Official Protocol Title:	A Phase I Study of MK-3475 Alone in Subjects with Advanced Solid Tumors and in Combination with Platinum-Doublet Chemotherapy or immunotherapy in Subjects with Advanced Non-Small Cell Lung Cancer/ Extensive-Disease Small Cell Lung Cancer.
NCT number:	NCT01840579
Document Date:	24-Sep-2019

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(hereafter referred to as the Sponsor or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100, U.S.A.

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

TITLE:

A Phase I Study of MK-3475 Alone in Subjects with Advanced Solid Tumors and in Combination with Platinum-Doublet Chemotherapy or immunotherapy in Subjects with Advanced Non-Small Cell Lung Cancer/ Extensive-Disease Small Cell Lung Cancer.

IND NUMBER: Not Applicable
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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-3475-011-08	24-SEP-2019	Remove 2nd course treatment phase and follow up phase including survival follow up.
MK-3475-011-07	16-OCT-2017	Add part E cohort 3 to evaluate regimen (pembrolizumab + cisplatin + etoposide) with prophylactic use of granulocyte colony-stimulating factor (lasting G-CSF).
MK-3475-011-06	12-DEC-2016	Add New parts [Part D (pembrolizumab + ipilimumab for NSCLC) and Part E (pembrolizumab + cisplatin/carboplatin + etoposide for SCLC)]
MK-3475-011-05	05-JUL-2016	Addition of SpO2 and SP-D measurements for screening and on treatment period.
MK-3475-011-04	15-APR-2016	Add Part C; In the Part C (combination), 6 to 9 subjects with advanced squamous NSCLC will receive MK-3475 200mg Q3W in combination with carboplatin/paclitaxel (Cohort 1), or carboplatin/nab-paclitaxel (Cohort 2), respectively.
MK-3475-011-03	14-JUL-2015	Changed dose of MK-3475 in Part B from 10 mg/kg to 200 mg fixed dose. Changed the drugs of chemotherapy in Cohort 2 from carboplatin/ paclitaxel to carboplatin/pemetrexed.
MK-3475-011-02	04-APR-2013	Subject exclusion criteria #1 was changed from 4 weeks to 2 weeks prior to the first dose of trial treatment for palliative radiotherapy and kinase inhibitors. Added a section for demographics as Section 7.1.1.5 to collect information regarding cancer related gene mutation/translocation etc. Section 8.2.5.1 was changed; 90% confidence interval" is changed into "90% Bayesian prediction interval" to keep the consistent with TPI designs used in study.

Document	Date of Issue	Overall Rationale
MK-3475-011-01	14-MAR-2013	Add part B; MK-3475 and cytotoxic chemotherapy administration will be staggered in Cycle 1 only. 10 mg/kg of MK-3475 will be administered on Day 1 in Cycle 1 without the accompanying cytotoxic chemotherapy. On Day 8 in Cycle 1, either cisplatin/pemetrexed (Cohort 1) or carboplatin/paclitaxel(Cohort 2) will be administered while MK-3475 will be withheld.
MK-3475-011-00	04-FEB-2013	Initial version.

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0 2.1 5.8.1 6.2.4 6.2.5 6.2.6 7.1.1.8 7.1.3.4 7.1.5.4.2 7.1.5.5 7.1.5.6	TRIAL SUMMARY Trial Design Discontinuation of Treatment Follow-up phase-Part B, C, D and E Part B, C and E- Second Course phase and Follow-up phase Part D- Second Course phase and Follow-up phase Subsequent Antineoplastic Therapy Status Tumor Imaging and Assessment of Disease (irRC and irRECSIT) Observation visit Survival Follow-up (Part B, C, D and E) Second Course Phase (Part B, C, D and E only)	Patients who have already started the second course phase of administration before the approval of the protocol version 08, may continue in the second course phase (up to 12 months) if applicable. For other patients, the second course phase is not applicable. After the approval of the protocol version 08, the final visit of this study will be a safety follow-up visit, and imaging follow-up and survival follow-up will not be performed. Participants in the follow-up phase or survival follow-up phase will discontinue the study and no further visits are required.	The primary objective of this study was achieved and additional data is not required.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.1.3.2.1	Blood Collection for Serum Pharmacokinetics of MK-3475	Serum samples collection for pharmacokinetic measurements will be discontinued after the completion of discontinuation visit after approval of the protocol version 08.	Based on the results already obtained, no further data is required.
7.1.3.2.2	Blood Collection for Serum Anti-pembrolizumab Antibodies	Blood samples collection for anti-pembrolizumab antibodies measurements will be discontinued after the completion of discontinuation visit after approval of the protocol version 08.	Based on the results already obtained, no further data is required.
7.1.3.4 7.1.3.5	Tumor Imaging and Assessment of Disease (irRC and irRECSIT) Pulmonary Radiographic Evaluation for pembrolizumab-Induced Pneumonitis	Images taken after July 20, 2019 need not be submitted to the central vendor nor Sponsor.	Based on the results already obtained, no further data is required.
7.1.5.4.3	Follow-Up Visit 1 and 2	After the approval of the protocol version 08, all follow-up visits, including serum or blood sample collection for pharmacokinetic or anti-MK-3475 antibody assessment, will be discontinued after the 30 day of follow-up visit.	The primary objective of this study was achieved and additional data is not required.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase I study of MK-3475 in subjects with advanced solid tumors and NSCLC/ED-SCLC
Trial Phase	Phase I
Clinical Indication	Advanced solid tumors and non-small cell lung cancer (NSCLC)/Small Cell Lung Cancer (SCLC)
Trial Type	Interventional
Type of control	No treatment control
Route of administration	IV infusion
Trial Blinding	Unblinded Open-label
Treatment Groups	In the Part A (monotherapy, 3+3 design), 3 or 6 subjects with advanced solid tumors will receive escalating doses of pembrolizumab 2 mg/kg (Dose level 1) or 10 mg/kg (Dose level 2) every 2 weeks (Q2W), respectively. In the Part B (combination), 6 to 9 subjects with advanced NSCLC will receive pembrolizumab 200 mg every 3 week (Q3W) in combination with cisplatin/pemetrexed (Cohort 1), or carboplatin/ pemetrexed (Cohort 2), respectively. In the Part C (combination), 6 to 9 subjects with advanced squamous NSCLC will receive pembrolizumab 200 mg Q3W in combination with carboplatin/paclitaxel (Cohort 1), or carboplatin/nab-paclitaxel (Cohort 2), respectively. In the Part D (combination), 6 to 9 subjects with advanced NSCLC will receive pembrolizumab 200 mg (Q3W) in combination with 1 mg/kg ipilimumab [every 6 weeks (Q6W)]. In the Part E (combination), 6 to 9 subjects with untreated Extensive-Disease (ED) Small Cell Lung Cancer (SCLC) will receive pembrolizumab 200 mg Q3W in combination with cisplatin/etoposide (Cohort 1), or carboplatin/ etoposide (Cohort 2), respectively. Three to 9 subjects with untreated ED-SCLC will receive pembrolizumab 200 mg Q3W in combination with cisplatin/etoposide (Cohort 3). Subjects, who enrolled into cohort 3, will take prophylactic use of granulocyte colony-stimulating factor (lasting G-CSF) (pegfilgrastim).
Number of trial subjects	Approximately 84 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 6 years from the time the first subject signs the informed consent until the last subject's last visit.

Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, subjects will continue the treatment of study drugs until completion of 2 years of trial therapy, documented disease progression, unacceptable adverse event(s) etc. Pembrolizumab (in part D, pembrolizumab+ipilimumab) treated subjects who attain a complete response may consider stopping trial treatment. These subjects who attain Complete Response or stop trial therapy after 2 years of treatments for reasons other than disease progression or intolerability may be eligible for re-treatment if they meet the criteria for Second Course Phase. Patients who have already started the second course phase of administration before the approval of the protocol version 08, may continue the second course phase (up to 12 months) if applicable. For other patients, the second course phase is not applicable. After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring [serious adverse events (SAE) will be collected for up to 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier]. Subjects in Part B, C, D and E will have follow-up for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up. After the approval of the protocol version 08, the final visit of this study will be a safety follow-up visit, and imaging follow-up and survival follow-up will not be performed. Participants in the follow-up phase or survival follow-up phase will discontinue the study and no further visits are required.

2.0 TRIAL DESIGN

2.1 Trial Design

This study is an open-label, non-randomized, multi-center Phase I study of pembrolizumab alone in subjects with advanced solid tumors, and in combination with platinum-doublet chemotherapy or immunotherapy in subjects with previously untreated advanced Non-Small Cell Lung Cancer/ ED-SCLC. This study is designed to evaluate the safety and tolerability, and pharmacokinetics of pembrolizumab alone and in combination with platinum-doublet chemotherapy selected by each cohort or immunotherapy. As exploratory objectives, the presence of anti- pembrolizumab antibodies, anti-tumor activity, overall survival, correlation between objective response and PD-L1 expression levels, and pulmonary radiographic changes and its features will also be evaluated. The study has 5 parts; Part A, (monotherapy, 3+3 design), and Part B, C, D and E (combination).

In Part A, pembrolizumab will be administered as an IV infusion in repeating 2-week cycles, and 4 weeks period in the only first cycle (Cycle 1: 4 weeks, Cycle 2 and subsequent cycles: 2 weeks). 3 or 6 subjects will be enrolled sequentially to receive escalating doses of 2 mg/kg (Dose level 1) and 10 mg/kg (Dose level 2) of pembrolizumab, respectively.

In Part B, 200 mg of pembrolizumab and cytotoxic chemotherapy will be administered. A maximum of 4 cycles of cisplatin/pemetrexed (Cohort 1) or carboplatin/ pemetrexed (Cohort 2) will be administered along with pembrolizumab. After completion of the platinum-

containing doublet, maintenance therapy with pemetrexed in combination with pembrolizumab is permitted if the investigator thinks it is appropriate per standard of care (SOC), followed by a single agent of pembrolizumab. 6 to 9 subjects in each Cohort will be enrolled

In Part C, 200 mg of pembrolizumab and cytotoxic chemotherapy will be administered. A maximum of 4 cycles of carboplatin/paclitaxel (Cohort 1) or carboplatin/nab-paclitaxel (Cohort 2) will be administered along with pembrolizumab followed by pembrolizumab as maintenance therapy. 6 to 9 subjects in each Cohort will be enrolled.

In Part D, 200 mg (Q3W) of pembrolizumab and 1 mg/kg ipilimumab (Q6W) will be administered. Pembrolizumab plus ipilimumab will be administered up to 18 cycles of ipilimumab (35 times of pembrolizumab). 6 to 9 subjects will be enrolled.

In Part E, 200 mg of pembrolizumab and cytotoxic chemotherapy will be administered. A maximum of 4 cycles of cisplatin/etoposide (Cohort 1 and 3) or carboplatin/etoposide (Cohort 2) will be administered along with pembrolizumab followed by pembrolizumab as maintenance therapy. 6 to 9 subjects in each Cohort will be enrolled. Three to 9 subjects with untreated ED-SCLC will receive pembrolizumab 200 mg Q3W in combination with cisplatin/etoposide and prophylactic lasting G-CSF (pegfilgrastim). Patients who achieve a partial or complete response with platinum/etoposide plus 200 mg pembrolizumab for 4 cycle may be offered prophylactic cranial radiation (PCI) at the discretion of the Investigator; if given, PCI would begin within 4 to 6 weeks after the last with platinum/etoposide plus pembrolizumab 200 mg treatment. At least 2 weeks following completion of PCI, patients will continue 200 mg pembrolizumab Q3W as maintenance therapy.

6 subject in each cohort at part C and E (cohort 1 and 2) or in part D will be enrolled for PK sample evaluation even if 0/3 subjects develop a DLT and it is considered to be tolerated.

There are 3 cohorts in Part E. Preliminary data of the DLT assessment, no DLT was reported in Cohort 2, however in Cohort 1, Grade 3 febrile neutropenia (DLT) has been reported in 3 out of 6 patients in Cycle 1 [Grade 4 laryngeal stenosis has been reported in 1 out of 6 patients in Cycle 1, also]. Prophylactic use of G-CSF in SCLC patients is allowed based on a subject's condition in Japan clinical practice. A lasting G-CSF is used for prophylaxis of neutropenia due to chemotherapies. To minimize a patient's burden, only lasting G-CSF prophylactic use of G-CSF during DLT assessment period was selected to evaluate the safety and tolerability for untreated ED-SCLC patients treated with pembrolizumab 200 mg Q3W in combination with cisplatin/etoposide and prophylactic G-CSF.

Subjects will continue trial therapy until they meet 5.8 Subject Withdrawal/Discontinuation Criteria such as, documented disease progression, unacceptable adverse event(s) etc. Pembrolizumab (in part D, pembrolizumab+ipilimumab) treated subjects who attain a complete response may consider stopping trial treatment. These subjects and who stopped trial therapy after 2 years of treatments for reasons other than disease progression or intolerability may be eligible for re-treatment if they meet the criteria for Second Course Phase. Patients who have already started the second course phase of administration before the approval of the protocol version 08, may continue the second course phase (up to 12 months)

if applicable. For other patients, the second course phase is not applicable. After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring [serious adverse events(SAE) will be collected for up to 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier] Subjects in Part B, C, D and E will be followed-up for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up. After the approval of the protocol version 08, the final visit of this study will be a safety follow-up visit, and imaging follow-up and survival follow-up will not be performed. Participants in the follow-up phase or survival follow-up phase are completed and no further visits are required.

