained across all 3 arms, including the pembro only arm, trial randomization will be stratified by the investigator's choice of chemotherapy regimen, which must be specified prior to randomization. Cisplatin eligibility will have no impact on randomization into treatment arms.

Prior to 21-FEB-2018, subjects were equally randomized to one of the 3 treatment arms. As of 21-FEB-2018, subjects with tumors that are PD-L1 CPS≥10% will be equally randomized to one of the 3 treatment arms. Subjects with tumors that are PD-L1 CPS<10% will no longer be randomized to the pembro only arm; they will be equally randomized to either the combo arm or the chemo only arm. No change in study treatment is required for subjects randomized prior to 21-FEB-2018.

The primary efficacy endpoints will be the progression-free survival (PFS) for combo vs chemo only in the all-subject population using BICR and RECIST 1.1 to determine disease progression, and overall survival (OS) for combo vs chemo only in the all-subject population and OS for pembro only vs chemo only in the PD-L1 CPS ≥10% and all-subject population. Secondary endpoints will include objective response rates (ORR), disease control rate (DCR), and duration of response (DOR) using BICR and RECIST 1.1 to determine disease progression, for both the PD-L1 CPS ≥10% population and the all-subject population. The proportion of subjects who are progression-free at specific time points will also be assessed. Exploratory endpoints include health-related quality of life as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC

QLQ-C30) and European Quality of Life (EuroQol) EQ-5D™, as well as the relationship between genetic variations and response to treatment.

This trial will use an independent, external Data Monitoring Committee (DMC) to monitor safety and efficacy. The safety and feasibility of combination therapy will be assessed by means of a safety interim analysis. The interim safety analysis will be conducted when 10 subjects in the combo arm have completed 2 cycles of treatment. Refer to Section 8.7.1 – Safety Interim Analysis for details and criteria of the combination safety interim analyses. The interim PFS/OS analysis is event driven. More details are given in Section 8.7.2 – Efficacy Interim Analysis.

Subjects will be evaluated for safety at every visit and by radiographic imaging every 9 weeks (63 days ±7) after randomization, or more frequently if clinically indicated, to assess response to treatment. Subjects who remain on treatment beyond 54 weeks will have imaging performed every 12 weeks (84 days ±7) thereafter. All imaging obtained on trial will be submitted to a BICR that will assess the images using RECIST 1.1 for determination of ORR, DOR, DCR, and PFS.

Subjects in either pembrolizumab arm (pembro only or combo) who stop trial treatment after receiving 35 administrations for reasons other than disease progression or intolerability, or who attain a confirmed CR and stop trial treatment after 2 additional doses beyond the initial determination of CR, may be eligible for up to 17 administrations of re-treatment upon experiencing disease progression. The decision to re-treat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of pembrolizumab, the subject still meets the safety parameters listed in the inclusion/exclusion criteria, and the trial remains open (refer to Section 7.1.5.2.1 – Second Course Phase for details).

The protocol does not allow subjects to cross over to pembrolizumab if they have progression on chemotherapy.

After the end of trial treatment, subjects will be followed for 30 days for AE monitoring and events of clinical interest (ECI), or until the subject initiates new anticancer therapy, whichever comes first. Serious AEs (SAEs) will be collected for 90 days after the trial treatment or 30 days after the end of treatment, if the subject initiates new anti-cancer therapy, whichever is earlier.

Subjects who discontinue or complete the entire regimen of trial therapy for reasons other than documented confirmed disease progression must have posttreatment follow-up for disease status every 9 weeks (63 days ±7) during the first year of the trial until Week 54 and, then every 12 weeks (84 days ±7) until one of the following occurs: verification of disease progression by BICR, a new nontrial cancer treatment is initiated, consent is withdrawn, death, becoming lost to follow-up, or the end of the trial, whichever comes first. All subjects will be followed up for OS every 12 weeks (84 days ±7) until death, withdrawal of consent, or the end of the trial. This can be performed in a variety of manners including phone, e-mail, chart review, or review of public records.

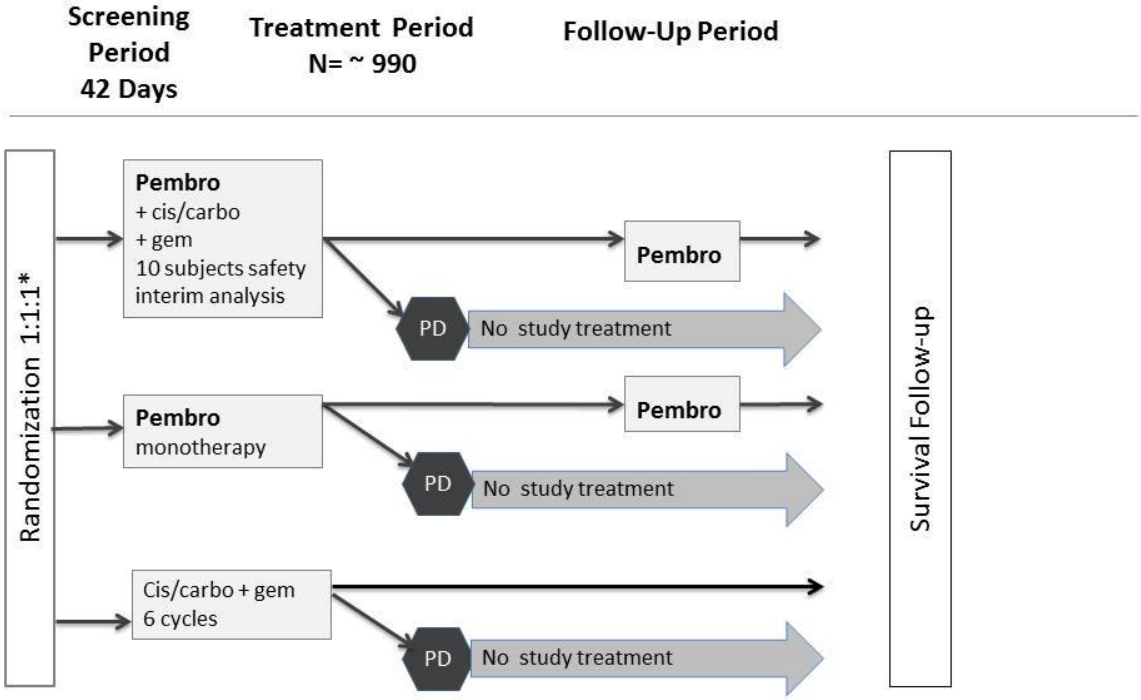
This study will be conducted in compliance with the Merck Code of Conduct for Clinical Trials (refer to Appendix 12.1), Good Clinical Practices, and the ethical principles that have their origin in the Declaration of Helsinki.

Refer to Appendix 12.6 for a list of abbreviations used in the text of this protocol.

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 design of the trial is shown in Figure 1, below.



PD=progressive disease; pembro=pembrolizumab; cis=cisplatin; carbo=carboplatin; gem=gemcitabine
*Subjects with CPS PD-L1 <10% will no longer be enrolled in the pembrolizumab only arm after 21 February 2018

Figure 1 Trial Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

In male and female subjects with advanced/unresectable (inoperable) or metastatic urothelial carcinoma of the renal pelvis, ureter [upper urinary tract], bladder, or urethra at least 18 years of age:

3.1 Primary Objective(s) & Hypothesis(es)

Objectives: To compare PFS using RECIST 1.1 as assessed by BICR in the all-subject population for combo vs chemo only, and to compare OS for combo vs chemo only in the all-subject population and for pembro only vs chemo only in the PD-L1 CPS ≥10% and all-subject population.

Hypothesis (H1): Combo is superior to chemo only with respect to PFS using RECIST 1.1 as assessed by BICR in all subjects (both PD-L1 CPS ≥10% and CPS <10%).

Hypothesis (H2): Combo is superior to chemo only with respect to OS in all subjects (both PD-L1 CPS ≥10% and CPS <10%).

Hypothesis (H3a): Pembro only is noninferior to chemo only with respect to OS in PD-L1 CPS ≥10% subjects.

Hypothesis (H3b): Pembro only is superior to chemo only with respect to OS in PD-L1 CPS ≥10% subjects.

Hypothesis (H4a): Pembro only is noninferior to chemo only with respect to OS in all subjects (both PD-L1 CPS ≥10% and CPS <10%).

Hypothesis (H4b): Pembro only is superior to chemo only with respect to OS in all subjects (both PD-L1 CPS ≥10% and CPS <10%).

Refer to Table 1 for a list of the primary hypotheses and their abbreviations in this protocol.

Table 1 Primary Hypotheses

Hypothesis Number	Hypothesis
H1	PFS, all subjects, superiority, combo vs chemo only
H2	OS, all subjects, superiority, combo vs chemo only
H3a	OS, PD-L1 CPS ≥10%, noninferiority, pembro only vs chemo only
H3b	OS, PD-L1 CPS ≥10%, superiority, pembro only vs chemo only
H4a	OS, all subjects, noninferiority, pembro only vs chemo only
H4b	OS, all subjects, superiority, pembro only vs chemo only

Note: The success of the trial will ultimately depend on the demonstration of superiority related to H1 (PFS) or H2 (OS) due to the multiplicity strategy detailed in Section 8.8.
Abbreviations/Terms: all subjects=PD-L1 CPS ≥10% and CPS <10%; chemo only=chemotherapy (cisplatin or carboplatin+gemcitabine)+SOC; combo=pembrolizumab+chemotherapy (cisplatin or carboplatin+gemcitabine)+SOC; CPS=combined positive score for PD-L1 positivity; H=hypothesis; OS=overall survival; PD-L1=programmed cell death-ligand 1; pembro=pembrolizumab; PFS=progression-free survival; SOC=standard of care.

3.2 Secondary Objective(s) & Hypothesis(es)

1. **Objective**: To evaluate the safety and tolerability profile in all subjects (PD-L1 CPS ≥10% and CPS <10%) in the following treatment groups:
    a) Pembro only
    b) Combo
    c) Chemo only

2. **Objective:** To compare the ORR using RECIST 1.1 as assessed by BICR between the following treatment comparisons:

    a) Combo versus chemo only

    b) Pembro only versus chemo only

    Hypothesis (H5a): Combo is superior to chemo only with regard to ORR in all subjects (PD-L1 CPS ≥10% and CPS <10%).

    Hypothesis (H5b): Pembro only is superior to chemo only with regard to ORR in all subjects (PD-L1 CPS ≥10% and CPS <10%).

3. **Objective:** To evaluate the DOR in all subjects (PD-L1 CPS ≥10% and CPS <10%) using RECIST 1.1 as assessed by BICR in the following treatment groups:

    a) Pembro only

    b) Combo

    c) Chemo only

4. **Objective:** To evaluate the disease control rate (DCR=combined complete response, partial response, and stable disease rates) in all subjects (PD-L1 CPS ≥10% and CPS <10%) using RECIST 1.1 as assessed by BICR in the following treatment groups:

    a) Pembro only

    b) Combo

    c) Chemo only

5. **Objective:** To estimate PFS at milestone time points (6 months, 12 months, 18 months, 24 months) in all subjects (PD-L1 CPS ≥10% and CPS <10%) using RECIST 1.1 as assessed by BICR in the following treatment groups:

    a) Pembro only

    b) Combo

    c) Chemo only

6. **Objective:** To evaluate time to deterioration (TTD), defined as the time from baseline to first onset of patient-reported outcome (PRO) deterioration, and score change from baseline in health-related quality of life scores assessed using the EORTC QLQ-C30 among all subjects (both PD-L1 CPS ≥10% and CPS <10%) in the following treatment groups:

    a) Pembro only

    b) Combo

    c) Chemo only

3.3 Exploratory Objectives

1. **Objective**: To evaluate changes in health-related quality of life and characterize health utilities in all treatment groups, including change from baseline in health-related quality of life using the multi-item and single-item scales of the EORTC QLQ-C30 and health state and utility scores using EuroQol EQ-5D among all subjects.
2. **Objective:** To characterize utilities using EuroQol EQ-5D among all subjects (both PD-L1 CPS ≥10% and CPS <10%).
3. **Objective:** To compare PFS as assessed by BICR using immune-related RECIST (irRECIST) in PD-L1 CPS ≥10% subjects and in all subjects (both PD-L1 CPS ≥10% and CPS <10%) between the following treatment comparisons:
    a) Combo versus chemo only
    b) Pembro only versus chemo only
4. **Objective:** To compare the ORR as assessed by BICR using irRECIST in all subjects (PD-L1 CPS ≥10% and CPS <10%) between the following treatment comparisons:
    a) Combo versus chemo only
    b) Pembro only versus chemo only
5. **Objective**: To characterize the pharmacokinetic (PK) and pharmacodynamic profiles of treatment with pembrolizumab in the pembro only and combo treatment groups.
6. **Objective:** To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with PD-L1 and programmed cell death-ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. KEYTRUDA™ (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T-cell.

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

4.1.1 Pharmaceutical and Therapeutic Background

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 in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignances such as ovarian, colorectal, and pancreatic cancer. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [2] [3].

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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [4] [5].

The structure of murine PD-1 has been resolved [6]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (IgV-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 [4] [7] [8] [9]. 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 [10] [11]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in advanced urothelial carcinoma.

4.1.2 Preclinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatments. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have shown antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [2] [3] [12] [13] [14]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models. (For more information, refer to the IB.)

4.1.3 Ongoing Clinical Trials

The safety, tolerability, and antitumor activity of pembrolizumab were assessed in subjects with recurrent or metastatic urothelial cancer in the Phase 1b KN012 (NCT01848834), an open-label nonrandomized trial of pembrolizumab 10 mg/kg, IV once every 2 weeks (Q2W)

in advanced solid tumors. Archival or newly obtained tumor samples from subjects with advanced carcinoma of the renal pelvis, ureter, bladder, or urethra were screened for PD-L1 expression using a prototype IHC assay. PD-L1 expression in stroma or ≥1% of tumor cells was required for trial entry. Subjects received pembrolizumab 10 mg/kg Q2W until CR, progression, or unacceptable toxicity. Subjects deriving benefit could remain on pembrolizumab beyond initial progression. Response was assessed every 8 weeks per RECIST 1.1 by independent central review (primary efficacy end point).

In the KN012 trial, a total of 33 subjects with bladder cancer were enrolled and received pembrolizumab 10 mg/kg Q2W. Median age was 70 years (range 44 to 85); 72.7% of subjects had an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 1, 51.6% had received ≥2 prior therapies for advanced disease, and 30.3% had liver metastases.

As of the data cutoff date, the ORR (CR+PR) in 33 urinary tract cancer subjects was 21.2% (7/33) as measured by RECIST 1.1 by BICR. Similarly, the ORR was 21.2% by site assessment and when measured by irRECIST. The ORR was 25.9% (7/27) in the primary endpoint FAS population both by BICR and site assessment. Notably, 48% (16/33) of urinary tract cancer subjects showed tumor reduction, and this shows benefit in a larger pool of subjects beyond those who experienced a confirmed response from pembrolizumab as measured by RECIST 1.1. A response of at least 6 months in duration based on Kaplan-Meier estimate was seen in 4 subjects (67% based on Kaplan-Meier estimation) who had a response as measured by RECIST 1.1. The predefined efficacy objective (a 95% lower confidence limit of the observed ORR greater than 10%) was not met in the ASaT population, but was met in the FAS population. The median follow-up duration (defined as the time from randomization to the date of death, or database cutoff date if the subject was still alive) was 11.4 months. The PFS rate in the ASaT population of urinary tract cancer subjects was 22.6% at 6 months and 12.9% at 12 months, and was similar to the FAS population. The median OS was 9.3 months. The OS rate was 56.1% at 6 months and 42.1% at 12 months.

Overall, the number, type, and frequency of AEs and SAEs reported in this study, noting the limitation of the small sample size, were not indicative of any new safety concerns for pembrolizumab. A total of 60.6% (20/33) of subjects experienced a drug-related AE and those most frequently reported (in greater than 10% of subjects) were fatigue (18.2%) and edema peripheral (12.1%). A total of 9 immune-mediated AEs of special interest (AEOSI) were reported in 7 (21.2%) subjects. Each AEOSI was reported in only one subject, except for myositis which was reported in 2 subjects. Grade 3 AEOSI included myositis, colitis, rhabdomyolysis, rash pruritic, rash maculopapular, and stasis dermatitis. Grade 2 AEOSI included myositis and uveitis. The median time to onset for the first AEOSI was 44 days. The median episode duration was 27 days. These findings did not result in any changes to the previously established safety profile of pembrolizumab.

KN045 (NCT02256436) is an ongoing randomized Phase 3 trial of pembrolizumab versus investigator's choice of chemotherapy with paclitaxel, docetaxel, or vinflunine in 542 subjects with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy [15]. The primary trial hypothesis is that pembrolizumab will prolong OS and PFS compared with paclitaxel, docetaxel, or vinflunine.

As of the data cutoff for the interim analysis, enrollment was complete with a total of 542 subjects randomized and included in the ITT population by BICR (control: 272; pembrolizumab: 270). Subjects were treated with 200 mg of pembrolizumab every 3 weeks (Q3W). Overall, the 2 groups were well matched: histology was reported as pure transitional for 383 subjects (control: 197; pembrolizumab: 186) predominantly transitional for 155 subjects (control: 73; pembrolizumab: 82), and "other" for 2 subjects in the pembrolizumab group. The median age was 66 years (range 26 to 88); 55.5% of subjects had an ECOG PS of 1, 10% had received prior BCG therapy, and 87% had visceral disease at baseline.

The primary efficacy endpoints were OS and PFS. For the primary analysis of OS, all subjects in the ITT population showed a statistically significant and clinically meaningful difference between the pembrolizumab and control treatment arms (the investigator's choice of paclitaxel, docetaxel, or vinflunine), favoring pembrolizumab. The HR for OS was 0.73 (95% CI: 0.59, 0.91), with a one-sided p-value of 0.0022, favoring pembrolizumab over the control. The median OS was 10.3 months in the pembrolizumab arm versus 7.4 months in the control arm. The treatment effect was similar for each chemotherapy comparator. The primary analysis of PFS among all subjects in the ITT population showed no statistically significant difference between the pembrolizumab and control treatment arms. Median PFS was 2.1 months (95% CI: 2.0, 2.2) in the pembrolizumab arm versus 3.3 months (95% CI: 2.3, 3.5) in the control arm (HR 95 [95% CI] = 0.98 [0.81, 1.19]; p = 0.416). Consistent findings were shown in the CPS ≥10% and CPS ≥1% subpopulations for both OS and PFS. Overall, the efficacy data from KN045 demonstrate substantial benefit of pembrolizumab in subjects with urothelial carcinoma who have received platinum-containing chemotherapy, in the overall population, regardless of PD-L1 status.

Overall, pembrolizumab demonstrated a more favorable tolerability in comparison to control in the target population. This was shown by a lower frequency of AEs, drug-related AEs, Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, drug-related SAEs, and drug-related AEs leading to treatment discontinuation in the pembrolizumab arm in comparison to the control arm. The most common drug-related adverse events (DRAEs) reported (>10% incidence) in the pembrolizumab compared with the control arm included fatigue (13.9% vs 27.8%), nausea (10.9% vs 24.3%), and pruritus (19.5% vs 2.7%). Among the drug-related AEs observed in ≥10% of the subjects on pembrolizumab, with the exception of pruritus, all were reported in a lower or similar frequency among the subjects receiving pembrolizumab versus control. Pruritus has been previously identified as an adverse drug reaction for pembrolizumab. Adverse events of special interest (AEOSI) for this study were immune-mediated events and infusion-related reactions considered to be risks for pembrolizumab. There were 45 (16.9%) subjects in the pembrolizumab arm with 1 or more AEOSIs. In general, the frequency and severity of each AEOSI observed during the trial was similar to the previously described characterization of the safety profile of pembrolizumab. No indication-specific AEOSI was identified (new immune-mediated event causally associated with pembrolizumab). In summary, the safety data from KN045 showed that pembrolizumab is well tolerated in the target population: pembrolizumab showed a more favorable tolerability in comparison to control, and no new safety risk was observed in association with pembrolizumab.