The Dose limited toxicity (DLT) evaluation period will be defined as the first 4 weeks (in Part A), 3 weeks (in Part B, C and E) or 6 weeks (in Part D) after initiation of study treatment. As a general rule, all of the study procedures in the DLT evaluation period will be performed under hospitalization. In the DLT assessments of Part A, if 0 of the 3 subjects or ≤ 1 of the 6 subjects experience a DLT at a dose level, it will be considered to be tolerated. In Part B, C, D and E, if 0 of the 3 subjects or ≤ 2 of the 6 subjects or ≤ 4 of the 9 subjects experience a DLT at each combination cohort/part, it will be considered to be tolerated.

Time points of serum pharmacokinetics of pembrolizumab are described in section 7.1.3.2.1. The anti-tumor activity will be assessed by radiographic (CT or MRI), and standard tumor markers evaluations (as appropriate for a given tumor type) approximately every 6 (in Part A) calendar weeks or every 6 calendar weeks for the first 24 weeks and every 9 calendar weeks from the date of imaging assessment at the week 24 (in Part B, C, D and E). Tumor response will be assessed using the immune related Response Criteria (irRC, See Section 12.6) for Part A or irRECIST for Part B, C, D and E by investigator, and tumor volumetric analysis for Part A or RECIST 1.1 (See Section 12.5) for Part B and C by central imaging vendor. Time points of serum anti- pembrolizumab antibodies are described in section 7.1.3.2.2.

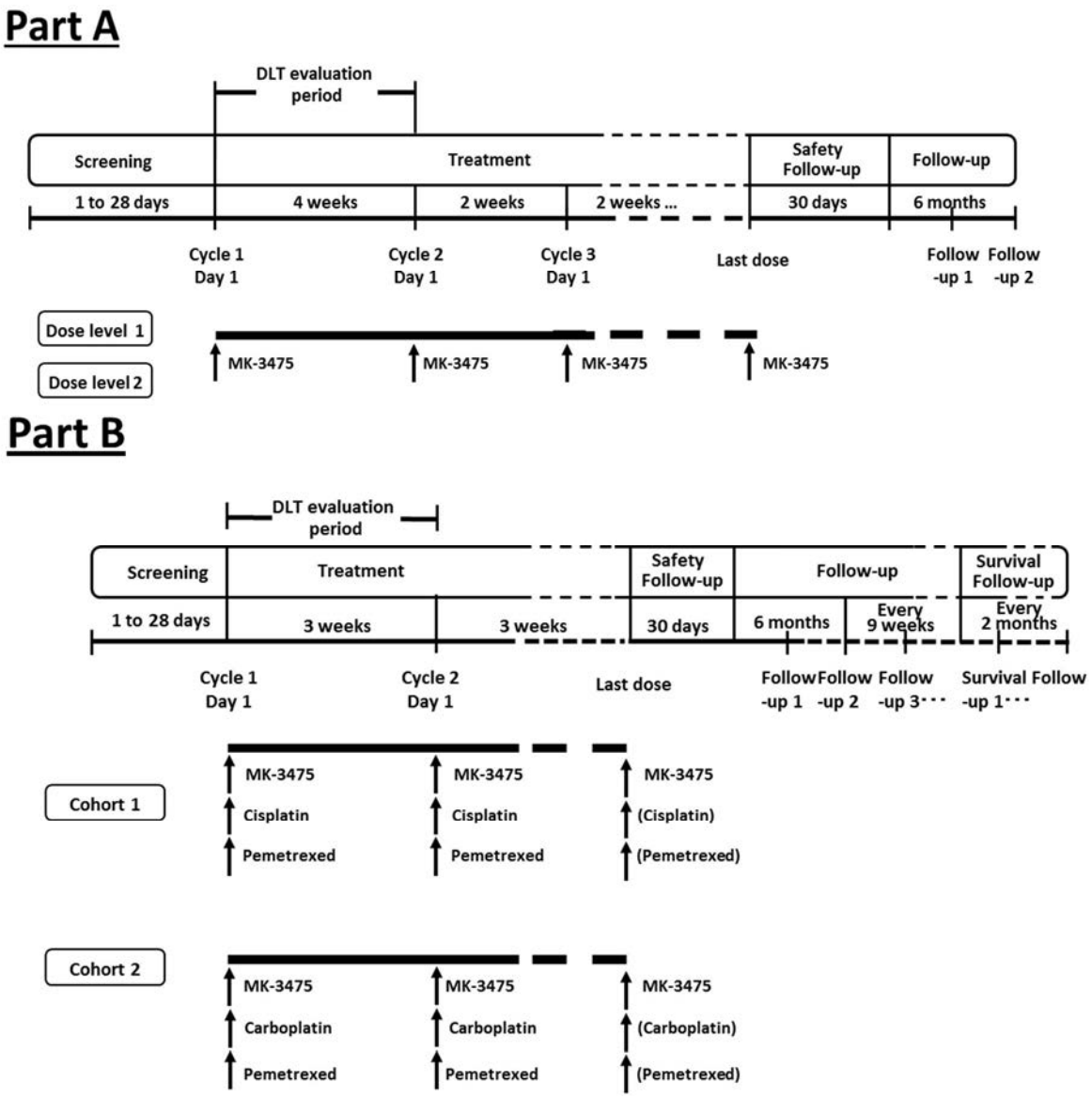
Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

Combination medications for Part B and, that with carboplatin/paclitaxel for Part C and with ipilimumab for part D were determined based on the results of ongoing overseas Phase I/II study (PN021). In PN021, tolerability, safety and efficacy were evaluated with 2 mg/kg or 10 mg/kg of pembrolizumab in combination with chemotherapy or immunotherapy and the triple combination were well tolerated. An ongoing overseas phase 1b/2 study (KEYNOTE-026) is exploring the combination of pembrolizumab with carboplatin and nab-paclitaxel.

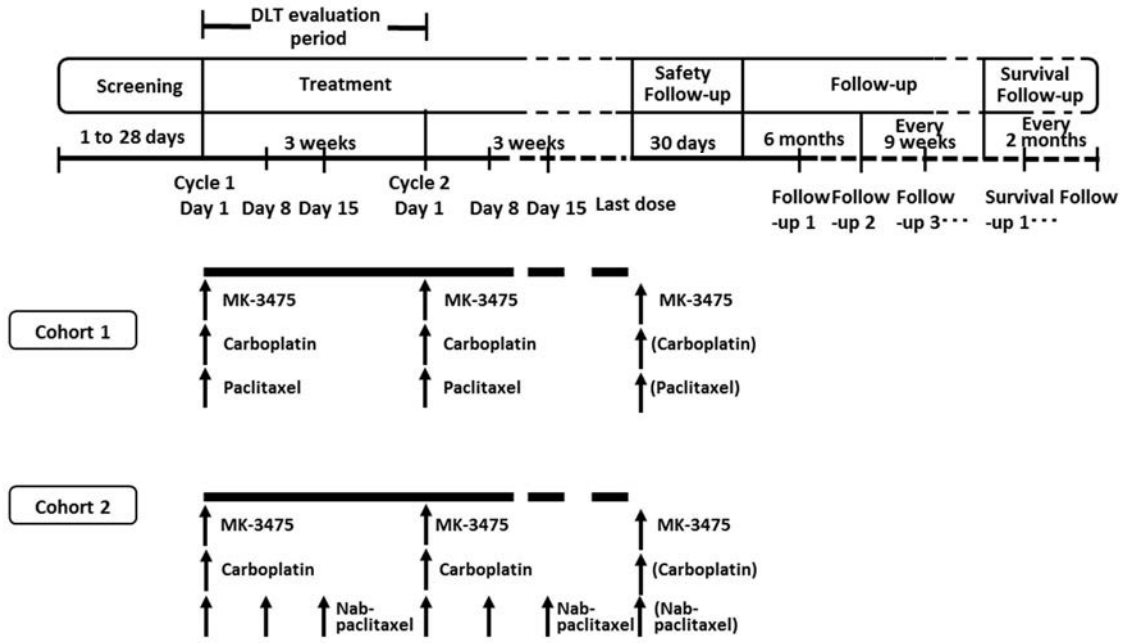
Combination medications for Part E were determined based on ongoing overseas Phase II study (REACTION, ClinicalTrials.gov Identifier: NCT02580994).

2.2 Trial Diagram

The trial design is depicted in Figure 1



Part C


DLT evaluation period
Screening
Treatment
Safety Follow-up
Follow-up
Survival Follow-up
1 to 28 days
3 weeks
3 weeks
30 days
6 months
Every 9 weeks
Every 2 months
Cycle 1 Day 1
Day 8
Day 15
Cycle 2 Day 1
Day 8
Day 15
Last dose
Follow-up 1
Follow-up 2
Follow-up 3···
Survival Follow-up 1···
Cohort 1
MK-3475
Carboplatin
Paclitaxel
MK-3475
Carboplatin
Paclitaxel
MK-3475
(Carboplatin)
(Paclitaxel)
Cohort 2
MK-3475
Carboplatin
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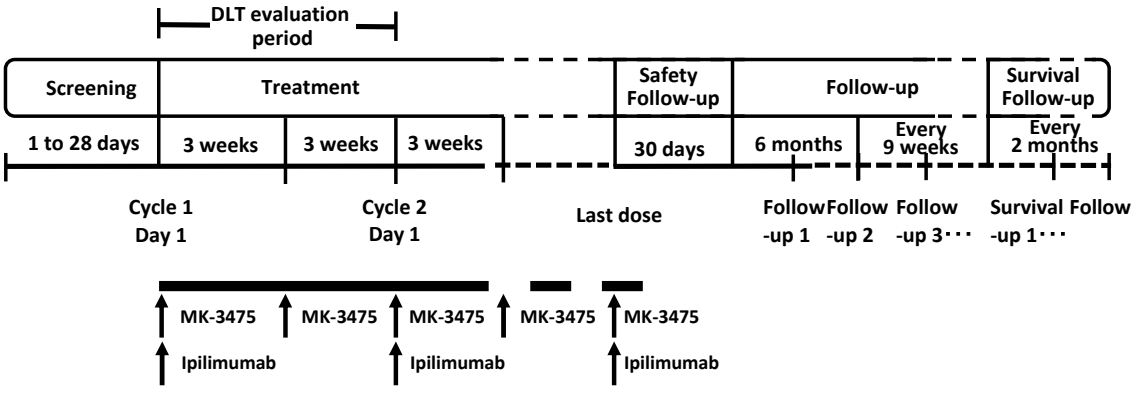
MK-3475
Carboplatin
Nab-paclitaxel
MK-3475
(Carboplatin)
(Nab-paclitaxel)

Part D


DLT evaluation period
Screening
Treatment
Safety Follow-up
Follow-up
Survival Follow-up
1 to 28 days
3 weeks
3 weeks
3 weeks
30 days
6 months
Every 9 weeks
Every 2 months
Cycle 1 Day 1
Cycle 2 Day 1
Last dose
Follow-up 1
Follow-up 2
Follow-up 3···
Survival Follow-up 1···
MK-3475
MK-3475
MK-3475
MK-3475
MK-3475
Ipilimumab
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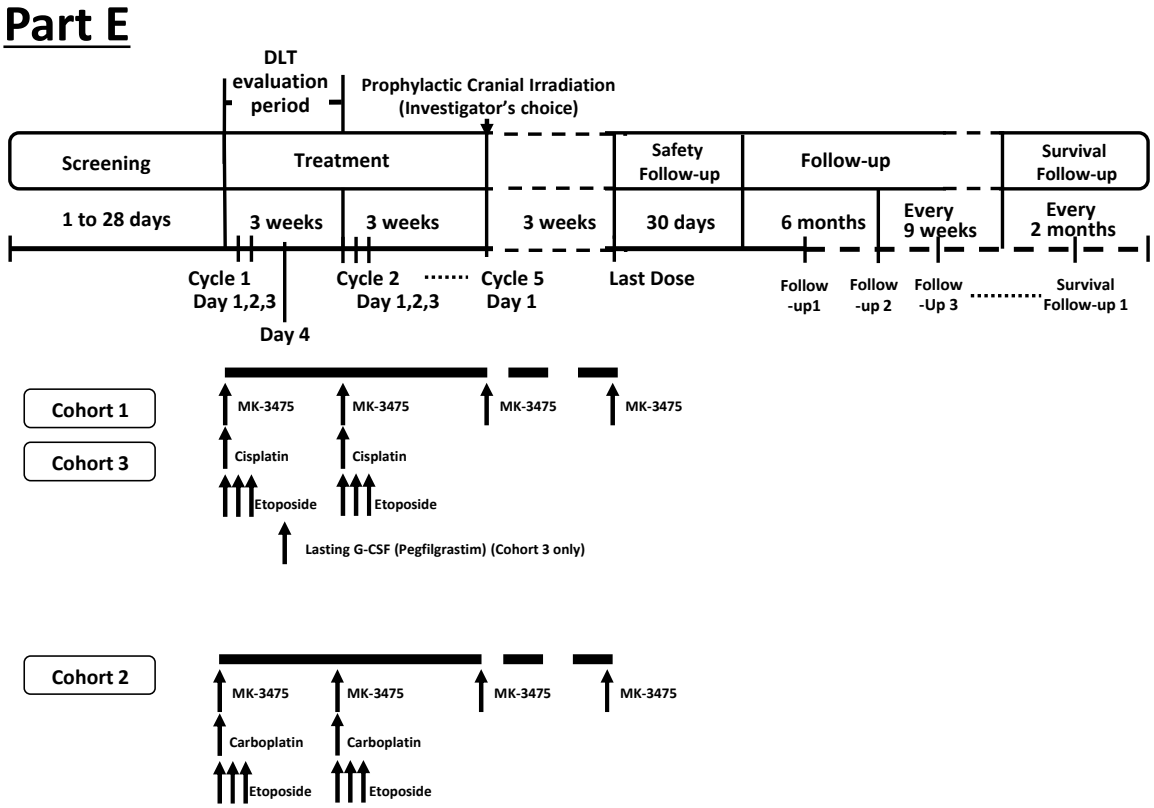