KN052 (NCT02335424) is an ongoing open-label, Phase 2 trial of pembrolizumab for first-line treatment in 374 subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer who are not fit for cisplatin-based therapy. Subjects in KN052 are considered unfit for cisplatin if they meet at least 1 of the following criteria: **a**. ECOG PS of 2 (the proportion of ECOG 2 subjects will be limited to approximately 50% of the total population); **b**. Creatinine clearance (CrCl) (calculated or measured) <60 mL/min, but ≥30 mL/min (Note: Subjects with a CrCl [calculated or measured] <30 mL/min, or on dialysis are excluded from the trial); **c.** Common Terminology for Adverse Events (CTCAE) v.4.0, Grade ≥2 audiometric hearing loss (25 decibels in 2 consecutive wave ranges); **d**. CTCAE v.4.0, Grade ≥2 peripheral neuropathy; or **e.** New York Heart Association Class III heart failure. The primary trial hypothesis was that pembrolizumab treatment would result in a clinically meaningful ORR in all participants and in participants with high CPS biomarker determination. As of the data cutoff date, a total of 370 subjects with advanced/unresectable (inoperable) or metastatic urothelial cancer were enrolled and treated with 200 mg of pembrolizumab every 3 weeks (Q3W). Median age was 74 years; 32.4% of subjects had an ECOG PS of 2, 49.2% had renal dysfunction, 85.1% had visceral disease, 21.1% had liver metastasis, 81.9% were chemotherapy naïve, 90.3% had not received prior adjuvant or neoadjuvant platinum-based chemotherapy, and 85.4% had not received prior BCG therapy.

At the time of data cutoff, treatment with pembrolizumab resulted in a clinically meaningful ORR of 24.1% (95% CI: 19.8, 28.7) in all subjects and 27.0% (95% CI: 22.1, 32.4) among subjects who had the opportunity for at least 2 postbaseline imaging assessments. The CPS of ≥10% was found to be the optimal PD-L1 strongly positive or high cut point. The ORR for subjects with CPS ≥10% in the discovery set (first 100 subjects) was 36.7% (95% CI: 19.9, 56.1). This was confirmed in the validation set where ORR for CPS ≥10% was 38.8% (95% CI: 28.1, 50.3). Pembrolizumab treatment effect was observed in all subgroups including the elderly, those with poor ECOG PS, and those with CPS <1% tumors. Radiographic responses typically occurred within 2 months and were durable. Most responses were ongoing at the time of data cutoff. The median DOR had not been reached at the time of data cutoff, but the lower bound of the 95% confidence interval was found to be 8.7 months. For the longest responder, DOR was 13.6 months and ongoing. The estimated DOR rate at 6 months was 78% (Kaplan-Meier estimate). The DOR with pembrolizumab compares favorably to conventional chemotherapy where responses are typically short-lived.

Overall the frequency of AEs, SAEs, drug-related AEs, and fatal AEs were either consistent with previous experience with pembrolizumab or considered related to the underlying medical condition (advanced/unresectable or metastatic urothelial carcinoma) of the all patients as treated population. The most common DRAEs reported (>10% incidence) were fatigue (16.8%) and pruritus (14.1%). In general, the frequencies and severity of each of the AEOSIs observed during the trial were similar to the previously described characterization of the safety profile of pembrolizumab. No indication specific AEOSI was identified (new immune-mediated event causally associated with pembrolizumab). One subject had an AEOSI of severe myositis with a fatal outcome. Pembrolizumab was well tolerated in the target population as shown by the low frequency of drug-related AEs leading to treatment discontinuation (5.1%), and no new safety risk was observed in association with pembrolizumab.

KN057 (NCT02625961) is an ongoing open-label, Phase 2 trial of pembrolizumab for the treatment of approximately 260 subjects with high-risk nonmuscle invasive bladder cancer (NMIBC) unresponsive to *Bacillus* Calmette-Guerin (BCG) vaccine. The primary hypotheses of this trial are that treatment with pembrolizumab will result in CR for subjects with carcinoma in situ (Cis) at baseline - NMIBC (Cohort A) - and will result in disease-free survival for 12 months in subjects with focal tumors that are resected, but are at high risk for recurrence without adjunctive therapy (Cohort B).

Refer to Table 2 for a list of the Sponsor's ongoing trials in bladder cancer.

Table 2 Key Features of Ongoing KEYNOTE Bladder Trials

Trial Identifier	Type of Trial Design Features	Trial Population	Dosage, Regimen	Primary Efficacy Endpoint(s)
KN012 Ongoing	Multi-cohort, open-label, Phase 1b basket trial	33 subjects enrolled in Cohort C (enrollment complete); all subjects with PD-L1 positive tumors and recurrent or metastatic urinary tract cancer.	Pembrolizumab 10 mg/kg Q2W	Safety; ORR (RECIST 1.1)
KN045 Ongoing	Randomized, controlled, open-label Phase 3 trial	542 subjects randomized (enrollment complete); all subjects with 2L+ urothelial cancer; control is physician's choice chemotherapy (docetaxel, paclitaxel, vinflunine).	Pembrolizumab 200 mg Q3W	OS; PFS
KN052 Ongoing	Single arm, open-label Phase 2 trial	370 subjects enrolled; subjects are first-line advanced / unresectable (inoperable) or metastatic urothelial bladder subjects, cisplatin -ineligible; up to 150 subjects will constitute a training set for CPS strongly positive cutpoint determination.	Pembrolizumab 200 mg Q3W	ORR
KN057 Ongoing	Single arm, two-cohort Phase 2 trial	Up to 260 subjects with NMIBC unresponsive to BCG will be treated in 2 cohorts: Cohort A: Cis ± Ta/T1; Cohort B: HG Ta and/or T1.	Pembrolizumab 200 mg Q3W	CR rate in high-risk nonmuscle invasive bladder cancer (Cohort A); DFS (Cohort B)

Abbreviations: 2L=second-line; BCG=*Bacillus* Calmette-Guerin tuberculosis vaccine; Cis=carcinoma in situ; CPS=combined positive score; CR=complete response; DFS=disease-free survival; HG=High Grade; KN=Keynote; NMIBC=nonmuscle invasive bladder cancer; ORR=objective response rate; PD-L1=programmed death-ligand; Q2W=every 2 weeks; Q3W=every 3 weeks; RECIST=Response Evaluation Criteria in Solid Tumors; Ta and T1=WHO 2004 pathologic classifications of NMIBC; WHO=World Health Organization.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Urothelial (transitional cell) carcinoma describes a range of tumors that arise from the urothelial endothelium, which lines 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 [16]. Urothelial carcinoma (as distinct from squamous cell or adenocarcinoma) is the predominant histologic type of bladder cancer in the United States (US) and Western Europe, where it accounts for approximately 90% of bladder cancers [17]. In other areas of the world, nonurothelial histologies are more frequent.

Bladder cancer is more common in men than women; the global incidence of bladder cancer among men and women is 37 and 9 per 100,000 person-years, respectively. Incidence in white, black, Hispanic, and Asian men is 40, 21, 20, and 16 per 100,000 person-years, respectively. Bladder cancer becomes more common with age, with the highest incidence rates reported in people aged 75 to 84 years [17].

Along with age, smoking, and occupational exposure to carcinogens, certain medical treatments (including pelvic radiation and cyclophosphamide), and genetic predisposition are risk factors for bladder cancer [18] [19] [20] [21].

Notably, bladder cancer is associated with the highest cost per patient from diagnosis to death of all malignancies, largely because of the frequent procedures required for disease monitoring and treatment [22].

Bladder cancer can be categorized as NMIBC, which represents approximately 75% of primary diagnoses and is characterized by frequent recurrence and high morbidity, but a low risk of mortality, or muscle-invasive bladder cancer, which represents the other 25% of primary diagnoses and is potentially lethal in approximately 50% of individuals [17] and includes anatomically the bladder vesicle itself as well as the upper urinary tract and the accompanying lymph node compartments.

Patients with advanced or metastatic urothelial carcinoma present unique challenges. These are clinical scenarios in which patients present with locally advanced disease that cannot be treated with definitive intent or as metastatic disease from the beginning, or with recurrent disease that is inoperable or with metastatic disease that has progressed following initial treatment with definitive intent. Although a variety of chemotherapeutic agents are used in this setting and initially are associated with response, the prognosis for patients is poor – median survival from studies in these setting ranges from 8 to 15 months, and the majority of patients die from complications related to disease [23] [24]. The advanced/metastatic setting represents a clinical area in need of novel therapeutic approaches such as with checkpoint inhibitor therapy with or without chemotherapy [17].

Cisplatin-based combination chemotherapy is standard first-line treatment for patients with advanced bladder cancer based on randomized trials [23] [25] [26] [27] [28]. The median survival with these regimens is 13 to 15 months, and 5% to 15% of patients attain long-term survival. However, cisplatin ineligibility is common [29] [30].

Carboplatin is often substituted for cisplatin in such patients, but it is associated with inferior outcomes, as shown in a meta-analysis of randomized Phase 2 trials [31]. Galsky et al

conducted a meta-analysis of published trials in patients with metastatic urothelial carcinoma to assess clinical outcomes with cisplatin- versus carboplatin-based regimens. The meta-analysis evaluated 4 trials (one Phase 3 and three Phase 2 trials) with a total of 286 patients; results showed that there was a significantly higher likelihood of achieving an objective response, and in particular, a complete response, with cisplatin-based therapy. These results supported the notion that cisplatin-based regimens "are favored for the first-line treatment of metastatic urothelial carcinoma (UC)" [29].

Established guidelines (i.e., National Comprehensive Cancer Network [NCCN] and European Society of Medical Oncology [ESMO]) include the following considerations in determining if a subject is clinically ineligible for cisplatin: CTCAE v.4.0, Grade ≥2 peripheral neuropathy; CTCAE v.4.0, Grade ≥2 audiometric hearing loss (25 decibels in 2 consecutive wave ranges); CrCl (calculated or measured) <60 mL/min, but ≥30 mL/min (note: Subjects with a CrCl [calculated or measured] <30 mL/min are excluded from this trial); New York Heart Association Class III heart failure; and ECOG PS of 2.

A Phase 3 trial comparing gemcitabine/carboplatin (GC) with methotrexate/ carboplatin/vinblastine (MCAVI) in cisplatin-ineligible patients showed a median survival of only 8 to 9 months with both regimens [24]. Notably, those with both poor renal function and poor PS fared especially poorly with combination chemotherapy in this trial. Thus, there remains a significant unmet medical need for well tolerated active therapies in this population. According to the NCCN Guidelines, clinical trials of potentially less toxic therapies are recommended for this population of patients. A Phase 1 combination of nivolumab plus platinum doublets (including pembrolizumab-cisplatin) showed tolerability in non–small cell lung cancer (NSCLC) [32] [33]. However, small numbers limit the efficacy evaluation. Papadimitrakopoulou, et al reported data on the combination of pembrolizumab and chemotherapy (carboplatin/paclitaxel [Cohort A] or carboplatin/pemetrexed [Cohort C]) at the American Society of Clinical Oncology [34], with results from 49 subjects. The treatment-related Grade 3 to 4 AE rate was 32% to 38%. Potentially immune-related AEs were reported in 2 patients (8%) in Cohort A (Grade 3 rash and Grade 2 colitis), and 4 subjects (17%) in Cohort C (Grade 3 colitis, Grade 2 hypothyroidism, and Grade 1 colitis and hyperthyroidism). The preliminary response rate was 28% for the combination with carboplatin/paclitaxel and 58% for the combination with carboplatin/pemetrexed. Thus, preliminary evidence suggests that the combination of an immune-checkpoint inhibitor with chemotherapy would be expected to be safe and tolerable and to have the potential for enhanced efficacy.

A Phase 2 combination of ipilimumab with platinum doublet (carboplatin-paclitaxel) showed tolerability in NSCLC and improved immune-related PFS when given in a phased approach [35]. A Phase 2 combination of ipilimumab with gemcitabine-cisplatin in bladder cancer has shown in pharmacodynamic (PD) data that the addition of ipilimumab leads to immunostimulatory effects in circulating cells, suggesting that chemotherapy may not necessarily abrogate immune effects of checkpoint blockade [31]. Numerous ongoing investigator-sponsored studies are investigating the safety and efficacy signal of pembrolizumab with chemotherapy in a variety of malignancies.

Pembrolizumab monotherapy was associated with an ORR of 27% in patients with chemotherapy-refractory metastatic PD-L1 positive urothelial carcinoma [36].

Sixty-four percent of subjects in this cohort experienced reductions in the size of their tumors, and responses were durable. Other compounds have shown similar activity [37]. PD-L1 expression in the tumor microenvironment was associated with higher response rates. For this reason, the primary hypotheses have been designed to investigate efficacy both for "all comers" and for subjects with tumors with CPS ≥10% PD-L1 expression.

The prediction of response to anti-PD-1 therapy is based on the results from a trial by Topalian et al [38] who examined PD-LI expression in the archival specimens of 42 of the 296 subjects treated with the PD-1 inhibitor nivolumab. Of those 17 subjects whose tumor cells did not stain positive for PD-L1 using a 5% threshold of tumor cell surface expression, no objective response by RECIST 1.1 was observed. But among the 25 subjects whose tumor cells were considered positive for PD-L1, 9 responded (36%). Therefore, it is hypothesized that PD-L1 expression may be a predictive biomarker of anti-PD-1 activity and subjects will be allocated by PD-L1 expression in this trial.

The present trial has been designed to confirm and elaborate on findings from prior and ongoing pembrolizumab trials in advanced urothelial carcinoma (KN012, KN045, and KN052) by investigating the use of pembrolizumab in an earlier disease setting as well as the potential for additive or synergistic therapeutic advantage associated with combining pembrolizumab with chemotherapy. The primary trial hypothesis is that combo is superior to chemo only with respect to PFS using RECIST 1.1 as assessed by BICR in all subjects (both PD-L1 CPS ≥10% and CPS <10%)."

4.2.2 Rationale for Dose Selection/Regimen/Modification

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

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W.
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications.
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based pharmacokinetic [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched and all comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W vs 10 mg/kg Q2W (KN001 B2, KN001 D, KN002, KN010 and KN021), and 3 studies compared 10 mg/kg Q3W vs 10 mg/kg Q2W (KN001 B3, KN001 F2, and KN006). All of these studies showed flat dose- and exposure-response relationships across the doses studied representing an approximate 5 to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including

head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

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

4.2.2.1 Rationale for the Use of Comparators

Cisplatin-based combination chemotherapy with gemcitabine is standard first-line treatment in the US (NCCN Guidelines) and Europe (ESMO guidelines for patients with advanced bladder cancer based on randomized trials) [17] [39] [40] [41] [23] [25] [26] [27] [28]. The median survival with these regimens is 13 to 15 months, but only 5% to 15% of patients attain long-term survival [29] [42] [30].

A Phase 3 trial comparing carboplatin plus gemcitabine with MCAVI in cisplatin-ineligible patients showed a median survival of only 8 to 9 months with both regimens. [24]. Gemcitabine with cisplatin provides a similar long-term PFS advantage to methotrexate/vinblastine/doxorubicin/cisplatin with a better safety profile and tolerability [23] [28].

Approximately 40% of patients with urothelial carcinoma who are usually elderly and suffering from serious comorbid medical conditions are not fit to be treated with cisplatin-based regimens [43] [30] [42]. Multiple trials have been performed in the “unfit” population, albeit using heterogeneous eligibility criteria to define cisplatin-ineligible. While several regimens have been explored in this population (e.g., gemcitabine/oxaliplatin, gemcitabine/paclitaxel, gemcitabine/vinorelbine, gemcitabine /epirubicin), the most commonly explored has been the doublet of carboplatin plus gemcitabine, evaluated in at least 3 Phase 2 trials and one Phase 2/3 trial and recommended in the NCCN Guidelines [17] [24] [44] [40] [45]. Thus, for this clinical trial, subjects treated with SOC chemotherapy will be treated either with cisplatin and gemcitabine or carboplatin and gemcitabine.

A number of lines of evidence support the rationale to add pembrolizumab therapy to these chemotherapies. First, gemcitabine has been shown to lead to immunogenic cell death. In an MC38 model, gemcitabine may have additive/synergistic effects with muDX400 (murine anti-PD-1) [39]. There is no antagonistic effect of GC in combination with concurrent pembrolizumab.

Phase 1 combinations of an immune-checkpoint inhibitor therapy with platinum-containing doublet chemotherapy have been reported to show tolerability in NSCLC [34]. However, small numbers limit the efficacy evaluation. A Phase 2 checkpoint inhibitor-platinum combination has been reported to have shown tolerability and improved immune-related PFS in NSCLC [35]. Because of these encouraging early findings and because not all patients derive clinical benefit with checkpoint inhibitor monotherapy or with chemotherapy alone, KN361 has been designed to include a combination arm, pembrolizumab with chemotherapy.

Additionally, KN021 (NCT02039674), KN048 (NCT02358031), and KN059 (NCT02335411) have been investigating the addition of pembrolizumab to chemotherapy in lung cancer, head and neck cancer, and gastric cancer, respectively, since February 2014. In KN021, these combinations included cisplatin, carboplatin, and gemcitabine, each combined with pembrolizumab. KN048 and KN059 have been designed to investigate pembrolizumab therapy with or without cisplatin/carboplatin and 5-flourouracil (5-FU), and pembrolizumab with or without cisplatin and 5-FU.

The doses and schedules of chemotherapy treatment, with and without pembrolizumab, have been based on these trials and will be as follows: cisplatin 70 mg/m^2 or carboplatin AUC 5 on Day 1; gemcitabine on Days 1 and 8 of a 3-week cycle.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary Endpoints

Progression-free Survival

Given the current paradigm changes, in the treatment continuum of metastatic bladder cancer an appropriate primary endpoint for this Phase III pivotal study in the form of PFS was chosen.

RECIST 1.1, as assessed by BICR, will be used to determine the dates of progression, as this methodology is accepted by regulatory authorities. The BICR will be blinded to the treatment assignment of the subjects to minimize bias in the response assessments. Progression-free survival is an acceptable measure of clinical benefit for a late stage trial that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be read by a central imaging vendor blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Real time determination of radiologic progression as determined by central review will be communicated to the site.

In addition, final determination of radiologic progressive disease (PD) will be based on the BICR assessment of progression, rather than local site investigator/radiology assessment. Expedited assessment by BICR in instances of suspected radiologic progression identified at the site (verification of PD) will be communicated to the site trial team.

Overall Survival

Overall survival is defined as the time from randomization until death from any cause. Survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint [46]. (Food and Drug Administration [FDA] Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, 2007, page 5.)

4.2.3.1.2 Secondary Endpoints

The secondary efficacy endpoints of this trial are to evaluate DOR, DCR, and ORR per RECIST 1.1 assessed by BICR.

4.2.3.2 Exploratory Endpoints

4.2.3.2.1 Patient-reported Outcomes

The EORTC QLQ-C30 and EuroQoL-5D (EQ-5D) PROs are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

EORTC QLQ-C30

The EORTC QLQ-C30 is the most widely used cancer-specific health-related quality of life (QoL) instrument, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and QoL scale [47]. The EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing QoL in oncology trials [47].

eEuroQoL EQ-5D

The eEuroQol-5D (eEQ-5D) is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in economic analyses [48]. The 5 health state dimensions in the EQ-5D include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [49]. Each dimension has 3 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. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [50].

4.2.3.3 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in subjects with recurrent/progressive urothelial cancer. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE Version 4.0 criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including SAEs and ECIs. The attribution to drug, time of onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. Adverse events will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. The mandatory Safety Follow-up Visit will be conducted approximately 30 days after the last dose of trial treatment or before the

initiation of a new antineoplastic 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 to 1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. Serious AEs will be collected for 90 days after the trial treatment or 30 days after the end of treatment, if the subject initiates new anticancer therapy, whichever is earlier.