Figure 1 Study Design Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To evaluate the tolerability and safety profile of pembrolizumab alone in subjects with advanced solid tumors and in combination with platinum-doublet chemotherapy in subjects with advanced NSCLC or ED-SCLC, or in combination with immunotherapy in subjects with advanced NSCLC.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To evaluate the pharmacokinetic profiles of pembrolizumab alone and in combination with platinum-doublet chemotherapy or immunotherapy.

3.3 Exploratory Objectives

1) **Objective:** To evaluate the presence of anti- pembrolizumab antibodies.

2) **Objective:** To evaluate the anti-tumor activity of pembrolizumab alone in advanced solid tumors and in combination with platinum-doublet chemotherapy in advanced NSCLC or ED-SCLC, or in combination with immunotherapy in subjects with advanced NSCLC.

3) **Objective:** To evaluate the correlation between PD-L1 expression levels and tumor response of pembrolizumab.

4) **Objective:** To evaluate the pulmonary radiographic changes and its features for a diagnosis of pembrolizumab-induced pneumonitis

5) **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 (Part B, C, D and E only).

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

Pembrolizumab is a potent and highly selective humanized monoclonal anti-PD-1 antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 (programmed cell death-1) and its ligands PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

The PD-1 pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T cell immune surveillance. 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 is an Ig superfamily member which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [1, 2]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types including renal cell carcinoma (RCC), pancreatic carcinoma [3], hepatocellular carcinoma [4], ovarian carcinoma [5] and NSCLC [6]. The high expression of PD-L1 on tumor cells has been found to correlate with poor prognosis and survival in various cancers. The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor evasion

and is thus an attractive target for therapeutic intervention. Actually in the clinical trial using other anti-PD-1 antibody, nivolumab, objective response were observed in subjects with NSCLC, melanoma, and other advanced solid tumors and the safety profile does not appear to preclude its use [7]. Nivolumab was also well tolerated up to the dose of 20 mg/kg in phase I study in Japanese subjects with advanced solid tumors, and showed anti-tumor activities in melanoma, CRC, and thyroid carcinoma [8].

Lung cancer has the highest incidence of malignancies in 2008 with more than 1.6 million cases in world wide. Mortality from lung cancer was similar with over 1.4 million deaths from lung cancer. In Japan also, lung cancer is the leading cause of cancer death. The incidence of lung cancer in 2007 is more than 90 thousands cases and around 70 thousands patients die annually from lung cancer. Most lung cancer patients, approximately 85%, have NSCLC. Of those, approximately 40%-60% have adenocarcinoma histology; 10%-15%, squamous histology; 5%, neuroendocrine histology; and the rest, "not otherwise specified" [9, 10].

Current standard in a first-line for advanced NSCLC except EGFR mutated type and EML4-ALK is platinum-based doublet therapy. The median survival was 12.3 months for NSCLC subjects who were treated with carboplatin/paclitaxel in a first line setting. Frequent (>5%) Grade 3 or 4 toxicities were leukopenia, neutropenia, anemia, thrombocytopenia, febrile neutropenia, nausea, vomiting, anorexia and constipation [11]. While platinum doublets have similar outcomes [12, 13], cisplatin/pemetrexed or carboplatin/paclitaxel have been clinically well used mainly on the basis of safety. Carboplatin/pemetrexed is more often used in clinical practice in recent years. Median survival months were 10.3 months of NSCLC patients who were treated with cisplatin/pemetrexed in a first line therapy. Key (>5%) grade 3 or 4 drug-related toxicities were neutropenia, anemia, nausea, vomiting, and fatigue [12]. The median survival months were 10.5 months of NSCLC patients who were treated with carboplatin/pemetrexed in a first therapy. Key (>5%) grade 3 or 4 toxicities were neutropenia, anemia, thrombocytopenia and any hemorrhagic events [14].

A randomized phase III trial compared the efficacy and safety of albumin-bound paclitaxel (nab-paclitaxel) plus carboplatin with solvent-based paclitaxel (sb-paclitaxel) plus carboplatin in advanced NSCLC. A total of 1,052 untreated subjects with stage IIIB to IV NSCLC were randomly assigned 1:1 to receive 100 mg/m2 nab-paclitaxel weekly and carboplatin at AUC of 6 Q3W (nab-paclitaxel) or 200 mg/m2 sb-paclitaxel plus carboplatin AUC 6 Q3W (sb- paclitaxel). The primary end point was objective response rate (ORR). The ORR of nab-paclitaxel arm and sb-paclitaxel arm was 33% v 25%, respectively, (response rate ratio, 1.313; 95% CI, 1.082 to 1.593) in overall population and 41% v 24%, respectively, (response rate ratio, 1.680; 95% CI, 1.271 to 2.221) in patients with squamous histology [15].

When pembrolizumab was administrated in combination with other chemotherapeutic agents in mouse models, synergistic antitumor effects were observed (refer to the IB)

Ipilimumab is a fully human monoclonal antibody (IgG1) that blocks CTLA-4, which down-regulates pathways of T-cell activation but not the distinct mechanisms of PD-1, to promote anti-tumor immunity [16]. Ipilimumab is approved in more than 50 countries including Japan

since it was approved in the USA in March, 2011 for the treatment of patients with unresectable or metastatic melanoma.