4.2.3.4 Planned Exploratory Biomarker Research

Introduction

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood, and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy as well as determinants of AEs in the course of our clinical trials. These efforts will identify novel predictive/ pharmacodynamic biomarkers and generate information that will better guide single agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, we will collect biospecimens (blood components, tumor material, etc.) to support analyses of cellular components (e.g., protein, deoxyribonucleic acid [DNA], ribonucleic acid [RNA], metabolites) and other circulating molecules. Investigations may include, but are not limited to:

Germline (Blood) Genetic Analyses (e.g., single-nucleotide polymorphism [SNP] Analyses, Whole Exome Sequencing, and Whole Genome Sequencing)

This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome to interpret tumor-specific DNA mutations. Finally, microsatellite instability (MSI) may be evaluated, as this is an important biomarker for some cancers (e.g., colorectal cancer).

Genetic (DNA) Analyses from Tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (i.e., mutations, methylation status, MSI etc.). Key molecular changes of interest to immune-oncology drug development include (for example) the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a "hyper-mutated" state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that to understand tumor-specific mutations; it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated, as this is an important biomarker for some cancers (e.g., colorectal cancer).

Tumor and Blood RNA Analyses

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

Proteomics and Immunohistochemistry Using Blood or Tumor

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

Other Blood-derived Biomarkers:

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

4.2.3.5 Future Biomedical Research

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

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

4.3 Benefit/Risk

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

Several lines of evidence suggest that immune-checkpoint inhibitor therapy can be highly active as monotherapy in advanced urothelial cancer. For example, pembrolizumab monotherapy was associated with an ORR of 27% in patients with chemotherapy-refractory metastatic PD-L1 positive urothelial carcinoma [36]. Sixty-four percent of patients in this cohort experienced reductions in the size of their tumors. Responses were durable (range 8 to 64 weeks), and 19% of patients remained on pembrolizumab treatment after 1 year of initiating treatment [36]. Recently published data from atezolizumab, a PD-L1 antagonist, has shown similar activity [51].

Importantly, PD-L1 expression in the tumor microenvironment was associated with higher response rates. For this reason, this study will also investigate efficacy for both, all comers as well as for subjects with PD-L1 positive tumors.

In KN361, the Sponsor considers that superior efficacy associated with one or both experimental treatment arms, pembrolizumab and/or pembrolizumab with chemotherapy, in terms of either a PFS or OS advantage, would constitute a seminal improvement of treatment options for subjects with advanced or metastatic urothelial cancer.

The chemotherapy arm is the current SOC, with well-characterized risks listed in the labeling.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB, approved labeling, and informed consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects with advanced/unresectable (inoperable) or metastatic urothelial carcinoma of the renal pelvis, ureter [upper urinary tract], bladder, or urethra at least 18 years old on the day of signing the informed consent 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. Have a histologically or cytologically confirmed diagnosis of advanced/unresectable (inoperable) or metastatic urothelial carcinoma of the renal pelvis, ureter [upper urinary tract], bladder, or urethra. Both transitional cell and mixed transitional/non-transitional cell histologies are allowed, but transitional cell carcinoma must be the predominant histology.

2. Have measurable disease based on RECIST 1.1 as determined by the local site investigator/radiology assessment. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
3. Voluntarily agree to participate by providing written informed consent/assent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
4. Be ≥18 years of age on the day of signing informed consent.
5. Have received no prior systemic chemotherapy for advanced or metastatic urothelial carcinoma, with the following exceptions:
    a. Neoadjuvant platinum-based chemotherapy with recurrence >12 months from completion of therapy is permitted.
    b. Adjuvant platinum-based chemotherapy following radical cystectomy with recurrence >12 months from completion of therapy is permitted.

    Note: Low-dose chemotherapy (e.g., low-dose cisplatin, cisplatin plus 5-FU, mitomycin plus 5-FU, or cisplatin plus paclitaxel) given concurrently with radiation to the primary tumor site is not considered systemic therapy. In the clinical setting, chemotherapy is given with the sole purpose of sensitizing the tumor to local radiation. It is not administered at doses with any systemic efficacy. Surgery is not considered first-line therapy following diagnosis of advanced/metastatic disease.
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 from a muscle-invasive urothelial carcinoma or a metastatic biopsy, originating from the original tumor. A newly obtained biopsy is strongly preferred, but not required if archival tissue is evaluable. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut. Refer to Section 7.1.2.12 in the protocol for an explanation. PD-L1 status (CPS ≥10% or CPS <10%) must be determined by the central laboratory during the screening period prior to enrollment.
7. Have an ECOG PS of 0, 1, or 2.
8. Demonstrate adequate organ function as defined in Table 3. (All screening labs should be performed within 2 weeks prior to treatment initiation.)

Table 3 Adequate Organ Function

System	Laboratory Value
Hematological	
ANC	≥1,500/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without a red blood cell transfusion within 2 weeks of the screening test
Renal – refer to Appendix 12.5 for country-specific requirements	
Serum creatinine **OR** calculated creatinine clearance [a] (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN **OR** ≥30 mL/min for subjects with creatinine levels >1.5 × institutional ULN
Hepatic	
Serum total bilirubin	≤1.5 × ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN **OR** ≤5 × ULN for subjects with active liver metastases
Alkaline Phosphatase	If >2.5 × ULN, then liver fraction should be ≤2.5 × ULN
Coagulation	
INR PT aPTT	≤1.5 × ULN This can vary if subject is receiving anticoagulant therapy, as long as PT or aPTT remains within therapeutic range of the anticoagulant's intended use

Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; CrCl=creatinine clearance; GFR=glomerular filtration rate; INR=International Normalized Ratio; mcL=microliters; PT=prothrombin time; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal.

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

9. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of trial medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
10. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the trial through 120 days after the last dose of pembrolizumab or 180 days after chemotherapy treatment.

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

11. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, starting with the first dose of trial therapy through 120 days after the last dose of pembrolizumab or 180 days after chemotherapy.

    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. An example of local therapy with curative intent is treatment with chemotherapy and radiation for Stage 3 disease. A subject with nonurothelial carcinoma of the urinary tract is also ineligible.
2. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of 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 randomization.
4. Has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
    a) Brief (<7 days) use of systemic corticosteroids is allowed when use is considered SOC.
    b) Subjects with vitiligo, type I diabetes mellitus, hypothyroidism, or resolved childhood asthma/atopy would be an exception to this rule.
    c) Subjects who require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the trial.
    d) Subjects with hypothyroidism stable on hormone replacement or Sjøgren's syndrome will not be excluded from the trial.
    e) If a subject is on a stable dose of steroids for central nervous system (CNS) metastases at screening, the subject will need to stop steroids 7 days prior to first dose in order to qualify for the trial.
5. Has had a prior anticancer mAb for direct antineoplastic treatment within 4 weeks prior to the first dose of trial treatment (6 weeks for nitrosoureas or mitomycin C) or who has not recovered (i.e., ≤Grade 1 or at baseline) from AEs due to mAbs administered more than 4 weeks earlier. Subjects previously treated with a mAb will be eligible to participate after a 28-day washout period.

6. Has not recovered (i.e., AE ≤Grade 1 or at baseline) from AEs due to a previously administered agent.
    a) Subjects with ≤Grade 2 neuropathy or ≤Grade 2 alopecia are an exception to this criterion and may qualify for the trial.
    b) If subjects received major surgery they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting trial therapy.
7. Has a known additional malignancy that is progressing or requires active treatment within the past 5 years.
    a) 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.
    b) 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; prostate-specific antigen (PSA) undetectable.
8. Has a history of (noninfectious) pneumonitis that required steroids or current pneumonitis.
9. Has a known history of active tuberculosis (TB) (*Bacillus tuberculosis*).
10. Has an active infection requiring systemic therapy.
11. Has a history of severe hypersensitivity reaction (e.g., generalized rash/erythema, hypotension, bronchospasm, angioedema or anaphylaxis) to pembrolizumab, gemcitabine, carboplatin, or cisplatin or their analogs, and/or to any of their excipients.
12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. At the time of signing informed consent is a known regular user (including "recreational use") of any illicit drug(s) or had a recent history (within the last year) of drug or alcohol abuse.
14. 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 pembrolizumab or 180 days after the last dose of chemotherapy treatment.
15. Has received prior therapy with an anti-PD-1, or anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another coinhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137).
16. Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).

17. Has known active hepatitis B (e.g., HBsAg reactive) or hepatitis C (e.g., HCV RNA [qualitative] is detected).
18. Has received a live virus vaccine within 30 days of planned start of trial therapy.
19. Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of trial treatment.
20. Has symptomatic ascites or pleural effusion; a subject who is clinically stable following treatment for these conditions is eligible.
21. Has had a prior allogeneic stem cell or bone marrow transplant.

5.2 Trial Treatment

The treatments to be used in this trial are outlined below in Table 4.

Table 4 Trial Treatments

Drug	Dose/ Potency	Cycle Length	Route of Administration	Regimen	Use
Pembrolizumab Regimens:					
Pembrolizu-mab (MK-3475)	200 mg	Q3W	IV infusion	Day 1 of each 3-week cycle	Pembro Monotherapy: Experimental regimen Pembro + Chemotherapy: Experimental regimen
Chemotherapy Regimens:					
Gemcitabine	1000 mg/m^2	Q3W	IV infusion	Day 1 and 8 of each 3-week cycle	Pembro + Chemotherapy: Experimental regimen Chemotherapy alone: Comparator
PLUS					
Cisplatin	70 mg/m^2	Q3W	IV infusion	Day 1 (or Day 2)[a] of each 3-week cycle	Pembro + Chemotherapy: Experimental regimen Chemotherapy alone: Comparator
OR					
Carboplatin (to be used only in subjects who are ineligible for cisplatin)	AUC 5[b] (or AUC 4.5)[b]	Q3W	IV infusion	Day 1 (or Day 2)[a] of each 3-week cycle	Pembro + Chemotherapy: Experimental regimen Chemotherapy alone: Comparator

Abbreviations: AUC=area under the curve; IV=intravenous; Q3W=every 3 weeks.
[a] Day 1 is the preferred day of dosing; however, treatment may be given on Day 2 if required per local guidelines.
[b] AUC 5 is preferred dose; however, AUC 4.5 is acceptable if required per local guidelines.

Note: A subject can switch from cisplatin to carboplatin during the course of the trial if required by clinical factors such as impairment of renal function. A maximum of 6 cycles of chemotherapy should be administered.

Trial Treatment should begin within 3 days of randomization.

All supplies indicated in Table 4 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

Dose selection rationale has been provided in Section 4.2.2 – Rationale for Dose Selection/Regimen/Modification. Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

Carboplatin will be prepared and administered per local guidelines and practices.

AUC 5 (Using Calvert formula). Carboplatin dose not to exceed 750 mg for AUC 5 and 675 mg for AUC 4.5

Calvert Formula:

Total Dose (mg) = (target AUC) × (CrCl + 25)

The estimated GFR used in the Calvert formula should not exceed 125 mL/min

Maximum carboplatin dose (mg) =

Target AUC 5 (mg•min/mL) × (125 + 25) = 5 × 150 mL/min = 750 mg

Target AUC 4.5 (mg•min/mL) × (125 + 25) = 4.5 × 150 mL/min = 675 mg

Cisplatin will be prepared and administered per local guidelines and practices.

Gemcitabine will be prepared and administered per local guidelines and practices.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

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

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

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other

causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 5.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 6.

Table 6 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

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

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

Other Allowed Dose Interruption for Pembrolizumab

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

5.2.1.2.2 Dose Modifications for Cisplatin or Carboplatin

Dose modifications for cisplatin or carboplatin will be implemented according to local guidelines and practices.

5.2.1.2.3 Dose Modifications for Gemcitabine

Dose modifications for gemcitabine will be implemented according to local guidelines and practices.

5.2.1.2.4 Dose Modifications for Combination Therapy or Chemotherapy

All components of the regimen should be administered together. If one of the components in the regimen is interrupted/delayed, other medications in the regimen should also be interrupted/delayed. If one or all of the chemotherapy components in the combo arm is discontinued, subjects can continue with pembrolizumab up to the full 35 cycles. Dose modifications or dose interruptions should not be used to resolve Grade 2 or Grade 3 AEs of

anemia or leukopenia that are related to chemotherapy. To ensure that subjects can receive adequate SOC chemotherapy dosing, standard supportive care measures (e.g., erythrocyte infusion, thrombocyte infusion, G-CSF, and erythropoietin) should be utilized first before dose modification if there are no other reasons to modify SOC dosing for chemotherapy agents.

5.2.2 Timing of Dose Administration

Study treatment will be administered after all procedures/assessments have been completed (as detailed in Section 6.0 – Trial Flow Chart), and in the following order: pembrolizumab infusion will be administered first, followed by premedication for the assigned chemotherapy (if applicable; see Section 5.6.2 – Supportive Care Guidelines for Chemotherapy-related Adverse Events) and then administration of chemotherapy, according to local guidelines and practices.

After Cycle 1 Day 1, trial treatment may be administered up to 3 days before or after the scheduled dosing date for administrative reasons per investigator's judgment.

5.2.2.1 Pembrolizumab

MK-3475 200 mg will be administered as a 30-minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of - 5 minutes and + 10 minutes is permitted (i.e., infusion time is 30 minutes: - 5 min/+10 min).

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

5.2.2.2 Cisplatin/Gemcitabine

Cisplatin will be administered as an IV infusion on Day 1 of a 3-week cycle according to local guidelines and procedures. Cisplatin may be administered on Day 2, if required per local guidelines; however, Day 1 is the preferred day for treatment administration. Gemcitabine will be administered as an IV infusion on Days 1 and 8 of a 3-week cycle, according to local guidelines and procedures.

5.2.2.3 Carboplatin/Gemcitabine

Carboplatin will be administered as an IV infusion on Day 1 of a 3-week cycle according to local guidelines and practices. Carboplatin may be administered on Day 2, if required as per local guidelines; however, Day 1 is the preferred day for treatment administration. Gemcitabine will be administered as an IV infusion on Days 1 and 8 of a 3-week cycle, according to local guidelines and procedures.

5.2.3 Trial Blinding

Trial treatment will be open-label. 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 DMC interim analyses, who will have no other responsibilities associated with the study.

Imaging data for the primary analysis will be centrally reviewed by BICR without knowledge of subject treatment assignment.

The trial team at the Sponsor consisting of clinical, statistical, statistical programming and data management personnel will not be blinded to subject-level PD-L1 biomarker results obtained at baseline to monitor PD-L1 prevalence.

5.3 Randomization

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 3 treatment arms. Subjects will be assigned randomly in a 1:1:1 ratio to one of the treatment arms below:

1. Pembro only
2. Combo, either with
    - Cisplatin and gemcitabine, or
    - Carboplatin and gemcitabine
3. Chemo only, either
    - Cisplatin and gemcitabine, or
    - Carboplatin and gemcitabine

Investigators must select 1 chemotherapy treatment option (cisplatin or carboplatin) before randomization to use in the event that the subject is randomized either to the combo treatment arm or the chemo only treatment arm. As of 21-FEB-2018, subjects who have tumors that are PD-L1 CPS <10% will be randomized only to combo arm or chemo only arm. There is no change to randomization for subjects who have tumors that are PD-L1 CPS ≥10%.

5.4 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

- Chemotherapy drug: Investigator choice cisplatin or carboplatin
- PD-L1 expression (CPS ≥10% or CPS <10%)

5.5 Concomitant Medications/Vaccinations (Allowed and 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. Note that subjects receiving bone resorptive therapy (including, but not limited to bisphosphonate or RANK-L inhibitor) must have been on stable doses for ≥4 weeks prior to first dose of trial treatment.

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 up to 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 – Assessing and Recording Adverse Events.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including re-treatment for post-CR 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
- 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 the Sponsor (except during screening).

- Live vaccines within 30 days prior to the first dose of pembrolizumab treatment and while participating in the trial if in 1 of the pembrolizumab-containing regimen groups (combo or pembro only). Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
  - If precluded by local regulations, live vaccines should not be given for 120 days after the last dose of pembrolizumab is administered.
- Any chronic immunological-suppressive treatment for any reason other than the management of AEs, as described in Section 5.2.1.2.1 (Table 5).

  Note: Inhaled or topical steroids are allowed, and systemic steroids at doses ≤10 mg/day prednisone or equivalents are allowed, as described in Section 5.2.1.2.1,

and immune suppressants are allowed as prophylaxis for contrast allergy for imaging procedures.

- Any medication prohibited in combination with chemotherapy as described in the respective product labels for cisplatin, carboplatin, and gemcitabine.

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 medically necessary.

The exclusion criteria describe other medications prohibited in this trial.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Subjects Receiving Pembrolizumab

See Section 5.2.1.2.1 - Dose Modifications for Pembrolizumab

5.6.2 Supportive Care Guidelines for Chemotherapy-related Adverse Events

Cisplatin/gemcitabine-related and GC-related AEs should be managed according to local guidelines and practices.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

Female subjects will be considered of nonreproductive potential if they meet 1 of the following criteria:

- She is postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age who are not using hormonal contraception or hormonal replacement therapy, a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state). In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- She had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion at least 6 weeks prior to screening;
- She has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, for the course of the trial through 120 days after the last dose of pembrolizumab or 180 days after chemotherapy treatment, by complying with one of the following (refer to Appendix 12.5 for country-specific requirements):

- Practice abstinence from heterosexual activity;

  Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and European Research Councils (ERCs)/Institutional Review Boards (IRBs). Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

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

Acceptable methods of contraception are‡:

- Single method (one of the following is acceptable):
  - intrauterine device (IUD)
  - vasectomy of a female subject's male partner
  - contraceptive rod implanted into the skin
- Combination method (requires use of 2 of the following):
  - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
  - cervical cap with spermicide (nulliparous women only)
  - contraceptive sponge (nulliparous women only)
  - male condom or female condom (cannot be used together)
  - hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection.

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

Subjects should be informed that taking the trial medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the trial. To participate in the trial, subjects of childbearing potential must adhere to the contraception requirements (described above) from the day of trial medication initiation (or 14 days prior to the initiation of trial medication for oral contraception) for the course of the trial through 120 days after the last dose of pembrolizumab or 180 days after chemotherapy treatment. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the trial. For women of childbearing potential, monthly pregnancy testing should be conducted as per local regulations where applicable.

Below are the required contraceptives for countries where the health authority requests compliance with the Clinical Trial Facilitation Group Guidance:

Subjects should use birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
- Oral
- Injectable
- Implantable
- IUD
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab or carboplatin, cisplatin or gemcitabine, the subject will immediately be removed from study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is an SAE (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The trial 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 trial 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 – Reporting of Pregnancy and Lactation to the Sponsor. Subjects should then be followed for Survival Follow-up. (Refer to Section 7.1.5.3.4)

5.7.4 Use in Nursing Women

It is unknown whether pembrolizumab, carboplatin, and gemcitabine are excreted in human milk. Cisplatin is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5.3. – Posttreatment Visits

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

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

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the subject at unnecessary risk from continued administration of study treatment.
- The subject has a confirmed positive serum pregnancy test. Refer to Section 5.7.3 – Use in Pregnancy.
- Investigator's decision to withdraw subject.
- Verified radiographic disease progression by BICR.

  Note: For unconfirmed radiographic progression, refer to Section 7.1.2.8.2 – Tumor Imaging During the Trial.
- Unacceptable adverse experiences as described in Section 7.2.

  Note: Subjects on the combo arm who discontinue one or all components of chemotherapy due to toxicity or AEs prior to the full 6 cycle chemotherapy treatment regimen, can continue with pembrolizumab up to the full 35 cycles.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 5.2.1.2

- A confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Investigator's decision to withdraw the subject
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

Note: The number of treatments is calculated starting with the first dose. Subjects who stop the combination or pembrolizumab after receiving 35 doses may be eligible for re-treatment if they progress after stopping trial treatment provided they meet the requirements detailed in Section 7.1.5.2.1 - Second Course Phase (Re-treatment Period). Subjects may be re-treated in the Second Course Phase (Re-treatment) for up to an additional 17 cycles (approximately 1 year).

- Discontinuation of treatment in subjects enrolled to the pembro only or the combo arm may be considered for subjects who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab beyond the date when initial CR was declared. Subjects in the combo arm must have received at least 4 cycles of chemotherapy to ensure that subjects receive adequate SOC.
- Administrative reasons.

For subjects who are discontinued from treatment, but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed.

For subjects who are discontinued from treatment, but continue to be monitored in the trial, see Section 6.0 – Trial Flow Chart, and Section 7.1.5.3 – Posttreatment Visits for those procedures to be completed at each specified visit.

Subjects may be allowed to begin treatment again if deemed medically appropriate.

5.8.2 Withdrawal from the Trial

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

A subject must be withdrawn from the trial if:

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

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

5.8.3 Treatment After Initial Radiologic Progression

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of immunotherapeutic agents such as pembrolizumab which 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 a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may, thus, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of patients with melanoma enrolled in KN001, 7% of evaluable patients experienced delayed or early tumor pseudoprogression. Of note, patients who had PD by RECIST 1.1, but not by immune-related Response Criteria had longer OS than patients with PD by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of patients. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enables treatment beyond initial radiographic progression. Immune-related RECIST (irRECIST) is RECIST 1.1 adapted to account for the unique tumor response seen with immuno-therapeutics as described in [52]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, Merck has implemented an adaptation related to new lesions, nontarget and tumor burden assessment to confirm radiographic progression. irRECIST will be used by local site investigators to assess tumor response and progression, and to make treatment decisions by a BICR in support of PFS endpoint.

For further information on irRECIST, see Section 7.1.2.10.

5.8.4 Discontinuation of Trial Therapy After Complete Response

Discontinuation of treatment may be considered for subjects on the pembrolizumab arms (combo and pembro only) who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks) with pembrolizumab, and had at least 2 cycles of pembrolizumab beyond the date when the initial CR was declared. Subjects on the combination treatment must have received at least 4 cycles of chemotherapy.

These subjects should remain on study and continue in the Follow-up period of the trial with protocol-specified disease assessments, including imaging, as outlined in the Trial Flow Chart (see Section 6.0). Subjects who then experience radiographic disease progression may be eligible for up to 1 year (17 cycles) of additional treatment with pembrolizumab at the discretion of the investigator, if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Additional details are provided in Section 7.1.5.2.1. Response or progression in the Second Course Phase will not count toward the OS and PFS of the primary endpoint in this trial.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator). Upon study completion, participants are discontinued and enrolled in a pembrolizumab extension study.

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 external 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 trials indicates a potential health hazard to subjects.
5. Plans to modify or discontinue the development of the trial drug.

In the event of Sponsor decision to no longer supply trial 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 – Pembrolizumab Only (Pembro Only)

Trial Period:	**Screening Phase**	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Posttreatment Visits**		
							To be repeated beyond 8 cycles [a]							
Treatment Cycle/Title	Screening (Visit 1)		1	2	3	4	5	6	7	8	End of Treatment Visit	Safety Follow-up	Efficacy Follow-up[b]	Survival Follow-up
Scheduling Window (Days)	-42 to -1	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+3 days)	Every 9 or 12 weeks (±7 days)	Every 12 weeks (±7 days)
Administrative Procedures														
Informed Consent	X [c]													
Informed Consent for Future Biomedical Research	X [d]													
Inclusion/Exclusion Criteria		X												
Subject Identification Card	X													
Demographics and Medical History		X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X		
Obtain randomization number and trial drug assignment using IVRS/IWRS			X [e]											
Trial Treatment Administration			X	X	X	X	X	X	X	X				
Posttrial Anticancer Therapy Status												X	X	X [f]
Survival Status [f]			<----------											X [f]
Clinical Procedures/Assessments														
Review Adverse Events [g]		X	X	X	X	X	X	X	X	X	X	X [g]	X [g]	
12-Lead ECG (Locally Performed)		X												
Full Physical Examination		X									X			
Directed Physical Examination			X	X	X	X	X	X	X	X				
Height, Weight, and Vital Signs (T, P, RR, BP) [h]		X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status		X	X	X	X	X	X	X	X	X	X	X	X	

Trial Period:	**Screening Phase**	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Posttreatment Visits**		
							To be repeated beyond 8 cycles [a]				End of Treatment	Safety Follow-up	Efficacy Follow-up[b]	Survival Follow-up
Treatment Cycle/Title	Screening (Visit 1)		1	2	3	4	5	6	7	8	Visit			
Scheduling Window (Days)	-42 to -1	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+3 days)	Every 9 or 12 weeks (±7 days)	Every 12 weeks (±7 days)
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory														
Pregnancy Test [i]		X [j]												
PT/INR and aPTT		X [j]												
CBC with Differential		X [j]		X	X	X	X	X	X	X	X	X		
Comprehensive Chemistry Panel		X [j]		X	X	X	X	X	X	X	X	X		
Urinalysis [k]		X [j]					X [k]					X		
T3, FT4, and TSH		X [j]					X [k]					X		
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory														
Blood for RNA Analyses [l]			X	X			X				X			
Blood for Plasma Biomarker Analyses [l]			X	X							X			
Blood for Serum Biomarker Analyses [l]			X	X							X			
Blood for Genetic Analysis [m]			X											
Efficacy Measurements														
Tumor Imaging [n]		X [n]				X			X		X		X	
Tumor Tissue Collection														
Archival or Newly Obtained Tissue Collection for Biomarker Analysis [o]	X[o]													
Patient-reported Outcomes														
EuroQol EQ-5D [p]			X	X	X	X			X		X	X		
EORTC QLQ-C30 [p]			X	X	X	X			X		X	X		

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; BP=blood pressure; discon=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; EuroQol=European Quality of Life; FT4=free thyroxine; EORTC=European Organisation for Research and Treatment of Cancer Quality of Life; ePRO=electronic patient-reported outcomes; FBR=future biomedical research; INR=International Normalized Ratio; IRB/IEC=institutional review board/independent ethics committee; IVRS/IWRS=interactive voice response system/integrated web response system; P=pulse; pembro=pembrolizumab; PT=prothrombin time; Q9W=every 9 weeks; Q12W=every 12 weeks; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; T=temperature; T3=triiodothyronine; TSH=thyroid-stimulating hormone.

[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. Imaging should be performed at 9 weeks (63 days ±7) from randomization until Week 54 and every 12 weeks (84 days ±7) thereafter, regardless of any treatment delays.

[b] Subjects who complete the protocol-required cycles of study intervention or who discontinue study therapy without documented disease progression should enter Efficacy Follow-up and continue disease monitoring per study schedule (i.e., Q9W before Week 54 or Q12W after Week 54). See Section 7.1.2.8.3 for more details.

[c] Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

[d] Signing the informed consent for FBR samples is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.

[e] The window for each visit is ±3 days unless otherwise noted. Cycle 1 treatment must be given within 3 days of randomization.

[f] After the start of new anticancer treatment or documented disease progression, the subject should be contacted approximately every 12 weeks (84 days ±7) to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).

[g] After the end of treatment, each subject will be followed for 30 days for AE monitoring. SAEs will be collected for 90 days after the trial treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. All drug-related SAEs and ECIs will be reported regardless of time frame.

[h] Height will be measured at the screening visit only. Refer to Section 7.1.2.4.

[i] 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 trial site laboratory will be required. Monthly pregnancy testing should be conducted as per local regulations where applicable. Refer to Appendix 12.5 for country-specific requirements.

[j] Laboratory tests for screening and determining eligibility are to be performed within 14 days prior to the first dose of trial treatment. Refer to Section 7.1.3.2 for details regarding laboratory tests.

[k] Urinalysis and thyroid tests (T3, FT4, and TSH) are to be repeated every 4 cycles after Cycle 5 (Cycles 9, 13, 17, etc.).

[l] Blood for RNA analyses should be collected predose on Day 1 of Cycle 1, Cycle 2, Cycle 5 and again at discontinuation. Blood for plasma and serum biomarker analyses should be collected predose on Day 1 of Cycle 1, Cycle 2, and again at discontinuation. See Procedures Manual. Any leftover samples from the RNA analyses, plasma biomarker analyses, and serum biomarker analyses will be stored for FBR if the subject signs the FBR consent.

[m] This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the subject signs the FBR consent. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

[n] The initial tumor imaging will be performed within 28 days prior to randomization. Refer to Section 7.1.2.8 for details on tumor imaging and assessment of disease.

[o] Baseline tumor tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy. Refer to Section 7.1.2.11. Detailed instructions for tissue collection, process and shipment are provided in the Procedures Manual.

[p] It is strongly recommended that ePROs are administered prior to drug administration, AE evaluation, and disease status notification starting with EuroQol EQ-5D, followed by EORTC QLQ-C30. Refer to Section 7.1.2.7 for details on collection of ePROs.

6.2 Pembrolizumab + Chemotherapy (Combo)

Trial Period:	Screening Phase		Treatment Cycles [a]												End of Treatment	Posttreatment Visits		
Treatment Cycle/Title	Screening (Visit 1)		1		2		3		4		5		6 [b]		End of Treatment Visit	Safety Follow-up	Efficacy Follow-up[c]	Survival Follow-up
			1	8	1	8	1	8	1	8	1	8	1	8				
Scheduling Window (Days)	-42 to -1	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+3 days)	Every 9 or 12 weeks (±7 days)	Every 12 week (±7 days)
Administrative Procedures																		
Informed Consent	X [d]																	
Informed Consent for Future Biomedical Research	X [e]																	
Inclusion/Exclusion Criteria		X																
Subject Identification Card	X																	
Demographics and Medical History		X																
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Obtain randomization number and trial drug assignment using IVRS/IWRS			X [f]															
Pembro + Chemo			X	X	X	X	X	X	X	X	X	X	X	X				
Posttrial Anticancer Therapy Status																X	X	X [g]
Survival Status [g]			<----------															X [g]

Trial Period:	Screening Phase		Treatment Cycles [a]												End of Treatment	Posttreatment Visits		
Treatment Cycle/Title	Screening (Visit 1)		1		2		3		4		5		6 [b]		End of Treatment Visit	Safety Follow-up	Efficacy Follow-up[c]	Survival Follow-up
			1	8	1	8	1	8	1	8	1	8	1	8				
Scheduling Window (Days)	-42 to -1	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+3 days)	Every 9 or 12 weeks (±7 days)	Every 12 week (±7 days)
Clinical Procedures/Assessments																		
Review Adverse Events [h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [h]	X [h]	
12-Lead ECG (Local)		X																
Full Physical Examination		X													X			
Directed Physical Examination			X	X	X	X	X	X	X	X	X	X	X	X				
Height, Weight, and Vital Signs (T, P, RR, BP) [i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status		X	X		X		X		X		X		X		X	X	X	
Laboratory Procedures/Assessments: LOCAL laboratory																		
Pregnancy Test [j]		X [k]																
PT/INR and aPTT		X [k]																
CBC with Differential		X [k]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Comprehensive Chemistry Panel		X [k]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis [l]		X [k]									X [l]					X		
T3, FT4, and TSH [l]		X [k]									X [l]					X		

Trial Period:	**Screening Phase**		**Treatment Cycles [a]**												**End of Treatment**	**Posttreatment Visits**		
Treatment Cycle/Title	Screening (Visit 1)		1		2		3		4		5		6 [b]		End of Treatment Visit	Safety Follow-up	Efficacy Follow-up[c]	Survival Follow-up
			1	8	1	8	1	8	1	8	1	8	1	8				
Scheduling Window (Days)	-42 to -1	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+3 days)	Every 9 or 12 weeks (±7 days)	Every 12 week (±7 days)
Laboratory Procedures/Assessments: Analysis performed by CENTRAL laboratory																		
Blood for RNA Analyses [m]			X		X						X				X			
Blood for Plasma Biomarker Analyses [m]			X		X										X			
Blood for Serum Biomarker Analyses [m]			X		X										X			
Blood for Genetics Analysis [n]			X															
Efficacy Measurements																		
Tumor Imaging [o]		X [o]							X						X [p]		X	
Tumor Tissue Collection																		
Archival or Newly Obtained Tissue Collection for Biomarker analysis [q]	X [q]																	

Trial Period:	Screening Phase		Treatment Cycles [a]												End of Treatment	Posttreatment Visits		
Treatment Cycle/Title	Screening (Visit 1)		1		2		3		4		5		6 [b]		End of Treatment Visit	Safety Follow-up	Efficacy Follow-up[c]	Survival Follow-up
			1	8	1	8	1	8	1	8	1	8	1	8				
Scheduling Window (Days)	-42 to -1	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+3 days)	Every 9 or 12 weeks (±7 days)	Every 12 week (±7 days)
Patient-reported Outcomes																		
EuroQol EQ-5D [r]			X		X		X		X						X	X		
EORTC QLQ-C30 [r]			X		X		X		X						X	X		

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; BP=blood pressure; chemo=chemotherapy; combo=pembro+chemo+SOC; discon=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; EuroQol=European Quality of Life; FT4=free thyroxine; EORTC=European Organisation for Research and Treatment of Cancer Quality of Life; ePRO=electronic patient-reported outcomes; FBR=future biomedical research; INR=International Normalized Ratio; IRB/IEC=institutional review board/independent ethics committee; IVRS/IWRS=interactive voice response system/integrated web response system; P=pulse; Pembro=pembrolizumab; PT=prothrombin time; Q9W=every 9 weeks; Q12W=every 12 weeks; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; T=temperature; T3=triiodothyronine; TSH=thyroid-stimulating hormone.

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. Day 1 is the preferred day of treatment administration for both cisplatin and carboplatin; however, these chemotherapy treatments may be given on Day 2 if required by local guidelines. Treatment cycles are 3 weeks. Imaging should be performed at 9 weeks (63 days ±7) from randomization and until Week 54 and every 12 weeks (84 days ±7) thereafter, regardless of any treatment delays.

b Subjects in chemotherapy plus pembrolizumab treatment arm will continue receiving pembrolizumab treatment and continue repeating Treatment Cycles Visits in the Trial Flow Chart.

c Subjects who complete the protocol-required cycles of study intervention or who discontinue study therapy without documented PD should enter Efficacy Follow-up and continue disease monitoring per study schedule (i.e., Q9W before Week 54 or Q12W after Week 54). See Section 7.1.2.8.3 for more details.

d Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

e Signing the informed consent for FBR samples is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.

f The window for each visit is ±3 days unless otherwise noted. Cycle 1 treatment must be given within 3 days of randomization.

g After the start of new anticancer treatment or documented disease progression, the subject should be contacted approximately every 12 weeks (84 days ±7) to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).

Trial Period:	Screening Phase		Treatment Cycles [a]												End of Treatment	Posttreatment Visits		
	Screening		1		2		3		4		5		6 [b]		End of Treatment	Safety	Efficacy Follow-up[c]	Survival Follow-up
Treatment Cycle/Title	(Visit 1)		1	8	1	8	1	8	1	8	1	8	1	8	Visit	Follow-up		
Scheduling Window (Days)	-42 to -1	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+3 days)	Every 9 or 12 weeks (±7 days)	Every 12 week (±7 days)

h After the end of treatment, each subject will be followed for 30 days for AE monitoring. SAEs will be collected for 90 days after the trial treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. All drug-related SAEs and ECIs will be reported regardless of time frame.

i Height will be measured at the screening visit only. Refer to Section 7.1.2.4. Weight, and vital signs (T, P, RR, and BP) will also be measures during cycles repeating after Cycle 6 for pembrolizumab administration.

j 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 trial site laboratory will be required. Monthly pregnancy testing should be conducted as per local regulations where applicable. Refer to Appendix 12.5 for country-specific requirements.

k Laboratory tests for screening and determining eligibility are to be performed within 14 days prior to the first dose of trial treatment. Refer to Section 7.1.3.2 for details regarding laboratory tests.

l Urinalysis and thyroid tests (T3, FT4, and TSH) are to be repeated every 4 cycles after Cycle 5 (Cycles 9, 13, 17, etc.).

m Blood for RNA analyses should be collected predose on Day 1 of Cycle 1, Cycle 2, Cycle 5 and again at discontinuation. Blood for plasma and serum biomarker analyses should be collected predose on Day 1 of Cycle 1, Cycle 2, and again at discontinuation. See Procedures Manual. Any leftover samples from the RNA analyses, plasma biomarker analyses and serum biomarker analyses will be stored for FBR research if the subject signs the FBR consent

n This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the subject signs the FBR consent. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

o The initial tumor imaging will be performed within 28 days prior to randomization. Refer to Section 7.1.2.8 for details on tumor imaging and assessment of disease.

p In subjects who discontinue study therapy without confirmed PD by the site per irRECIST, tumor imaging should be performed at the time of treatment discontinuation (± 4 weeks). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.

q Baseline tumor tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy. Refer to Section 7.1.2.12. Detailed instructions for tissue collection, process and shipment are provided in the Procedures Manual.

r It is strongly recommended that ePROs are administered prior to drug administration, AE evaluation, and disease status notification starting with EuroQol EQ-5D, followed by EORTC QLQ-C30. Refer to Section 7.1.2.7 for details on collection of ePROs.