As for combination of anti-PD-1 and anti-CTLA-4 antibody, nivolumab in combination with ipilimumab was approved in Oct, 2015 for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma in US. In addition, recent clinical study demonstrated that the combination of PD-1 and CTLA-4 blockade has demonstrated durable responses with untreated NSCLC patients. A phase I trial was conducted to evaluate the safety and efficacy of first-line nivolmab and ipilimumab in advanced NSCLC (CheckMate 012). A total of 129 untreated subjects with stage IIIB/IV NSCLC were received nivolmab 3 mg/kg Q2W + ipilimumab 1 mg/kg (Q6W or Q12W) or nivolmab 3 mg/kg Q2W. The confirmed ORR (confirmed) was 39% (n=39, nivolmab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W), 47% (n=38, nivolmab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q12W) and 23 % (n=52, nivolmab 3 mg/kg Q2W) respectively. One year OS rate was 69% (95%CI: 52-81%), Not Reached, and 73% (95%CI: 59-83%). PFS was 3.9 months (95%CI: 2.6-13.2 months), 8.1 month (95%CI: 5.6-13.6 months) and 3.6 months (95%CI: 2.3-6.6 months), respectively. The Efficacy with nivolmab plus ipilimumab was enhanced with increasing PD-L1 expression. The rate of grade 3-4 treatment-related AEs was 33%, 37% and 19% in Nivolumab+Ipilimumab (Q6W) arm, Nivolumab+Ipilimumab (Q12W) arm and Nivolumab monotherapy arm respectively. There was no treatment-related death [17].

SCLC is characterized by a rapid high growth fraction and a high frequency of somatic mutations [18]. SCLC is also characterized early development of widespread metastases. Most patients with SCLC present with hematogenous metastases (ED-SCLC); approximately one third present with limited disease confined to the chest. SCLC is highly sensitive to initial chemotherapy and radiotherapy; however, most patients have recurrent disease and eventually die [19, 20].

Current standard in a first-line for ED-SCLC is platinum-based doublet therapy with etoposide and irinotecan in Japan. Small randomized trials and a meta-analysis of 4 randomized studies compared cisplatin-based versus carboplatin-based regimens in patients with SCLC have suggested similar efficacy of cisplatin and carboplatin in patients with SCLC [21, 22].

The combination of irinotecan and a platinum agent has provided the greatest challenge to EP. Initially, a small phase III trial performed in Japan reported that patients with ED-SCLC who were treated with irinotecan plus cisplatin experienced a median survival of 12.8 months compared with 9.4 months for patients treated with etoposide with a platinum agent [23]. However, 2 subsequent large phase III trials performed in the United States comparing irinotecan plus cisplatin with etoposide with a platinum agent failed to show a significant difference in response rate or OS between the regimens [24, 25].

Therefore, clinical development of pembrolizumab, an anti-PD-1 antibody, would have a great significance in patients with advanced solid tumors including NSCLC/SCLC.

4.1.2 Ongoing Clinical Trials

Refer to the latest IB for detailed information of clinical trials of pembrolizumab.

In overseas Phase I/II study (PN021), subject with stage IIIB/IV NSCLC and no prior systemic therapy were randomized 1:1 to pembrolizumab 2 or 10 mg/kg Q3W plus carboplatin/ paclitaxel (cohort A) or carboplatin/pemetrexed (cohort C) in phase I cohort. Subjects with IIIB/IV NSCLC who have failed previous treatment were randomized to pembrolizumab 2 or 10 mg/kg Q3W plus ipilimumab 1 mg/kg or 3 mg/kg (cohort D and H).

Twenty-five subjects (pembrolizumab 2 mg/kg; n=13 and pembrolizumab 10 mg/kg; n=12) in cohort A, 24 subject (2 mg/kg; n=12 and 10 mg/kg; n=12) in cohort C, and 51 subjects (pembrolizumab 2 mg/kg/ipilimumab 1 mg/kg; n=45, pembrolizumab 10 mg/kg/ipilimumab 3 mg/kg; n=3, pembrolizumab 10 mg/kg/ipilimumab 1 mg/kg; n=3) in cohort D and H received study therapy. One DLT was reported (Grade 3 rash in cohort C, pembrolizumab 10 mg/kg).

Grade 3 or 4 toxicities in part A were anemia and febrile neutropenia (n=2 each), fatigue, hypertension, Infectious pleural effusion, leukopenia, neutropenia, rash, urticaria and white blood cell count decreased (n=1 each). Grade 3 or 4 toxicities in part C were AST increased (n = 3), ALT increased (n=2), anemia, atrial fibrillation, colitis, diarrhea, drug eruption and hyponatremia (n=1 each). Grade 3 or 4 toxicities reported by in cohort D and H were syncope and diarrhea (n=3 each), dyspnea, fatigue, hypokalemia, pneumonia (n=2 each), diabetic ketoacidosis, large intestine perforation, pancytopenia, pericardial effusion, sepsis, adrenal insufficiency, ALT increased, AST increased, back pain, cardiac failure, cerebral ischemia, colitis, constipation, drug eruption, gastroenteritis, hepatocellular injury, hypoglycemia, hyponatremia, hypoxia, noncardiac chest pain, pneumonitis, pulmonary embolism, rash maculopapular, rash pruritic, retroperitoneal hematoma, intestinal perforation, lymphocyte count decreased (n=1 each). The rate of grade 3-5 treatment-related AEs was 49%, 33% and 67% in MK-3475 2 mg/kg + ipilimumab1 mg/kg arm, MK-3475 10 mg/kg + ipilimumab 3 mg/kg arm and MK-3475 10 mg/kg + ipilimumab1 mg/kg arm respectively. One treatment-related death (pancreatitis) was reported (MK-3475 2 mg/kg + ipilimumab 1 mg/kg).

ORR (confirmed and unconfirmed) was 28 % (n=7: 2 mg/kg; n=5 and 10 mg/kg; n=2) in cohort A and 58% (n=14: 2 mg/kg; n=5 and 10 mg/kg; n=9) in cohort C. Disease control rate (DCR) was 84% (n=21: 2 mg/kg; n=12 and 10 mg/kg; n=9) in A and 100% (n=24: 2 mg/kg; n=12 and 10 mg/kg; n=12) in cohort C. The efficacy results are encouraging a flat dose–exposure relationship since no difference was observed across pembrolizumab dose level in each cohort. Based on the promising ORR observed for pembrolizumab in combination with carboplatin and pemetrexed, this combination is being further explored - in a prespecified phase 2 cohort of PN021.

In cohort D and H, ORR was 25% and DCR was 64% in overall population (n=44, MK-3475 2 mg/kg/ipilimumab 1 mg/kg) and ORR was 20% and DCR was 70% in PD-L1 negative population (n=20, MK-3475 2 mg/kg/ipilimumab 1 mg/kg).