6.3 Chemotherapy Only (Chemo Only)

Trial Period:	Screening Phase		Treatment Cycles [a]												End of Treatment	Posttreatment Visits		
Treatment Cycle/Title	Screening (Visit 1)		1		2		3		4		5		6 [b]		End of Treatment Visit	Safety Follow-up	Efficacy Follow-up[c]	Survival Follow-up
			1	8	1	8	1	8	1	8	1	8	1	8				
Scheduling Window (Days)	-42 to -1	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+3 days)	Every 9 or 12 weeks (±7 days)	Every 12 weeks (±7 days)
Administrative Procedures																		
Informed Consent	X [d]																	
Informed Consent for Future Biomedical Research	X [e]																	
Inclusion/Exclusion Criteria		X																
Subject Identification Card	X																	
Demographics and Medical History		X																
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Obtain randomization number and trial drug assignment using IVRS/IWRS			X [f]															
Chemo only Administration			X	X	X	X	X	X	X	X	X	X	X	X				
Posttrial Anticancer Therapy Status																X	X	X [g]
Survival Status [g]			<----------															X [g]

Trial Period:	Screening Phase		Treatment Cycles [a]												End of Treatment	Posttreatment Visits		
Treatment Cycle/Title	Screening (Visit 1)		1		2		3		4		5		6 [b]		End of Treatment Visit	Safety Follow-up	Efficacy Follow-up[c]	Survival Follow-up
			1	8	1	8	1	8	1	8	1	8	1	8				
Scheduling Window (Days)	-42 to -1	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+3 days)	Every 9 or 12 weeks (±7 days)	Every 12 weeks (±7 days)
Clinical Procedures/Assessments																		
Review Adverse Events [h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [h]	X [h]	
12-Lead ECG (Local)		X																
Full Physical Examination		X													X			
Directed Physical Examination			X	X	X	X	X	X	X	X	X	X	X	X				
Height, Weight, and Vital Signs (T,P, RR, BP) [i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status		X	X		X		X		X		X		X		X	X	X	
Laboratory Procedures/Assessments: LOCAL laboratory																		
Pregnancy Test [j]		X [k]																
PT/INR and aPTT		X [k]																
CBC with Differential		X [k]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Comprehensive Chemistry Panel		X [k]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis		X [k]									X					X		
T3, FT4, and TSH		X [k]																

Trial Period:	Screening Phase		Treatment Cycles [a]												End of Treatment	Posttreatment Visits		
Treatment Cycle/Title	Screening (Visit 1)		1		2		3		4		5		6 [b]		End of Treatment Visit	Safety Follow-up	Efficacy Follow-up[c]	Survival Follow-up
			1	8	1	8	1	8	1	8	1	8	1	8				
Scheduling Window (Days)	-42 to -1	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+3 days)	Every 9 or 12 weeks (±7 days)	Every 12 weeks (±7 days)
Laboratory Procedures/Assessments: Analysis performed by CENTRAL laboratory																		
Blood for RNA Analyses [i]			X		X						X				X			
Blood for Plasma Biomarker Analyses [i]			X		X										X			
Blood for Serum Biomarker Analyses [i]			X		X										X			
Blood for Genetics Analysis [m]			X															
Efficacy Measurements																		
Tumor Imaging [n]		X [n]							X						X [o]		X	
Tumor Tissue Collection																		
Archival or Newly Obtained Tissue Collection for Biomarker analysis [p]	X [p]																	

Trial Period:	Screening Phase		Treatment Cycles [a]												End of Treatment	Posttreatment Visits		
Treatment Cycle/Title	Screening (Visit 1)		1		2		3		4		5		6 [b]		End of Treatment Visit	Safety Follow-up	Efficacy Follow-up[c]	Survival Follow-up
			1	8	1	8	1	8	1	8	1	8	1	8				
Scheduling Window (Days)	-42 to -1	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+3 days)	Every 9 or 12 weeks (±7 days)	Every 12 weeks (±7 days)
Patient-reported Outcomes																		
EuroQol EQ-5D [q]			X		X		X		X						X	X		
EORTC QLQ-C30 [q]			X		X		X		X						X	X		

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; BP=blood pressure; chemo=chemotherapy; discon=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; EuroQol=European Quality of Life; FT4=free thyroxine; EORTC=European Organisation for Research and Treatment of Cancer Quality of Life; ePRO= electronic patient-reported outcomes; FBR=future biomedical research; INR=International Normalized Ratio; IRB/IEC=institutional review board/independent ethics committee; IVRS/IWRS=interactive voice response system/integrated web response system; P=pulse; Pembro=pembrolizumab; PK=pharmacokinetic(s); PT=prothrombin time; Q9W=every 9 weeks; Q12W=every 12 weeks; RNA=ribonucleic acid; RR=respiratory rate; SAE=serious adverse event; T=temperature; T3=triiodothyronine; TSH=thyroid-stimulating hormone.

[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. Day 1 is the preferred day of treatment administration for both cisplatin and carboplatin; however, these chemotherapy treatments may be given on Day 2 if required by local guidelines. Treatment cycles are 3 weeks. Imaging should be performed at 9 weeks (63 days ±7) from randomization and until Week 54 and every 12 weeks (84 days ±7) thereafter, regardless of any treatment delays.

[b] Subjects in the chemo only treatment arm will discontinue treatment after 6 cycles of trial drug administration. These subjects would then be followed according to Posttreatment procedures.

[c] Subjects who complete the protocol-required cycles of study intervention or who discontinue study therapy without documented PD should enter Efficacy Follow-up and continue disease monitoring per study schedule (i.e., Q9W before Week 54 or Q12W after Week 54). See Section 7.1.2.8.3 for more details.

[d] Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

[e] Signing the informed consent for FBR samples is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.

[f] The window for each visit is ±3 days unless otherwise noted. Cycle 1 treatment must be given within 3 days of randomization.

[g] After the start of new anticancer treatment or documented disease progression, the subject should be contacted approximately every 12 weeks (84 days ±7) to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).

Trial Period:	Screening Phase		Treatment Cycles [a]												End of Treatment	Posttreatment Visits		
Treatment Cycle/Title	Screening (Visit 1)		1		2		3		4		5		6 [b]		End of Treatment Visit	Safety Follow-up	Efficacy Follow-up[c]	Survival Follow-up
			1	8	1	8	1	8	1	8	1	8	1	8				
Scheduling Window (Days)	-42 to -1	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+3 days)	Every 9 or 12 weeks (±7 days)	Every 12 weeks (±7 days)

[h] After the end of treatment, each subject will be followed for 30 days for AE monitoring. SAEs will be collected for 90 days after the trial treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. All drug-related SAEs and ECIs will be reported regardless of time frame.

[i] Height will be measured at the screening visit only. Refer to Section 7.1.2.4.

[j] 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 trial site laboratory will be required. Monthly pregnancy testing should be conducted as per local regulations where applicable. Refer to Appendix 12.5 for country-specific requirements.

[k] Laboratory tests for screening and determining eligibility are to be performed within 14 days prior to the first dose of trial treatment. Refer to Section 7.1.3.2 for details regarding laboratory tests.

[l] Blood for RNA analyses should be collected predose on Day 1 of Cycle 1, Cycle 2, Cycle 5 and again at discontinuation. Blood for plasma and serum biomarker analyses should be collected predose on Day 1 of Cycle 1, Cycle 2, and again at discontinuation. See Procedures Manual. Any leftover samples from the RNA analyses, plasma biomarker analyses and serum biomarker analyses will be stored for FBR research if the subject signs the FBR consent

[m] This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the subject signs the FBR consent. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

[n] The initial tumor imaging will be performed within 28 days prior to randomization. Refer to Section 7.1.2.8 for details on tumor imaging and assessment of disease.

[o] In subjects who discontinue study therapy without confirmed PD by the site per irRECIST, tumor imaging should be performed at the time of treatment discontinuation (± 4 weeks). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.

[p] Baseline tumor tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy. Refer to Section 7.1.2.12. Detailed instructions for tissue collection, process and shipment are provided in the Procedures Manual.

[q] It is strongly recommended that ePROs are administered prior to drug administration, AE evaluation, and disease status notification starting with EuroQol EQ-5D, followed by EORTC QLQ-C30. Refer to Section 7.1.2.7 for details on collection of ePROs.

6.4 Second Course Phase (Re-treatment for Pembrolizumab [Pembro Only and Combo] Arms ONLY)

Trial Period:	**Treatment Cycles [a]**								**End of Treatment**	**Posttreatment Visits**		
					To be repeated beyond 8 cycles [a]							
Treatment Cycle/Title	1	2	3	4	5	6	7	8	End of Treatment Visit	Safety Follow-up	Efficacy Follow-up [b]	Survival Follow-up
Scheduling Window (Days)	+3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+3 days)	Every 9 or 12 weeks (±7 days)	Every 12 weeks (±7 days)
Administrative Procedures												
Eligibility Criteria [c]	X											
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab Administration [d]	X	X	X	X	X	X	X	X				
Posttrial Anticancer Therapy Status										X	X	X [e]
Survival Status [e]	<----------											X [e]
Clinical Procedures/Assessments												
Review Adverse Events	X	X	X	X	X	X	X	X	X	X [f]	X [f]	
Full Physical Examination	X								X			
Directed Physical Examination		X	X	X	X	X	X	X				
Weight and Vital Signs (T, P, RR, BP)	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory												
Pregnancy Test –Urine or Serum [g]	X											
CBC with Differential	X [h]	X	X	X	X	X	X	X	X	X		
Comprehensive Chemistry Panel	X [h]	X	X	X	X	X	X	X	X	X		
T3, FT4, and TSH	X [h]				X [i]					X		
PT/INR and aPTT	X [h]											
Urinalysis	X				X [i]					X		

Trial Period:	Treatment Cycles [a]								End of Treatment	Posttreatment Visits		
					To be repeated beyond 8 cycles [a]							
Treatment Cycle/Title	1	2	3	4	5	6	7	8	End of Treatment Visit	Safety Follow-up	Efficacy Follow-up [b]	Survival Follow-up
Scheduling Window (Days)	+3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days from last dose (+3 days)	Every 9 or 12 weeks (±7 days)	Every 12 weeks (±7 days)
Efficacy Measurements												
Tumor Imaging [j]	X			X			X		X [j]		X [j]	

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; BP=blood pressure; CBC=complete blood count; CR=complete response; discon=discontinuation; ECI=event of clinical interest; ECOG=Eastern Cooperative Oncology Group; FT4=free thyroxine; INR=International Normalized Ratio; P=pulse; PT=prothrombin time; Q9W=every 9 weeks; Q12W=every 12 weeks; RR=respiratory rate; SAE=serious adverse event; SIM=site imaging manual; T=temperature; T3=triiodothyronine; TSH=thyroid-stimulating hormone.

[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. Imaging should be performed at 9 weeks (63 days ±7) from start of treatment until Week 54 and every 12 weeks (84 days ±7) after Week 54, regardless of any treatment delays.

[b] Subjects who complete the protocol-required cycles of study intervention or who discontinue study therapy without documented PD should enter Efficacy Follow-up and continue disease monitoring per study schedule (i.e., Q9W before Week 54 or Q12W after Week 54). See Section 7.1.2.8.3 for more details.

[c] Subjects who either a) attain a CR and discontinue treatment, or b) discontinue treatment after receiving 35 administrations on pembrolizumab 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.

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

[e] After the start of new anticancer treatment or documented disease progression, the subject should be contacted approximately every 12 weeks (84 days ±7) to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).

[f] After the end of treatment, each subject will be followed for 30 days for AE monitoring. SAEs will be collected for 90 days after the trial treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. All drug-related SAEs and ECIs will be reported regardless of time frame.

[g] 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 trial site laboratory will be required. Monthly pregnancy testing should be conducted as per local regulations where applicable.

[h] See Section 7.1.3.2 for details regarding laboratory tests.

[i] Urinalysis, and thyroid tests (T3, FT4, and TSH) to be repeated every 4 cycles after Cycle 5 (Cycles 9, 13, 17, etc.).

[j] A scan must be performed within 28 days prior to restarting treatment with pembrolizumab. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Refer to Section 7.1.2.8 for details on tumor imaging and assessment of disease. The processes for image collection and transmission for BICR are in the SIM.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

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

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 bladder 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.

Prior anticancer treatment for urothelial bladder cancer will be recorded separately and not listed as a prior medication.

The investigator or qualified designee will review and record all prior anticancer treatments including systemic treatments, radiation, and surgeries, regardless of the time prior to first dose of trial treatment.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial treatment and 30 days after the last dose of trial treatment. All medications

related to reportable SAEs should be recorded as defined in Section 7.2 – Assessing and Recording Adverse Events.

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

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

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

7.1.1.7 Assignment of Treatment/Randomization Number

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

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

In a situation where rerandomization of the participants is planned (eg, study extension periods), the rerandomization will be based on a new randomization schedule; however, each participant will retain his/her original treatment/randomization number. Only the study intervention regimen associated with the rerandomization period or phase may change.

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

Interruptions from the protocol specified treatment plan for ≥12 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

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

The total volume of pembrolizumab infused will be compared with the total volume prepared to determine compliance to each dose of pembrolizumab administered. The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 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 laboratory 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 indicating 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.

7.1.2.2 Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in Section 6.0 – Trial Flow Chart, and more frequently if clinically indicated. AEs will be graded and recorded throughout the trial and during the Follow-up Period according to National Cancer Institute (NCI) CTCAE Version 4.0 (see Section 12.4). Toxicities will be characterized in terms including seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to Section 7.2 – Assessing and Recording Adverse Events for detailed information regarding the assessment and recording of AEs.

7.1.2.3 Physical Examination

7.1.2.3.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical examination are described in Section 6.0 – Trial Flow Chart. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs. Refer to Appendix 12.5 for country-specific requirements.

7.1.2.3.2 Directed Physical Examination

For cycles that do not require a full physical examination per the Trial Flow Chart (Section 6.0), the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to trial treatment administration. New clinically significant abnormal findings should be recorded as AEs. Refer to Appendix 12.5 for country-specific requirements.

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, at trial discontinuation, and during the Follow-up Period as specified in the Trial Flow Chart (Section 6.0). Vital signs include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at the screening visit only.

7.1.2.5 12-Lead Electrocardiogram

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

7.1.2.6 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status at screening, prior to each cycle of trial treatment and during the Follow-up Period as specified in the Trial Flow Chart (Section 6.0). Section 12.3 shows the flow criteria for ECOG PS.

7.1.2.7 Patient-reported Outcomes

The EuroQol EQ-5D and EORTC QLQ-C30 questionnaires will be administered by trained trial site personnel and completed electronically by subjects to record PROs.

It is strongly recommended that electronic patient-reported outcomes (ePROs) be administered prior to drug administration, AE evaluation, and disease status notification. The ePROs are completed in the following order: EuroQol EQ-5D first and then EORTC QLQ-C30 at the time points specified in the Trial Flow Chart (Section 6.0) and briefly summarized below.

All PROs (EuroQol EQ-5D, EORTC QLQ-C30) are completed at Cycle 1, Cycle 2, Cycle 3, Cycle 4, then every 3 cycles for the first 54 weeks and every 4 cycles thereafter (e.g., Cycle 7, 10, 13, 16, 19, 23, 27, 31, 35) until treatment discontinuation and the 30-day post-treatment Safety Follow-up Visit. If the subject does not complete the ePROs, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

7.1.2.8 Tumor Imaging and Assessment of Disease

The process for image collection and transmission for BICR can be found in the Site Imaging Manual (SIM).

Tumor imaging should be acquired by computed tomography (CT), which is strongly preferred. Magnetic resonance imaging (MRI) should be used when CT is contraindicated or for imaging of the brain. The same imaging technique regarding modality and use of contrast should be used in a subject throughout the trial to optimize the visualization of existing and new tumor burden.

All scheduled images for all study subjects from the sites will be submitted to the BICR. In addition, 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 BICR as well.

The BICR will verify PD following local site investigator-assessed first radiologic evidence of PD. Expedited verification of radiologic PD by BICR will be communicated to the study site and Sponsor (Refer to Section 7.1.2.10).

Local review of imaging will be used for subject management. The BICR team will receive radiologic images during the course of the trial and will perform a retrospective analysis of response to treatment.

7.1.2.8.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of randomization. The site trial team must review screening images to confirm the subject has measurable disease per RECIST 1.1. The screening images must be submitted for BICR retrospective review.

Scans performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of randomization and can be assessed by the site radiologist.

Local site investigator/radiology assessment based on RECIST 1.1 will be used to determine subject eligibility. Although RECIST 1.1 references to a maximum of 5 target lesions in total and 2 per organ, Merck allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

Subjects with previously treated brain metastases may participate provided they have stable brain metastases, i.e., without evidence of progression by imaging; (confirmed by MRI if MRI was used at prior imaging, or confirmed by CT imaging if CT was used at prior imaging) for at least 4 weeks prior to randomization. Any neurologic symptoms must have returned to baseline, and subjects must have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases at least 7 days prior to trial initiation as per local site assessment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

7.1.2.8.2 Tumor Imaging During the Trial

The first on-trial imaging assessment should be performed at 9 Weeks (63 days ±7), from the date of randomization for the first year (through Week 54 ±7) or more frequently if clinically indicated. Subjects who remain on treatment beyond 54 weeks will have imaging performed every 12 weeks (84 days ±7) thereafter. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. In determining response to treatment or progression, investigators must evaluate all target and nontarget lesions and search for new lesions at each imaging time point. For subjects who have stable brain metastases and who have undergone brain imaging at baseline, brain imaging should be performed if a site-assessed complete response was achieved.

Response

Per RECIST 1.1, PR and CR should be confirmed by a repeat tumor imaging assessment 4 weeks or longer from the date the response was first documented. The tumor imaging for confirmation of response may be performed 4 weeks after the first indication of a response, or at the next scheduled scan (i.e., 9 weeks or 12 weeks later, depending on the year of treatment), whichever is clinically indicated. Subjects will then return to regular scheduled imaging every 9 weeks or 12 weeks depending on the year of treatment, starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Progression

Radiographic progression will be determined according to RECIST 1.1. Subsequently, per irRECIST (Section 7.1.2.10 – irRECIST Assessment of Disease), disease progression in subjects treated with pembrolizumab should be confirmed by the site at least 4 weeks after central verification of site-assessed first radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed disease progression and are clinically stable may continue on treatment at the discretion of the site investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 7.1.2.10. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later. Tumor imaging may resume at the subsequent scheduled imaging time point

if clinically stable. Subjects who have confirmed disease progression as assessed by the site will discontinue treatment. Exceptions are detailed in Section 7.1.2.10.

If a subject with confirmed radiographic progression is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the Sponsor. To continue treatment, clinically stable subjects should also have at the confirmatory scan no further increase in the target lesions, no unequivocal increase in nontarget lesions, and no worsening in size of an initial new lesions or the development of additional new lesions (non-worsening PD).

Imaging should continue to be performed until verified by BICR (unless the site's principal investigator [PI] elects to continue treatment and follow irRECIST), the start of new anti-cancer treatment, or withdrawal of consent or death, whichever occurs first. All supplemental imaging must be submitted to the BICR.

7.1.2.8.3 End of Treatment and Follow-up of Tumor Imaging

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (±4-week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment, (every 9 weeks [63 days ±7] for the first 54 weeks or every 12 weeks [84 days ±7]) thereafter to monitor disease status until the start of new anticancer treatment, disease progression, death, or the end of the trial, whichever occurs first.

7.1.2.8.4 Second Course (Re-treatment) Tumor Imaging

Before a participant may enter the Second Course Phase, BICR verification of PD must have occurred. The PD imaging may also be used as the Second Course baseline imaging if it is within 28 days prior to restarting treatment and otherwise meets the baseline standards outlined in the SIM. Local reading (Investigator assessment with site radiology reading) will be used to determine eligibility. All Second Course imaging should be submitted to the central imaging vendor for quality control, storage, and possible retrospective review, though BICR verification of PD will not occur during Second Course Phase.

The first on-trial imaging assessment should be performed at 9 weeks (63 days ±7) after the restart of treatment up to 54 weeks. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7) or more frequently if clinically indicated.

Per irRECIST if tumor imaging shows initial PD (Section 7.1.2.10 – irRECIST Assessment of Disease), tumor assessment should be repeated ≥4 weeks later to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Subjects who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is <4 weeks later and may wait until the next scheduled imaging time point if clinically stable.

Imaging should continue to be performed until disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed at least 4 weeks after the first tumor imaging indicating PD in clinically stable subjects. Additional irRECIST detail is described in Section 7.1.2.10.

In subjects who discontinue trial treatment and will not continue to have scans performed in follow-up (e.g., subject is discontinuing treatment due to documented disease progression), final assessment tumor imaging should be performed at the time of treatment discontinuation (±4-week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

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 9 weeks (63 days ±7) for the first 54 weeks and then every 12 weeks (84 days ±7) thereafter until the start of new anticancer treatment, disease progression, death, or the end of the trial, whichever occurs first.

7.1.2.9 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be applied by BICR as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of trial therapy). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden. Initial tumor imaging showing site-assessed PD should be submitted to the central imaging vendor immediately for verification of PD by BICR. The site will be notified if the BICR verifies PD using RECIST 1.1.

Figure 2 illustrates the imaging flow involving verification of PD for clinically stable subjects.

7.1.2.10 irRECIST Assessment of Disease

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

When feasible, subjects in the treatment arms receiving pembrolizumab should not be discontinued until progression is confirmed by the local site investigator/radiology assessment. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy or at a later time point and then experience subsequent response. Subjects who are deemed clinically unstable are not required to have

repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

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

In subjects who have shown initial evidence of radiological PD by RECIST 1, as verified by BICR, it is at the discretion of the PI whether to continue a subject on trial treatment until repeat imaging is obtained (using irRECIST for subject management, see Table 7 and Figure 2).