An ongoing overseas phase 1b/2 study (KEYNOTE-026) is exploring the combination of pembrolizumab with carboplatin and nab-paclitaxel.

For chemotherapy-naïve patients with ED-SCLC, ongoing overseas Phase II study (REACTION, ClinicalTrials.gov Identifier: NCT02580994) is exploring the combination of pembrolizumab with cisplatin/carboplatin and etoposide.

In ongoing international multicohort phase Ib studies [KEYNOTE-028 (KN-028) and KEYNOTE-158 (KN-158)] are exploring the mono-therapy of pembrolizumab for relapsed SCLC patients (ClinicalTrials.gov Identifier: NCT02054806 and NCT02628067). KN-028 is a study of pembrolizumab in patients with PD-L1 positive advanced solid tumors. Preliminary data of KN-028 was released in ASCO 2015 annual meeting; pembrolizumab monotherapy is generally well tolerated and has promising antitumor activity in patients with PD-L1 positive SCLC who have progressed on prior platinum-based therapy. ORR was 35%. [26].

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

As described in 4.1 Background, non-clinical and clinical data obtained so far supports clinical development of pembrolizumab in Japan. This phase I study is the first in Japanese study using pembrolizumab. In the Part A (monotherapy), subjects with advanced solid tumors who have failed established standard medical anti-cancer therapies for a given tumor type or have been intolerant to such a therapy will be selected according to the "Guideline for clinical evaluation method of anti-malignant tumor agents [27]". In Part B, C and D (combination), the selected subject population is chemotherapy-naïve patients with advanced NSCLC. In Part E (combination), the selected subject population is chemotherapy-naïve patients with ED-SCLC. NSCLC and SCLC are considered to be one of the promising indications of potential tumors (refer to 4.1.1 Pharmaceutical and Therapeutic Background).

Given the safety profile of pembrolizumab observed thus far, it is not believed that there will be considerable overlapping toxicities with standard of care cytotoxic chemotherapy. In Part B, C and E of this study, pembrolizumab will be added to common platinum-containing doublet chemotherapy in chemotherapy-naïve patients with advanced NSCLC/ED-SCLC based on ethical considerations for the subjects.

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

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

4.2.2 Rationale for Dose Selection/Regimen

The dosing regimens of pembrolizumab in this study were mainly determined based on results from the overseas phase I study (PN001) in subjects with advanced solid tumors. No DLTs were observed at 1 mg/kg (n=4), 3 mg/kg (n=3), and 10 mg/kg (n=10) of pembrolizumab in the dose-escalation part (Part A) of the study. Up to 10 mg/kg of pembrolizumab was well tolerated in non-Japanese subjects. In the study, pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. Therefore, translational PK-PD evaluation that a surrogate PD-1 antibody was dosed to a syngeneic mouse tumor model and tumor growth was determined together with blood and tissue sampling for PK and receptor occupancy was conducted. This model was then updated with human relevant parameters on human PK from PN001, MK-3475 affinity and melanoma growth patterns to perform in silico predictions. The predictions concluded that the lowest dose of pembrolizumab with the potential to be equivalent to 10 mg/kg of pembrolizumab was 2 mg/kg for subjects with melanoma. Based on these results, randomized phase II and III studies are planned to evaluate the efficacy and safety profiles of 2 mg/kg and 10 mg/kg of pembrolizumab in melanoma and NSCLC.

This study is the first clinical trial of MK-3475 in Japan. Based on the above results, 2 mg/kg of pembrolizumab was selected as the initial dose considering safety and efficacy in Japanese subjects in Part A. After confirming the safety and tolerability of 2 mg/kg, the safety and tolerability of 10 mg/kg will be evaluated in Part A.

The rationale for further exploration of lower doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden, indication or tumor type on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of PD-1 target engagement will not vary meaningfully with tumor type. In addition, preliminary data from 45 previously treated, advanced or metastatic NSCLC patients treated at the 2 mg/kg Q3W dose/schedule indicates a 20% BOR by RECIST (35% by irRC). This is in comparison to the 22.4% ORR observed at the 10 mg/kg Q2W, suggesting lack of dose responsiveness and additional justification of inclusion of a low dose of pembrolizumab in Part B, C, D and E.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally similar to those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma and NSCLC as associated with maximal efficacy response and 3) will maintain individual patients exposure in the e exposure range established in melanoma and NSCLC that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity

in the logistical chain at treatment facilities and reduce wastage. Thus, 200 mg Q3W was selected in Part B, C, D and E in this study.

The PK profile obtained in the overseas phase I study (PN001) shows slow systemic clearance, limited volume of distribution, and a dose related increase in exposure. The long half-life (t1/2) (13-21 days) supports dosing intervals of every 2 weeks (Q2W) and every 3 weeks (Q3W).

The dose of ipilimumab (1 mg/kg Q6W) was based upon KEYNOTE-021(cohort D and H) and CheckMate 012 study. The results of these studies are described in section 4.1.1 and 4.1.2.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

The safety primary endpoint in this study is the incidence of DLTs observed in the DLT evaluation period in Japanese subjects according to the "Guideline for clinical evaluation method of anti-malignant tumor agents [27]". Adverse events and laboratory tests values observed in this study are also safety endpoints. In addition to general laboratory tests, immune laboratory test will be evaluated considering the mode of action of pembrolizumab. Since pneumonitis has been previously reported in clinical studies of anti-PD-1 antibodies including pembrolizumab, pulmonary radiographic changes and its features will be evaluated by investigators or their designees, and an independent radiologist from a potential risk of pneumonitis.

4.2.3.2 Efficacy Endpoints

The anti-tumor activity will be evaluated as an efficacy endpoints based on imaging (CT or MRI), and tumor markers evaluations (as appropriate for a given tumor type). The immune related Response Criteria (irRC) (Part A only, Section 12.6), irRECIST (Part B, C, D and E) and RECIST 1.1 (Section 12.5) will be applied for evaluation of tumor response. irRC is a recently published set of guidelines proposed for immunotherapies in solid tumors [28].

RECIST 1.1 will also be used by the local site for treatment decisions for the study. However RECIST 1.1 will be adapted to account for the unique tumor response profile seen with immunotherapies such as pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses which may be functionally anergic. 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 criteria may not provide a complete response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, irRC will be used in Part A, and RECIST 1.1 will be used in Part B, C, D and E with the following adaptation, outlined in Section 7.1.3.4 termed irRECIST. When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a

transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response.

Tumor response will also be evaluated using tumor volumetric analysis at the central imaging vendor in Part A.