This clinical judgment decision by the site investigator should be based on the subject's overall clinical condition, including PS, clinical symptoms, and laboratory data. Subjects may receive trial treatment and tumor assessment should be repeated ≥4 weeks later to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

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

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

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

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

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

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

Disease progression will be considered to be "confirmed" at repeat imaging if ANY of the following occur (as assessed by irRECIST):

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

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

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

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

Table 7 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1, which has been verified by the blinded independent central review	Repeat imaging at ≥4 weeks at site to confirm PD	May continue trial treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST	Repeat imaging at ≥4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required	N/A
Repeat tumor imaging shows SD, PR or CR by irRECIST at the local site.	Continue regularly scheduled imaging assessments every 9 weeks (every 12 weeks after 12 months)	Continue trial treatment at the site investigator's discretion	Continue regularly scheduled imaging assessments	May restart trial treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule outlined in the protocol.

Abbreviations: CR=complete response; irRECIST=immune-related RECIST; N/A=not applicable; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

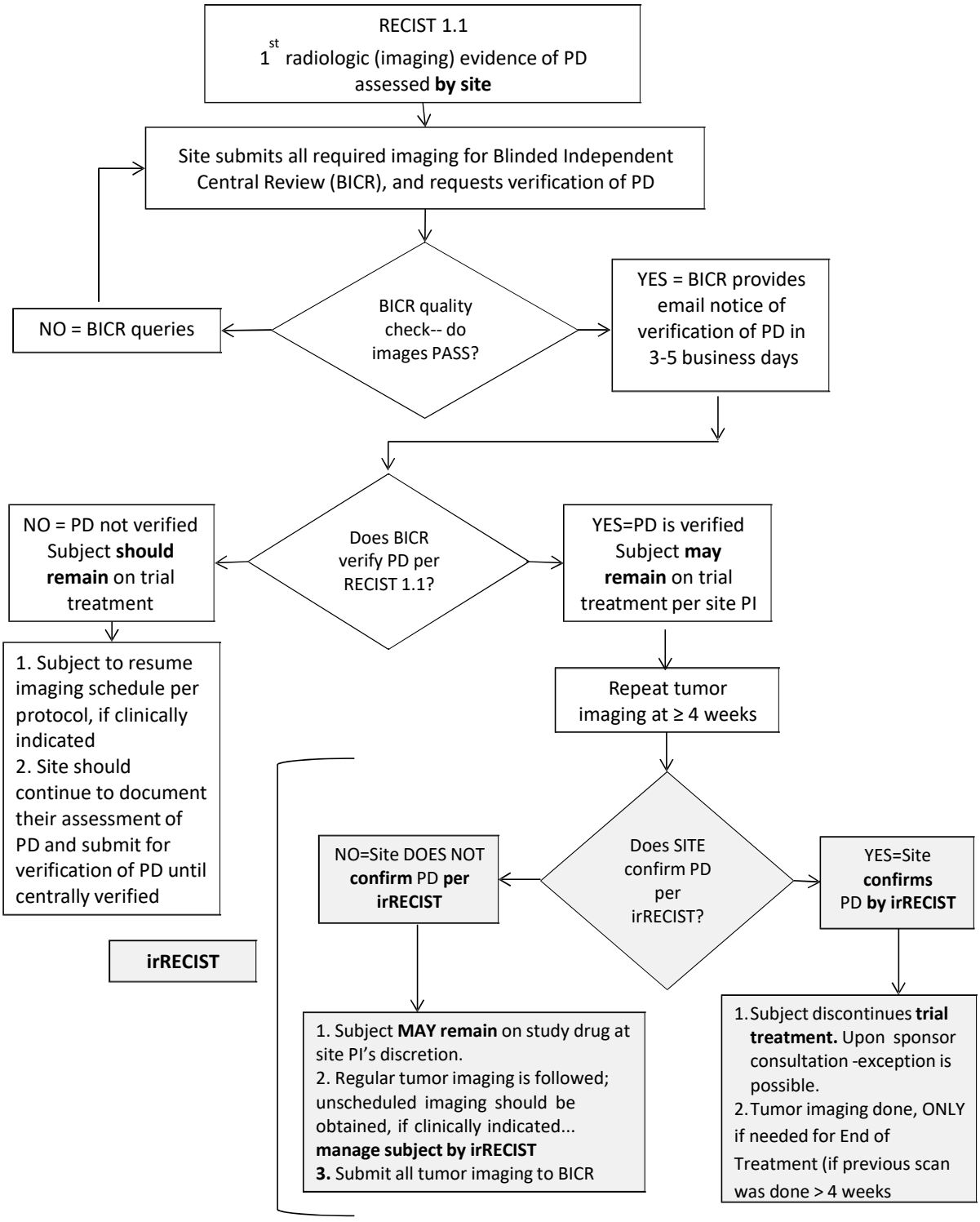


Figure 2 Flow Chart for Imaging After First Site-Identified Progression of Disease

7.1.2.11 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 laboratory for characterization of PD-L1 expression, which 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 an existing biopsy or surgical specimen is suboptimal for identification of subjects, only new biopsies will be acceptable for determination of PD-L1 status.

7.1.2.12 Tumor Tissue Collection: PD-L1 Status

All subjects should submit either a newly obtained core or excisional biopsy or archival tissue (fine needle aspirate is not adequate for both archival and new tissue samples) to a central laboratory for characterization of PD-L1 status prior to treatment allocation.

Submission of FFPE tumor tissue sample blocks is preferred; if submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory within 14 days from the site slide section date; otherwise a new specimen will be requested.

If the sample is determined to be nonevaluable prior to testing by the central laboratory, a new sample should be submitted if available. This may include additional cut slides that are outside the 14-day window noted above.

Individual subject PD-L1 status will not be disclosed to investigative sites or trial subjects.

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

If the subject signs the Future Biomedical Research consent, any leftover samples that would be ordinarily discarded at the end of the main trial will be retained for Future Biomedical Research.

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 pretrial to posttrial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedures Manual. Safety laboratory results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.1 Serum/Urine Pregnancy Test

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, will be tested for pregnancy within 72 hours of receiving the first dose of trial medication and must be excluded in the event of a positive or borderline-positive test result. If a urine test is positive or borderline, a serum pregnancy test will be required. The results of the pregnancy testing will not be recorded. Refer to Appendix 12.5 for country-specific requirements.

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

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 8. Refer to Appendix 12.5 for country-specific requirements.

Table 8 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (serum or urine) [a]
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR) [b]
Platelet Count	Alanine aminotransferase	Protein	aPTT [b]
White Blood Cell (total and differential) [g]	Aspartate aminotransferase	Specific gravity	Total triiodothyronine (T3)[c]
Red Blood Cell Count	Carbon dioxide (CO_2 or Bicarbonate) [d]	Microscopic examination, if abnormal results are noted	Free thyroxine (FT4)
Absolute Neutrophil Count	Calcium		Thyroid-stimulating hormone
Absolute Lymphocyte Count	Chloride		Blood for RNA analyses
	Creatinine		Blood for plasma biomarker analyses
	Glucose		Blood for serum biomarker analyses
	Magnesium		Blood for genetic analysis
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood urea nitrogen [g]		
	Uric acid		

[a] Perform on women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. For women of childbearing potential, monthly pregnancy testing should be conducted as per local regulations where applicable.
[b] 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.
[c] Total T3 is preferred; if not available, free T3 may be tested.
[d] If these tests are not performed as part of standard of care in your region then these tests do not need to be performed
[e] Blood draws for thyroid function tests should be performed prior to dosing at the scheduled time point; however, results can be reviewed after dosing.
[f] Blood Urea Nitrogen is preferred; if not available, urea may be tested.
[g] For white blood cell counts (absolute or %) can be provided as per institutional standards.

Laboratory safety tests will be performed within 2 weeks prior to the first dose of trial treatment. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours prior to dosing. An exception is thyroid serologies, which may be performed within 28 days prior to first dose. Subjects eligible for trial re-treatment should have imaging performed within 28 days and laboratory tests performed within 14 days prior to the first dose of trial treatment in the Second Course Phase. After Cycle 1, in both the Initial Treatment Phase and the Second Course Phase, predose laboratory safety tests can be conducted up to 72 hours prior to dosing unless otherwise noted on the flow charts. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment. Unresolved abnormal laboratory test results that are drug-related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if results are within normal range.

7.1.3.3 Pharmacokinetic/Pharmacodynamic Evaluations

The collection of PK and ADA samples is being discontinued, as consistent results have been seen in PK and ADA across multiple indications including urothelial carcinoma (based on data from KN045 and KN052). KN361 evaluates pembrolizumab in combination with small molecule drugs, which are not likely to impact pembrolizumab concentrations in any clinically meaningful way. Therefore, PK and ADA data from KN045 and KN052 support discontinuation of PK and ADA in KN361. Overall, the PK profile of pembrolizumab is consistent with that of other humanized mAbs, which typically have a low CL and a limited central volume of distribution (Vc). The observed incidence of treatment-emergent ADA in evaluable subjects based on a pooled analysis of multiple indication is low (<2%). In addition, total incidence rate of treatment-emergent neutralizing positive subjects is also low (<0.5%).

Blood samples collected for PK and ADA from subjects enrolled under the base protocol may be stored. Analyses will be performed only if required.

Pharmacokinetic data may also be analyzed using nonlinear mixed effects modeling. Based on PK data obtained in this trial as well as PK data obtained from other trials, a population PK analysis may be performed to characterize PK parameters (Clearance, Volume of Distribution) and evaluate the effect of extrinsic and intrinsic factors to support the proposed dosing regimen. Pharmacokinetic data will also be used to explore the exposure-response relationships for pembrolizumab antitumor activity/efficacy as well as safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately.

7.1.3.3.1 Exploratory Drug-drug Interaction Analysis

As pembrolizumab is an IgG4 antibody that is administered parentally and cleared by catabolism, drug-drug interactions are not anticipated to affect exposure of pembrolizumab, cisplatin, gemcitabine and carboplatin. Therefore, no investigation of drug-drug interaction is conducted in this protocol.

7.1.3.4 Blood for RNA Analyses, Plasma Biomarker Analyses, and Serum Biomarker Analyses

Sample collection, storage, and shipment instructions for blood for RNA analyses, plasma biomarker analyses and serum biomarker analyses samples will be provided in the Procedures Manual. Any leftover samples from the RNA analyses, plasma biomarker analyses and serum biomarker analyses will be stored for Future Biomedical Research if the subject signs the Future Biomedical Research consent.

7.1.3.5 Planned Genetic Analysis Sample Collection

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

7.1.3.6 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research.
- Leftover main trial tumor
- Leftover RNA from blood for RNA analyses
- Leftover plasma from blood for plasma biomarker analyses
- Leftover serum from blood for serum biomarker analyses

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the end of treatment visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who discontinue from trial treatment for any reason listed in Section 5.8 – Subject Withdrawal/Discontinuation Criteria should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.2). Thereafter, subjects who discontinued for confirmed radiographic disease progression by BICR should then proceed to the Survival Follow-up Phase of the trial (described in Section 7.1.5.3.4 – Survival Follow-up Assessments). All other subjects should remain on trial and should continue trial-related disease assessments including imaging on schedule until 1) the start of new anticancer treatment, 2) confirmed radiographic disease progression by the BICR, 3) death, or 4) the end of trial, whichever comes first.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by

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

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

7.1.4.2 Blinding/Unblinding

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

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the 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 laboratory tests and trial assessments
- Imaging equipment- as required for trial objectives
- Infusion equipment- as required for administering drug product.

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

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 enrollment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1 – Entry Criteria. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

After providing main trial consent, subjects will be assigned a screening number. Subjects must sign the main trial consent prior to submitting existing tissue samples and/or undergoing a new biopsy. Requirements pertaining to submission of tissue samples are found in Section 7.1.2.8 – Tumor Imaging and Assessment of Disease.

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 of 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.
- ICF 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.
- Laboratory tests are to be performed within 2 weeks of trial initiation.
- 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 trial 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.

The Subject Identification Card will be updated with the screening number.

7.1.5.2 Treatment Period

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

7.1.5.2.1 Second Course Phase (Re-treatment Period)

Subjects who stop pembro only or combo with stable disease (SD), partial response (PR), or CR, may be eligible for up to 1 year (17 cycles) of pembrolizumab if they experience disease progression after stopping pembro only or combo treatment. This re-treatment is termed the Second Course Phase of this trial and is only available if the trial remains open and the subject meets the following conditions.

EITHER

- Stops initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1
  - Is treated for at least 8 cycles with pembrolizumab before discontinuing therapy.
  - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.
  - If enrolled to the combo arm received at least 4 cycles of chemotherapy.

OR

- Subject has SD, PR, or CR and stops pembrolizumab treatment after 35 cycles of trial treatment for reasons other than disease progression or intolerability.

AND

- Experiences a BICR verification of radiographic disease progression after stopping their initial treatment with pembrolizumab.
- Does not receive any anticancer treatment since the last dose of pembrolizumab.
- Has a performance status of 0, 1, or 2 on the ECOG Performance Scale.
- Demonstrates adequate organ function as detailed in Section 5.1.2 – Subject Inclusion Criteria.
- Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving re-treatment with trial 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 trial through 120 days after the last dose of pembrolizumab or 180 days after chemotherapy treatment. (Reference Section 5.7.2 – Contraception). 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 trial therapy for the course of the trial through 120 days after the last dose of pembrolizumab or 180 days after chemotherapy treatment. (Reference Section 5.7.2 – Contraception).

  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 subjects to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be re-treated at the same dose frequency as when they last received pembrolizumab. Treatment will be administered for up to 1 additional year.

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

7.1.5.3 Posttreatment Visits

7.1.5.3.1 Discontinuation Visit

The Discontinuation Visit should occur at the time study treatment is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow-up Visit, procedures do not need to be repeated. Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures. Additional details regarding subject withdrawal and discontinuation are presented in Section 5.8 – Subject Withdrawal/Discontinuation Criteria.

7.1.5.3.2 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days (+3 days) after the last dose of trial treatment or before the initiation of a new anticancer 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 to 1 or until the beginning of a new anticancer therapy, whichever occurs first. Serious AEs that occur within 90 days of the end of treatment or before initiation of a new anticancer treatment should also be followed up and recorded

Subjects who are eligible for re-treatment with pembrolizumab (as described in Section 7.1.5.2.1 – Second Course Phase) may have up to 2 Safety Follow-up Visits, 1 after the Treatment Period and 1 after the Second Course Phase.

Procedures and assessments performed at the Safety Follow-up Visit and beyond should follow guidelines described in Section 6.0 – Trial Flow Chart. All AEs that occur within the 30-day Safety Follow-up Visit should be recorded. In subjects who start another anticancer therapy before 30 days after discontinuation of trial therapy, the Safety Follow-up Visit should occur prior to the subject receiving another cancer therapy.

7.1.5.3.3 Efficacy Follow-up

Subjects who complete the protocol-required cycles of study intervention or who discontinue trial treatment for a reason other than disease progression will remain on trial, will move into the Efficacy Follow-up, and will have tumor imaging to monitor disease status (including VS, ECOG, anticancer treatment and AE assessments, as outlined in the flow chart) every 9 weeks (63 days ±7) after randomization for the first 54 weeks and then every 12 weeks (84 days ±7) thereafter. Every effort should be made to collect information regarding disease

status until the start of new anticancer therapy, disease progression, death, end of study, or if the subject begins re-treatment with pembrolizumab as detailed in Section 7.1.5.2.1 – Second Course Phase. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Subjects who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

Subjects who are eligible to receive re-treatment with pembrolizumab according to the criteria in Section 7.1.5.2.1 will move from the Efficacy Follow-Up Phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.3 – Trial Flow Chart for Second Course Phase (Re-treatment for Pembrolizumab arms ONLY) for re-treatment with pembrolizumab.

7.1.5.3.4 Survival Follow-up Assessments

Once a subject experiences confirmed disease progression or starts a new anticancer therapy, the subject moves into the Survival Follow-up Phase and should be contacted approximately every 12 weeks (84 days +/-7) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. This can be performed in a variety of manners including phone, email, chart review, or review of public records. Post-trial treatments and the subject's response to them will also be collected.

The first survival follow-up assessment should be scheduled as described below:

For subjects who discontinue treatment intervention and who will not enter the Efficacy Follow-up Phase, the first survival follow-up assessment will be scheduled 12 weeks after the discontinuation visit and/or Safety Follow-up Visit (whichever is last).

For subjects who completed assessments in the Efficacy Follow-up Phase, the first survival follow-up assessment will be scheduled 12 weeks after the last Efficacy Assessment Follow-up Visit has been performed.

7.1.5.4 Survival Status

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

7.2 Assessing and Recording Adverse Events

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

frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

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

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

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

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

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

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

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

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.

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by ≥1,000 mg (5 times the dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is

reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and 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 AEs 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 another important medical event.

Note: In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to

meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

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

Refer to Table 9 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any SAEs, or follow-up to a SAE, 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 SAE, or follow up to a SAE, 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 SAE, 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 the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with SAEs must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

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

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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 trial will be forwarded to Global Safety as an SAE within 24 hours of determination that the event is not progression of the cancer under trial.

7.2.4 Evaluating Adverse Events

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

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

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

Table 9 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

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

7.3.2 Trial Steering Committee

This trial will be conducted in consultation with a Trial Steering Committee. The Trial Steering Committee comprises:

- Sponsor personnel
- Investigators participating in the trial
- Consulting therapeutic-area experts and clinical trialists

The Trial Steering Committee will include the PI and co-PI of the study, the representative regional senior investigators and help with recommendations and advice regarding enrollment and trial-specific questions. The Trial Steering Committee will work with the Sponsor clinical lead of the study to support the conduct of the study.

Specific details regarding responsibilities and governance of the Trial Steering Committee will be described in a separate charter.

7.3.3 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 DMC regarding the trial.

7.3.4 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 8.7 - Interim

Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

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

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the trial. If, after the trial has begun, but prior to any database lock for any interim or final analysis of the primary endpoints of the trial, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH [International Council for Harmonisation] Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the trial. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan (SAP) are summarized below. The comprehensive plan is provided in Sections 8.2 to 8.12.

Key Elements of the Statistical Analysis Plan

Trial Design Overview	A Phase III randomized controlled clinical trial of pembrolizumab (MK-3475) with or without platinum-based combination chemotherapy versus chemotherapy alone in subjects with advanced urothelial carcinoma.
Treatment Assignment	A total of approximately 990 eligible subjects will be randomized to receive pembrolizumab combined with chemotherapy (combo), pembrolizumab alone (pembro only), and chemotherapy alone (chemo only) with 1:1:1 allocation ratio (approximately 330 subjects in each arm). Randomization will be stratified for the following factors: 1. Chemotherapy: Cisplatin or Carboplatin 2. PD-L1 expression (CPS ≥10% or CPS <10%) This is an open-label trial. As of 21-FEB-2018, subjects who have tumors that are PD-L1 CPS <10% will only be randomized to the combo arm or chemo only arm. There will be no change to randomization for subjects who have tumors that are PD-L1 CPS ≥10%.

Analysis Populations	Efficacy: Intention-to-treat Population (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	1. Progression-free Survival (PFS) per RECIST 1.1 as assessed by BICR for all subjects. 2. Overall survival (OS) for PD-L1 CPS ≥10% and all subjects, respectively.
Key Secondary Endpoints	Objective Response Rate (ORR) per RECIST 1.1 as assessed by BICR for all subjects
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing combo to chemo only with respect to PFS; combo to chemo only, and pembro only to chemo only with respect to OS using a stratified log-rank test. Estimation of the hazard ratio (HR) will be performed using a Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. No Tier 1 events are defined for this trial. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The between-treatment CIs will be calculated using the Miettinen and Nurminen method [53]. No formal treatment comparisons with p-values will be conducted.
Interim Analyses	Two interim efficacy analyses will be performed in this trial. Results will be reviewed by an external DMC. Details are provided in Section 8.7. • Timing: The first interim analysis will be performed when approximately 347 PFS events have been observed in combo and chemo only arms in all subjects. The second interim analysis will be performed when approximately 357 OS events have been observed in combo and chemo only arms in all subjects. Testing: Inferential analyses for PFS will be provided for all subjects and for OS will be provided for PD-L1 CPS ≥10% and all subjects.

Multiplicity	The Type I error rate over the multiple treatment comparisons and multiple primary endpoints and key secondary endpoints will be strongly controlled by the graphical approach of Maurer and Bretz [54]. The primary and key secondary hypotheses are divided into 2 sets related to PFS and OS/ORR, respectively. A Bonferroni approach is used to control the Type I error rate alpha at 2.5% (one-sided), with respectively 0.5% and 2% allocated to PFS and OS initially. The hypotheses related to ORR will be tested after all OS related hypotheses are successfully tested. Within each set, a step-down approach is used to control the Type I error rate. The Type I error allocated to a set of hypotheses that is successfully tested will be re-distributed for the testing of hypotheses in another set.
Sample Size and Power	The planned sample size is 990 subjects. For the OS analysis in all subjects, the trial has about 94% power to show that pembrolizumab in combination with chemotherapy is superior to chemotherapy at an initially assigned one-sided 2.0% alpha level when the underlying HR is 0.7. The PFS analysis in all subjects has approximately 97% power to show that combo is superior to chemo only at an initially assigned one-sided 0.5% alpha level when the underlying HR is 0.675.

Abbreviations: BICR=blinded independent central review; chemo=chemotherapy only+SOC; CI=confidence interval; Combo=pembrolizumab+chemotherapy+SOC; CPS=Combined Positive Score for PD-L1 positivity; DMC=data monitoring committee; PD-L1=programmed death-ligand 1; pembro=pembrolizumab only; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.

8.2 Responsibility for Analyses/In-House Blinding

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

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

Although the trial is open-label, analyses or summaries generated by randomized treatment assignment, and actual treatment received status will be limited and documented. In addition, BICR evaluation of imaging data will be performed.

The external DMC will serve as the primary reviewer of the unblinded results of the interim analyses and will make recommendations for discontinuation of the trial or modification to an EOC of the Sponsor. Depending on the recommendation of the external DMC, the Sponsor may prepare a regulatory submission. If the external DMC recommends modifications to the design of the protocol or discontinuation of the trial, this EOC and limited additional Sponsor personnel may be unblinded to results at the treatment level to act

on these recommendations. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the DMC Charter.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the trial are stated in Section 3.0 – Objective(s) and Hypothesis(es).

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

8.4.1 Efficacy Endpoints

Primary

Progression-free survival – RECIST 1.1 by BICR

Progression-free-survival is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first. See Section 8.6 – Statistical Methods for the censoring rules.

Overall Survival

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

Key Secondary

Objective Response Rate – RECIST 1.1 by BICR

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

Information on other efficacy endpoints will be provided in sSAP.

8.4.2 Safety Endpoints

Safety measurements are as described in Section 7.1.2 – Clinical Procedures/Assessments.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The intention-to-treat (ITT) population will serve as the primary population for the analysis of efficacy data in this trial.

Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data using the ITT population. Details on the approach to handling missing data are provided in Section 8.6 – Statistical Methods.

8.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this trial. The ASaT population consists of all randomized subjects who received at least 1 dose of trial treatment. Subjects will be included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. For subjects who take incorrect trial treatment for only part of the treatment period, AEs will be analyzed based on the period when the correct treatment occurs. In addition, a narrative will be included to describe any AEs that occur during the time the subjects receive the incorrect treatment. 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 1 laboratory or vital sign measurement obtained subsequent to at least 1 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 8.6 – Statistical Methods.

8.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 8.6.2 – Statistical Methods for Safety Analyses. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8 – Multiplicity. Nominal p-values computed for other efficacy analyses should be interpreted with caution due to potential issues of multiplicity, sample size, etc.

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and key secondary objectives. Methods related to other objectives will be described in the sSAP. Table 11 summarizes the primary analysis approach for primary and key secondary efficacy endpoints.

8.6.1.1 Progression-free Survival (PFS)

The nonparametric 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 HR and its 95% confidence interval (CI) from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 5.4 – Stratification) will be applied to both the stratified log-rank test and the stratified Cox model. Note that the stratified analyses for primary and secondary objectives will use the stratification information collected in the IVRS.

Since disease progression is assessed periodically, 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 subjects who have PD or death documented after ≤ 1 missed disease assessment and before new anticancer therapy, if any, then these subjects will be counted as having events at date of documented PD or death. For subjects who have PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any, then the PFS will be censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any. For subjects who have no PD and no death, the PFS will be censored at last disease assessment unless there is new anticancer treatment initiated, when the PFS will be censored at last disease assessment before new anticancer treatment. Sensitivity analyses will be performed for comparison of PFS based on the investigator's assessment.

To evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 2 sensitivity analyses will be performed with a different set of censoring rules. For the first sensitivity analysis, all PD or death will be counted as an event; all no PD and no death will be censored at the last disease assessment. For the second sensitivity analysis, not only all PD or death will be counted as an event, no PD and no death will be counted as an event as well, except that the subject is still in treatment or discontinues the treatment due to complete response and no new anticancer therapy is initiated. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The details of censoring rules for primary and sensitivity analyses are summarized in Table 10.

Table 10 Censoring Rules for Primary and Sensitivity Analysis of PFS

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

Abbreviation: PD=progressive disease.

8.6.1.2 Overall Survival (OS)

The nonparametric 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 HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 5.4 – Stratification) will be applied to both the stratified log-rank test and the stratified Cox model. Subjects in the control arm may switch to another anti-PD-1 treatment following the verification of PD by BICR. Exploratory analyses to adjust for the effect of treatment switching to other PD-1 therapies on OS may be performed based on recognized methods, e.g., the Rank Preserving Structural Failure Time model proposed by Robins and Tsiatis [55], etc., based on an examination of the appropriateness of the data to the assumptions required by the methods.

8.6.1.3 Objective Response Rate

Stratified Miettinen and Nurminen's method will be used for comparison of the ORR between 2 treatment groups. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported. The stratification factors used for randomization (see Section 5.4 – Stratification) will be applied to the analysis.

Table 11 Analysis Strategy for Primary and Key Secondary Efficacy Objectives

Endpoint/Variable† (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Endpoint			
PFS per RECIST 1.1 as accessed by BICR	Testing: Stratified† Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2
OS	Testing: Stratified† Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at date the subject was known to be alive
Key Secondary Endpoint			
ORR per RECIST 1.1as accessed by BICR	Testing: Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered nonresponders

Abbreviations: ITT=intention-to-treat population; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors; BICR=blinded independent central review(er)

† The primary endpoints are under control of Type I error. They will be analyzed for 2 populations: all subjects and PD-L1 CPS ≥10% subjects, respectively. Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (see Section 5.4) will be applied to the analysis model.

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

8.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 12). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events that meet predefined limits of change in laboratory, vital signs, and ECG parameters are either prespecified as Tier 1 endpoints or will be classified as belonging to Tier 2 or Tier 3 based on observed proportions of subjects with an event.

Tier 1 Events

Safety parameters or AEOSIs that are identified a priori constitute Tier 1 safety endpoints that will be subject to inferential testing for statistical significance. AEs that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program, and determination of statistical significance is not expected to add value to the safety evaluation. Similarly, the combination of pembrolizumab and chemotherapy has not been associated with any new safety signals. Therefore, there are no Tier 1 events for this protocol.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of subjects with events using the Miettinen and Nurminen method [53], an unconditional, asymptotic method.

Membership in Tier 2 requires that at least 10% of subjects in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least 10% of subjects was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥5% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Table 12 Analysis Strategy for Safety Endpoints

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Specific AE (≥10% of subjects in one of the treatment groups)	X	X
	Any Grade 3 to 5 AE (≥5% of subjects in one of the treatment groups)	X	X
	Any SAE (≥5% of subjects in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Change from baseline results (laboratory test toxicity grade)		X
Abbreviations: AE=adverse event; CI=confidence interval; SAE=serious adverse event; X=results will be provided.			

Time to First Grade 3 to 5 AE

In addition to the tiered approach, exploratory analysis may be performed on the time to the first Grade 3 to 5 AE. Time to first Grade 3 to 5 AE is defined as the time from the first day of study treatment to the first event of Grade 3 to 5 AE. For subjects without a Grade 3 to 5 AE, the time to first Grade 3 to 5 AE is censored at 30 days after the last dose of study treatment. The Kaplan-Meier method will be used to estimate the curve of time to first Grade 3 to 5 AE. The treatment difference in time to first Grade 3 to 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.

8.6.3 Demographic and Baseline Characteristics

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

8.7 Interim Analyses

8.7.1 Safety Interim Analysis

A safety assessment will take place after 10 subjects in the combo arm have completed 2 cycles of therapy. If the majority of the enrolled subjects (more than 80%) require a dose modification of platinum and/or gemcitabine by the end of the second cycle, the dose of the chemotherapies may be reduced for the remainder of the trial. If 9 or 10 of the first 10 subjects require 2 dose modifications of platinum and/or gemcitabine by the end of the second cycle, the Sponsor will consider discontinuing or modifying the treatment dose levels in the combination arm. Although there is no plan to evaluate efficacy data at the safety interim analysis, an administrative alpha-spending of 0.0001 will be imposed for this analysis.

8.7.2 Efficacy Interim Analysis

Two interim efficacy analyses will be conducted. Both PFS and OS will be analyzed at the time of the interim analysis in the combo arm, pembro only arm, and chemo only arm.

The first interim analysis will be performed if 1) all subjects are enrolled; and 2) approximately 347 PFS events have been observed in the combo and chemo only arms in all subjects. The information fraction of PFS events observed is around 0.65. This is projected to occur around 20 months after the trial starts.

The second interim analysis will be performed if approximately 357 OS events have been observed among the combo and chemo only treatment arms in all subjects. The information

fraction of OS events observed is around 0.85. This is projected to occur around 28 months after the trial starts.

To account for potential delayed treatment effect, which was observed with immunotherapy study data external to this study, the final analysis (FA) will take place when all of the following requirements are met: 1) at least 22 months after the last subject is randomized; 2) approximately 616 OS events have been observed among the 3 treatment arms in all subjects; and 3) approximately 208 OS events have been observed in pembrolizumab monotherapy and chemo only arms in PD-L1 CPS ≥10. The additional follow-up time is incorporated into the trial to ensure that the FA is conducted at an appropriate time to characterize the potential benefit of immunotherapy, where the treatment effect is most pronounced toward the tail of the survival curve. The FA is projected to occur around 42 months after the trial starts.

Table 13 summarizes the decision guidance for the interim analysis and the FA. The stopping boundary shows the values of statistics at the decision boundary across which the corresponding null hypotheses will be rejected. The boundary information corresponds to tests of the primary hypotheses at each possible Type I error level (please see Section 8.8 – Multiplicity for details on possible alpha levels for each test). The actual alpha allocated at the interim analysis is based on the Hwang-Shih-DeCani alpha-spending function with gamma parameter (-4) for OS and Pocock alpha-spending function for PFS.

Table 13 Decision Guidance (Boundary Z Statistic, P-Value, and Approximate Hazard Ratio) for the Interim and Final Analysis of PFS and OS

Hypothesis	Alpha Level for Hypothesis (Alpha at IA) [a]	IA1			IA2			FA		
		Boundary			Boundary			Boundary		
		Z Statistic	p-value	Approximate Observed HR at Boundary	Z statistic	p-value	Approximate Observed HR at Boundary	Z statistic	p-value	Approximate Observed HR at Boundary
H1	0.50%	2.8002	0.0026	0.7398	2.8002	0.0026	0.7741	2.8002	0.0026	0.7843
	2.50%	2.2001	0.0139	0.789	2.2001	0.0139	0.8176	2.2001	0.0139	0.8261
H2	2%	2.7336	0.0031	0.6995	2.3469	0.0095	0.7796	2.1266	0.0167	0.8122
	2.50%	2.6593	0.0039	0.7061	2.2601	0.0119	0.7865	2.0307	0.0211	0.8196
H3a	2%	2.7336	0.0031	0.6597	2.3469	0.0095	0.7703	2.1266	0.0167	0.8168
	2.50%	2.6593	0.0039	0.6703	2.2601	0.0119	0.7816	2.0307	0.0211	0.8289
H3b	2%	2.7336	0.0031	0.6018	2.3469	0.0095	0.702	2.1266	0.0167	0.7441
	2.50%	2.6593	0.0039	0.6096	2.2601	0.0119	0.7108	2.0307	0.0211	0.7537
H4a	2%	2.7336	0.0031	0.7717	2.3469	0.0095	0.8593	2.1266	0.0167	0.8949
	2.50%	2.6593	0.0039	0.7795	2.2601	0.0119	0.8674	2.0307	0.0211	0.9035
H4b	2%	2.7336	0.0031	0.7021	2.3469	0.0095	0.7815	2.1266	0.0167	0.8139
	2.50%	2.6593	0.0039	0.7084	2.2601	0.0119	0.7883	2.0307	0.0211	0.8212

Abbreviations: HR=hazard ratio; IA1=first interim analysis; IA2=second interim analysis; FA=final analysis

[a] Except for the initially assigned alpha for H1 and H2, all other alphas are conditional on the outcomes of other hypotheses tests from the multiplicity control.

Please note that the HRs are approximations and the actual alpha levels and interim analysis boundaries will be determined from the actual number of events observed at the time of the interim analyses and the corresponding alpha-spending function. The boundaries for the FA will be adjusted according to the actual alpha spent at the interim analyses and the actual number of events observed at the interim analyses and FA.

More details on the FA are in Section 8.9 – Sample Size and Power Calculations.

Results of the interim analyses will be reviewed by an external DMC. Depending on the recommendation of the DMC, the Sponsor may prepare a regulatory submission if any of the primary objectives are met at interim analysis. Further details of interim analyses will be incorporated into the DMC Charter.

8.8 Multiplicity

The multiplicity strategy specified in this section will be applied to the primary hypotheses on superiority for PFS, superiority and noninferiority in OS, and key secondary hypotheses of superiority of ORR.

The overall Type I error across the testing of the PFS, OS, and ORR hypotheses is strongly controlled at α=2.5% (one-sided). The multiplicity strategy will follow the graphical approach of Maurer and Bretz [54]. Figure 3 provides the multiplicity strategy for the trial. The arrows on the diagram show how the Type I error allocated to a null hypothesis that is successfully rejected will be redistributed for the testing of the other hypotheses. Please note that the arrows do not necessarily indicate the testing order. The primary hypotheses are divided into a set for PFS testing and a second set for OS/ORR testing. A Bonferroni approach is used to control the Type I error rate alpha at 2.5% (1-sided), with 0.5% and 2% initially allocated to the PFS and OS/ORR set, respectively.

Within the PFS set, the hypotheses H1 will be tested. The alpha allocated to the PFS set will be shifted to the OS/ORR set if the null hypothesis of H1 is rejected at the interim or final analysis, and the alpha level for testing OS/ORR hypotheses at the interim and final analysis will be adjusted using the Hwang-Shih-DeCani alpha-spending function with gamma parameter (-4).

Within the OS/ORR set, a step-down approach will be used to control the Type I error rate. The primary OS hypotheses will be tested in the order of H2, H3a, H3b, H4a, and H4b based on the order of projected power and corresponding relationship between noninferiority and superiority tests. The noninferiority hypotheses are tested before corresponding superiority hypotheses. The superiority in ORR will be tested after the superiority in all OS related hypotheses is shown. After demonstrating the superiority in ORR, the alpha will be shifted from the OS/ORR set to the PFS set. In the PFS set, when the hypothesis H1 is tested, the possible alpha levels are 0.5% and 2.5% corresponding to without and with alpha level shifted from the OS/ORR set, respectively. In the OS/ORR set, when a hypothesis is tested, the possible alpha levels are 2% and 2.5% corresponding to without and with alpha level shifted from the PFS set, respectively.

Please note that both PFS and OS/ORR endpoints have initially been assigned an alpha level, 0.5% for PFS and 2% for OS/ORR set. Therefore, if the PFS hypothesis H1 is not rejected, only PFS testing will be stopped and there will be no impact on OS/ORR testing with its

initially assigned alpha and vice versa. Furthermore, if the null hypothesis in the PFS set H1 is rejected, then the initially assigned alpha level 0.5% will be recycled to the OS/ORR set and the hypotheses in the OS/ORR set will be tested at alpha level equal to 2.5%. The consequence of this recycling is that some null hypotheses in the OS/ORR set that could not be rejected at the alpha level equal to 2% might be rejected with a higher alpha level (2.5%). Similarly, if all null hypotheses related to OS/ORR are rejected, then the alpha level 2% will be recycled to the PFS set and increase the power of testing PFS related hypothesis H1.

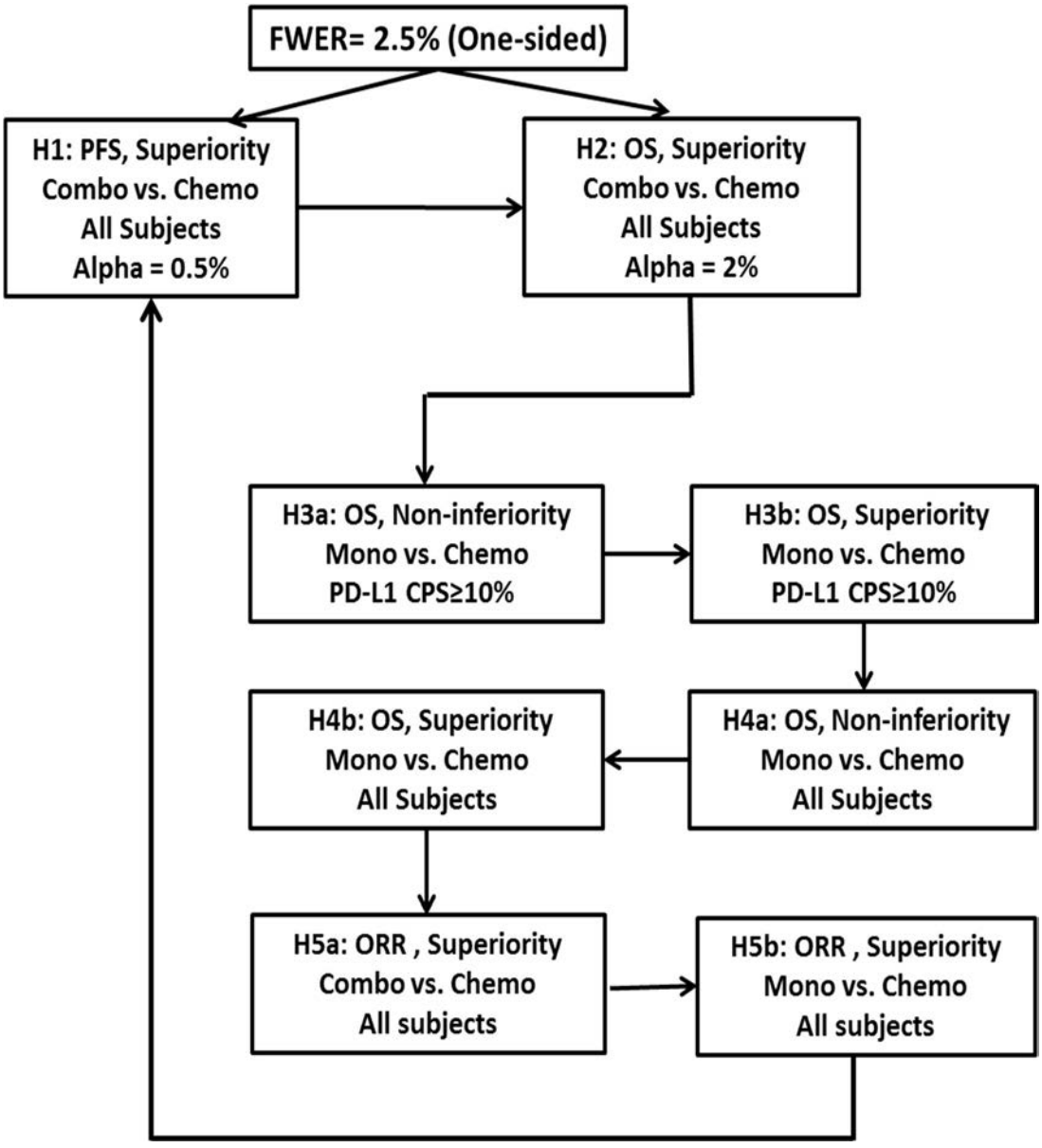


Figure 3 Multiplicity Strategy

Abbreviations: chemo=chemotherapy only+SOC; Combo=pembrolizumab +chemotherapy+SOC; FWER=family-wise error rate; ORR=objective response rate; OS=overall survival; PD-L1=programmed death-ligand 1; pembro=pembrolizumab only; PFS=progression-free survival; SOC=standard of care.

The ORR hypotheses in all subjects will be tested following a group sequential approach. The 2 ORR hypotheses are initially assigned Type I error rates of 0% and thus, cannot be tested unless the null hypothesis of H4b (superiority of OS pembro only vs chemo only in all subjects) is successfully rejected. The ORR hypothesis of pembro only vs chemo only in all subjects can only be tested after the ORR hypothesis of combo vs chemo only in all subjects is successful. 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 allowing tight control of the overall Type I error will be distributed by an alpha-spending function of Hwang-Shih-DeCani 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 3 scheduled scans if not discontinued. Only subjects with "mature ORR information" will be included into the ORR analysis.

8.9 Sample Size and Power Calculations

This trial was designed to randomize a total of approximately 990 subjects into the combo, pembro only, and chemo only arms with a 1:1:1 ratio. Beginning on 21-FEB-2018, subjects who had tumors that were PD-L1 CPS <10% were only randomized to the combo arm or chemo only arm. There was no change to randomization for subjects who had tumors that were PD-L1 CPS ≥10%. As a result of this change, there will be a small imbalance leading to more subjects in the combo and chemo only arms and fewer subjects in the pembro only arm. Among all subjects, approximately 50% were expected to be PD-L1 CPS ≥10%.

The interim analyses of the OS and PFS trial endpoints will be event driven (ie, the testing of the OS and PFS hypotheses are conducted upon accumulating a preset number of events).

The FA will take place when all of the following requirements are met: 1) at least 22 months after the last subject is randomized; 2) approximately 616 OS events have been observed among the 3 treatment arms in all subjects; and 3) approximately 208 OS events have been observed in pembrolizumab monotherapy and chemo only arms in PD-L1 CPS ≥10.

The sample size was calculated based on the following assumptions: 1) A total of 990 subjects and among them 495 are PD-L1 CPS ≥10% 2) both OS and PFS follow exponential distributions and with median of 13.5 and 7.5 months, respectively, in the chemo only arm; 3) the HRs are listed in Table 14; 4) a yearly dropout rate for OS and PFS is 2% and 5%, respectively; and 5) the noninferiority margin is set at HR equal to 1.1.

Table 14 Assumptions of Hazard Ratios for Superiority between Different Conditions

PFS all subjects Combo vs Chemo only	0.675
OS all subjects Combo vs Chemo only	0.7
OS PD-L1 CPS ≥10% Pembro only vs Chemo only	0.65
OS all subjects Pembro only vs Chemo only	0.75

Abbreviations: chemo=chemotherapy+SOC; combo=pembrolizumab+chemotherapy+SOC; PD-L1=programmed death-ligand 1; pembro=pembrolizumab; PFS=progression-free survival; OS=overall survival.

The assumptions on median survival months were based upon historical data. The noninferiority margin was based on the 25% of the effect of the assumed effect [56] of chemotherapy versus placebo with a HR of 0.7 (FDA Guidance for Non-Inferiority Clinical Trials) [57]. In addition, the HR 1.1 is also the lower bound of the range of margin for noninferiority cancer trials that used time-to-event primary outcomes [58].

Table 15 shows the approximate power of primary hypotheses tests under specific scenarios. Please note that this is marginal power for each hypothesis. Depending on the actual outcomes from the multiplicity control, a hypothesis could be tested at more than one alpha level. Please see Section 8.8 – Multiplicity for details on possible alpha levels. The other detailed information on boundary, and HR, etc. is shown in Table 13.

Table 15 Power of Primary Hypotheses Tests

Hypothesis	Alpha Level†	Power†
H1: PFS, all subjects superiority, Combo vs Chemo Only	0.5%	97%
	2.5%	99%
H2: OS, all subjects, superiority, Combo vs Chemo Only	2%	94%
	2.5%	95%
H3a: OS, PD-L1 CPS ≥10%, noninferiority, Pembro Only vs Chemo Only	2%	95%
	2.5%	96%
H3b: OS, PD-L1 CPS ≥10%, superiority, Pembro Only vs Chemo Only	2%	85%
	2.5%	87%
H4a: OS, all subjects, noninferiority, Pembro Only vs Chemo Only	2%	97%
	2.5%	97.5%
H4b: OS, all subjects, superiority, Pembro Only vs Chemo Only	2%	81%
	2.5%	84%

Abbreviations: chemo=chemotherapy+SOC; combo= pembrolizumab+chemotherapy+SOC; H=Hypothesis; PD-L1=programmed death-ligand 1; pembro=pembrolizumab; PFS=progression-free survival; OS=overall survival.

† Except for the initially assigned alpha for H1 and H2, all other alphas and powers are conditional on the outcomes of other hypotheses from the multiplicity control.

Note that power of noninferiority tests is based on the same hazard ratio assumptions as used in the corresponding superiority tests

Please note that the actual power may be adjusted based on the actual number of events observed at the time of the FA.

8.10 Subgroup Analyses and Effect of Baseline Factors

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

- Age category (<65 vs ≥65 years)
- Sex (female, male)

- PD-L1 subgroup (CPS ≥10% vs CPS <10%)
- ECOG (0/1 vs 2)
- Chemotherapy drug (Investigator choice of cisplatin or carboplatin)
- Smoking status (never vs former vs current)

Note that the subgroup identification information will be based on the actual value in the database.

8.11 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the trial. Compliance with trial treatment administration will be measured by subjects: 1) receiving unscheduled trial 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.

8.12 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 16.

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

Table 16 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Pembrolizumab (MK-3475) 100 mg/4 mL	Solution for infusion	Provided centrally by the Sponsor
Gemcitabine 1000 mg	Lyophilized powder for IV infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Carboplatin 10 mg/mL	Solution for infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Cisplatin 1 mg/mL	Solution for infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee

All supplies indicated in Table 16 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 16 will be provided 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 for recording 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.

All supplies will be provided open-label. Pembrolizumab will be provided as nonkitted single vials or as single/multi vials in a kit box. The other products will be provided as a kit with a single 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 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to

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

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Council for Harmonisation 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] 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.

[3] 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.

[4] Talmadge JE. Immune cell infiltration of primary and metastatic lesions: mechanisms and clinical impact. Semin Cancer Biol. 2011 Apr;21(2):131-8.

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

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

[7] 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.

[8] Diez M, Pollán M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, et al. Histopathologic prognostic score in colorectal adenocarcinomas. Anticancer Res 1998;18(1B):689-94.

[9] 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(5795):1960-4.

[10] Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol 2010;15(6):544-51.

[11] 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(3):426-30.

[12] Polcher 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 Jun;59(6):909-19.

[13] 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. Proc Natl Acad Sci U S A 2001;98(24):13866-71.

[14] Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.

[15] Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017 Mar 16;376(11):1015-1026.

[16] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.

[17] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology - Bladder Cancer: Version 2.2015. Fort Washington, PA: National Comprehensive Cancer Network (NCCN); 2015.

[18] Wu X, Ros MM, Gu J, Kiemeney L. Epidemiology and genetic susceptibility to bladder cancer. BJU Int. 2008 Nov;102(9 Pt B):1207-15.

[19] Zeegers MP, Tan FE, Dorant E, van Den Brandt PA. The impact of characteristics of cigarette smoking on urinary tract cancer risk: a meta-analysis of epidemiologic studies. Cancer. 2000 Aug 1;89(3):630-9.

[20] Garcia-Closas M, Malats N, Silverman D, Dosemeci M, Kogevinas M, Hein DW, et al. NAT2 slow acetylation, GSTM1 null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses. Lancet. 2005 Aug 20-26;366(9486):649-59.

[21] Nieder AM, Porter MP, Soloway MS. Radiation therapy for prostate cancer increases subsequent risk of bladder and rectal cancer: a population based cohort study. J Urol. 2008 Nov;180(5):2005-9; discussion 2009-10.

[22] Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R. The health economics of bladder cancer: a comprehensive review of the published literature. Pharmacoeconomics. 2003;21(18):1315-30.

[23] von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol. 2000 Sep;18(17):3068-77.

[24] De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012;30(2):191-9.

[25] Saxman SB, Propert KJ, Einhorn LH, Crawford ED, Tannock I, Raghavan D, et al. Long-term follow-up of a phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol. 1997 Jul;15(7):2564-9.

[26] Loehrer PJ Sr, Einhorn LH, Elson PJ, Crawford ED, Kuebler P, Tannock I, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol. 1992 Jul;10(7):1066-73. Erratum in: J Clin Oncol 1993 Feb;11(2):384.

[27] Sternberg CN, de Mulder P, Schornagel JH, Theodore C, Fossa SD, van Oosterom AT, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer 2006;42:50-4.

[28] von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol. 2005 Jul 20;23(21):4602-8.

[29] Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. Lancet Oncol. 2011 Mar;12(3):211-4.

[30] Dash A, Galsky MD, Vickers AJ, Serio AM, Koppie TM, Dalbagni G, et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer. 2006 Aug 1;107(3):506-13.

[31] Galsky MD, Chen GJ, Oh WK, Bellmunt J, Roth BJ, Petrioli R, et al. Comparative effectiveness of cisplatin-based and carboplatin-based chemotherapy for treatment of advanced urothelial carcinoma. Ann Oncol 2012;23(2):406-10.

[32] Antonia SJ, Gettinger SN, Man Chow LQ, Juergens RA, Borghaei H, Shen Y, et al. Nivolumab (anti-PD-1; BMS-936558, ONO-4538) and ipilimumab in first-line NSCLC: Interim phase I results [abstract]. J Clin Oncol. 2014;32 Suppl 1:5s. Abstract no. 8023.

[33] Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, et al. Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2015 Jun 20;33(18):2004-12.

[34] Papadimitrakopoulou V, Patnaik A, Borghaei H, Stevenson J, Gandhi L, Gubens MA, et al. Pembrolizumab (pembro; MK-3475) plus platinum doublet chemotherapy (PDC) as front-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021 cohorts A and C [abstract]. J Clin Oncol. 2015 May 29;33(Suppl). Abstract no. 8031.

[35] Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol. 2012 Jun 10;30(17):2046-54.

[36] Plimack ER, Bellmunt J, Gupta S, Berger R, Montgomery B, Heath K, et al. Pembrolizumab (MK-3475) for advanced urothelial cancer: updated results and biomarker analysis from KEYNOTE-012. Poster session presented at: 2015 ASCO Annual Meeting; 2015 May 29-Jun 2; Chicago, IL.

[37] Petrylak DP, Powles T, Bellmunt J, Braiteh FS, Loriot Y, Zambrano CC, et al. A phase Ia study of MPDL3280A (anti-PDL1): updated response and survival data in urothelial bladder cancer (UBC) [abstract]. Abstracts of the 2015 ASCO Annual Meeting; 2015; Chicago, IL: ASCO; 2015. p. 1-2.

[38] Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366(26):2443-54.

[39] Bellmunt J, Mullane SA, Werner L, Fay AP, Callea M, Leow JJ, et al. Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma. Ann Oncol. 2015 Apr;26(4):812-7.

[40] Bellmunt J, de Wit R, Albanell J, Baselga J. A feasibility study of carboplatin with fixed dose of gemcitabine in ‘unfit’ patients with advanced bladder cancer. Eur J Cancer 2001;37:2212-5.

[41] Logothetis CJ, Dexeus FH, Finn L, Sella A, Amato RJ, Ayala AG, et al. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol. 1990 Jun;8(6):1050-5.

[42] Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, et al. Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. J Clin Oncol 2011;29(17):2432-8.

[43] Lei AQ, Cheng L, Pan CX. Current treatment of metastatic bladder cancer and future directions. Expert Rev Anticancer Ther. 2011 Dec;11(12):1851-62.

[44] Bamias A, Lainakis G, Kastritis E, Antoniou N, Alivizatos G, Koureas A, et al. Biweekly carboplatin/gemcitabine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: report of efficacy, quality of life and geriatric assessment. Oncology. 2007;73(5-6):290-7.

[45] Linardou H, Aravantinos G, Efstathiou E, Kalofonos C, Anagnostopoulos A, Deliveliotis C, et al. Gemcitabine and carboplatin combination as first-line treatment in elderly patients and those unfit for cisplatin-based chemotherapy with advanced bladder carcinoma: Phase II study of the Hellenic Co-operative Oncology Group. Urology 2004;64(3):479-84.

[46] Food and Drug Administration (CDER, CBER). Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. Silver Spring: U.S. Department of Health and Human Services; 2007. 19 p.

[47] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.

[48] Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol group. Ann Med 2001;33:337-43.

[49] Mehanna HM, Morton RP. Patients' views on the utility of quality of life questionnaires in head and neck cancer: a randomised trial. Clin Otolaryngol 2006;31:310-6.

[50] Proakis AG, Harris GB. Comparative penetration of glycopyrrolate and atropine across the blood-brain and placental barriers in anesthetized dogs. Anesthesiologists 1978;48(5):339-44.

[51] Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016 Mar 4. [Epub ahead of print].

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

[53] Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.

[54] Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 2013;5(4):311-20.

[55] Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Commun Stat-Theor M 1991;20(8):2609-31.

[56] Food and Drug Administration (CDER, CBER). Guidance for Industry: non-Inferiority clinical trials. Silver Spring: U.S. Department of Health and Human Services; 2010. 63 p.

[57] CDER, CBER. Guidance for Industry Non-Inferiority Clinical Trials.

[58] Riechelmann RP, Alex A, Cruz L, Bariani GM, Hoff PM. Non-inferiority cancer clinical trials: scope and purposes underlying their design. Ann Oncol. 2013 Jul;24(7):1942-7.

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*

Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.3 – Future Biomedical Research Sample Collection7.1.3.3 – Future Biomedical Research Sample Collection7.1.3.3 – Future Biomedical Research Sample Collection7.1.3.3 – Future Biomedical Research Sample Collection7.1.3.3 – Future Biomedical Research Sample Collection7.1.3.3 – Future Biomedical Research Sample Collection7.1.3.3 – Future Biomedical Research Sample Collection7.1.3.3 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed,

present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

For Future Biomedical Research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

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

12. Questions

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

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Council for Harmonisation: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 ECOG Performance Status Categories

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655 http://ecog-acrin.org/resources/ecog-performance-status

12.4 Common Terminology for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI CTCAE Version 4.0 will be utilized for AE reporting. (http://ctep.cancer.gov/reporting/ctc.html).

12.5 Country-specific Requirements

12.5.1 France-specific Requirements

Section 5.1.2 Inclusion Criteria

Estimated creatinine clearance is used as an assessment of renal function.

Renal	
Estimated creatinine clearance (CrCl) [a] (estimated GFR can be used in place of estimated CrCl)	≥30 mL/min *(Note: Subjects are ineligible for cisplatin if their estimated creatinine clearance <60 mL/min)*
[a] Estimated CrCl should be calculated per institutional standard.	

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

Estimated creatinine clearance is used as an assessment of renal function.

Chemistry
Estimated Creatinine Clearance

Section 5.1.3 Exclusion Criteria

For subjects that will receive cisplatin if randomized to a chemotherapy arm:

Exclusion Criterion #22: Subjects with estimated creatinine clearance <60 mL/min are not eligible for treatment with cisplatin according to the SmPC of the product.

Exclusion Criterion #23: Subjects with Grade ≥2 audiometric hearing loss (25 decibels in 2 consecutive wave ranges) are not eligible for treatment with cisplatin according to the SmPC of the product.

Section 5.7.2 Contraception

For women of childbearing potential, a pregnancy test should be conducted prior to Day 1 of each cycle

Section 7.1.2.3.1 Full Physical Examination

An audiogram will be included as part of the screening examination.

Section 7.1.2.3.2 Directed Physical Examination

Audiograms will be included in the directed physical examinations as necessary, as determined by the investigator (ie, if subject experiences a hearing-related AE).

Section 7.1.3.1 Serum/Urine Pregnancy Test

Pregnancy testing will continue to be performed prior to each cycle and at the time of discontinuation from study treatment.

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

[a] For women of childbearing potential, pregnancy testing will continue prior to each cycle and at the time of discontinuation from study treatment.

12.6 List of Abbreviations

Abbreviation/Term	Definition
AE	Adverse Event
ADA	Antidrug Antibodies
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
ASaT	All Subjects as Treated
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BCG	*Bacillus* Calmette-Guerin(Tuberculosis vaccine)
BICR	Blinded independent central review(er)
Chemo	In this trial, cisplatin+gemcitabine or carboplatin+gemcitabine (the latter only in cisplatin-ineligible subjects) plus SOC
CI	Confidence Interval
Cis	Carcinoma in situ
CNS	Central Nervous System
Combo	In this trial, pembrolizumab plus chemotherapy (cisplatin+gemcitabine or carboplatin+gemcitabine [the latter only in cisplatin-ineligible subjects] plus SOC)
CPS	Combined Positive Score for PD-L1 positivity (combined expression of tumor cells and inflammatory markers)
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein-4
DCR	Disease Control Rate (CR, PR, and SD)
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DRAE	Drug-Related Adverse Event
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
eEQ-5D	eEuroQol-5 Dimensions
ePRO	Electronic Patient-Reported Outcome

Abbreviation/Term	Definition
ERC	Ethics Review Committee
ESMO	European Society of Medical Oncology
EuroQol	European Quality of Life
FA	Final analysis
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	Formalin-Fixed, Paraffin-Embedded
GC	Gemcitabine/Carboplatin
GCP	Good Clinical Practice
GEM	Gemcitabine
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IgV	Immunoglobulin Variable
IHC	Immunohistochemistry
irAE	Immune-related adverse event
IRB	Institutional Review Board
IrRECIST	Immune-related RECIST
ITT	Intention-To-Treat Population
IUD	Intrauterine Device
IV	Intravenous
IVD	In Vitro Diagnostic
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
KN	Keynote
mAb	Monoclonal Antibody
MCAVI	Gemcitabine plus carboplatin or methotrexate plus carboplatin plus vinblastine
Mg	Milligram
Mg/kg	Milligram per Kilogram
MK-3475 (formerly SCH90045)	Merck designation for pembrolizumab
mL	milliliter
MRI	Magnetic Resonance Imaging
MSI	Microsatellite instability
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MVAC	Methotrexate/Vinblastine/Doxorubicin/Cisplatin
NA or N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI	(US) National Cancer Institute
NMIBC	Nonmuscle Invasive Bladder Cancer

Abbreviation/Term	Definition
NSCLC	Non–Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-Counter (nonprescription)
PD	Progressive Disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death-Ligand 1
Pembro	Pembrolizumab (only)
PFS	Progression-free Survival
PI	Principal investigator
PIN	Personal Identification Number
PK	Pharmacokinetic(s)
PR	Partial Response
PRO	Patient-Reported Outcome
PS	Performance Status
PT	Prothrombin Time
PS	Performance Status
PSA	Prostate-specific Antigen
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RR	Response Rate
SAE	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SOC	Standard of Care
SOP	Standard Operating Procedure
sSAP	Supplemental Statistical Analysis Plan
T1DM	Type 1 Diabetes Mellitus
TIL	Tumor-Infiltrating Lymphocyte
TSH	Thyroid-Stimulating Hormone
US	United States

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	