4.2.3.3 Pharmacokinetic Endpoints

Serum samples will be obtained to measure pharmacokinetics of pembrolizumab alone and in combination with platinum-doublet chemotherapy or immunotherapy in Japanese subjects based on the "Guide line for clinical evaluation methods of anti-malignant tumor agents" [27]. As pharmacokinetics endpoints, pharmacokinetic parameters ($AUC_{0\text{-}28days}$, C_{max}, T_{max}, C_{trough}, $t_{1/2}$, etc.) of pembrolizumab will be evaluated. In part B, C, D and E, pharmacokinetic parameters (C_{max}, T_{max}, C_{trough}, etc.) of pembrolizumab will be evaluated.

4.2.3.4 Immunogenicity Endpoints

Serum samples will be obtained to evaluate the presence of anti- pembrolizumab antibodies in Japanese subjects. In general, human anti-humanized antibodies may have an effect on study results such as the pharmacokinetics, efficacy and safety of pembrolizumab though it is unknown for pembrolizumab.

4.2.3.5 Planned Exploratory Biomarker Research

The correlation between baseline PD-L1 expression levels and tumor response will be evaluated as an exploratory objective. PD-L1 expression levels will be measured by immunohistochemistry (IHC) in archival tumors or biopsy samples. PD-L1 is a ligand for PD-1 and pembrolizumab attempts to disrupt the interaction of two proteins. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma, pancreatic carcinoma, hepatocellular carcinoma, ovarian carcinoma, and NSCLC.

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

Assays may include but are not be limited to:

Immunohistochemistry

PD-L1 expression in tumor tissue will be characterized by immunohistochemistry to explore the relationship between tumor PD-L1 expression and response to treatment with pembrolizumab (MK-3475). Other biomarkers contributing to the PD-1/PD-L1 axis may also be explored.

Transcriptional Analyses

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

Proteomic analysis

Tissue samples can be subjected to proteomic profiling studies using a variety of platforms that could include but are not limited to immunoassay, liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

Gene Analyses

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to define certain tumor types at the genetic level as being 'hypermutated' or it can detect the presence of specific t-cell clones within the tumor microenvironment. There is a potential that this hypermutated state and the detection of increased T-cell clonality may correlate with response to pembrolizumab therapy, and/or that the converse, 'hypomutated' state or lack of t-cells clones may correlate with non-response.

Planned Genetic Analysis

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

4.2.3.6 Future Biomedical Research

Merck will conduct Future Biomedical Research on DNA (blood) or tumor tissue specimens collected during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analyses. Specimens may be used for future assay development.

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

pharmacogenetics (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs, and/or to ensure that subjects receive the correct dose of the correct drug at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2, Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with advanced solid tumor or advanced NSCLC or ED-SCLC of at least 20 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Meet the following corresponding requirements for the part of the study they will enroll into;

   In Part A (monotherapy), subjects must have a histological or cytological diagnosis of solid tumor, progressive metastatic disease, or progressive locally advanced disease not amenable to local therapy:

   - Subjects must have failed established standard medical anti-cancer therapies for a given tumor type or have been intolerant to such therapy, or in the opinion of the Investigator have been considered ineligible for a particular form of standard therapy on medical grounds.

   In Part B, C and D (combination), subjects must have a histologically-confirmed or cytologically confirmed diagnosis of NSCLC, for stage IIIB/IV.

   - (This criterion is applicable to Part C) Has a histological or cytological diagnosis of squamous cancer.

   - Subject must be naïve to systemic therapy.

- Subject who had disease progression >6 months after completing adjuvant therapy for stage I -IIIA disease are eligible, as long as no systemic therapy was given for the recurrent disease.

- Subject must have at least one radiographically measurable lesion as per RECIST 1.1 defined as a lesion that is ≥10 mm in longest diameter or lymph node that is ≥15 mm in short axis imaged by CT scan or MRI.

In Part E (combination), subjects must have a histologically-confirmed or cytologically confirmed diagnosis of SCLC for ED stage; American Joint Committee on Cancer (AJCC) (7th edition) Stage IV (T any, N any, M 1a/b), or T3-4 due to multiple lung nodules that are too extensive.

- Subject must be naïve to systemic therapy.

- Subject must have at least one radiographically measurable lesion as per RECIST 1.1 defined as a lesion that is ≥10 mm in longest diameter or lymph node that is ≥15 mm in short axis imaged by CT scan or MRI.

2. Be male or female and ≥20 years of age on day of signing informed consent.

3. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status (Section 12.4).

4. Have adequate organ function as indicated by the following laboratory values.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 /mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L– without transfusion
Renal	
Serum creatinine or calculated creatinine clearance [a]	≤1.5 X upper limit of normal (ULN) OR ≥60 mL/min for subjects with creatinine levels >1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels >1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases
Endocrine	
Adrenocorticotropic hormone (ACTH) level [b]	Within normal limits
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless the subject is receiving anticoagulant therapy ≤1.5 X ULN unless the subject is receiving anticoagulant therapy

System	Laboratory Value
[a] Creatinine clearance (Ccr) should be calculated per institutional standard or from one of the following numerical formulas: Men: Ccr (mL/min) = {(140–age) x Body weight (kg)}/{72 x Serum Creatinine (mg/dL)} Women: Ccr (mL/min) = {(140–age) x Body weight (kg) x 0.85}/{72 x Serum Creatinin (mg/dL)} Ccr (mL/min) = {Urine Creatinin (mg/dL)}x{Urine volume (mL/day)/1440 (min/day)} x{1.73 / body surface area (m^2)}/ Serum Creatine (mg/dL) [b] ACTH: Part D only	

5. (This criterion is applicable to Part B, C and D) Have resolution of toxic effect(s) of the most recent prior antineoplastic chemotherapy (such as neoadjuvant/adjuvant therapy) to Grade 1 or less (except alopecia). If subject received major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

6. (This criterion is applicable to Part B and C only) Have provided a formalin fixed tumor tissue sample from a biopsy of a tumor lesion from a site not previously irradiated to assess for PD-L1 status. Fine needle aspirates, Endobronchial Ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) or cell blocks are not acceptable. Needle or excisional biopsies, or resected tissue is required.

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

8. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study 120 days after the last dose of study medication and through 180 days after last dose of chemotherapeutic agents.

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

9. Male subjects of childbearing potential (Section 5.7.2) must agree to use an adequate method of contraception as outlined in Section 5.7.2- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy and through 180 days after last dose of chemotherapeutic agents.

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

10. Subject has voluntarily agreed to participate by giving written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

5.1.3 Subject Exclusion Criteria

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

1. Has had the following cancer therapy within 4 weeks (2 weeks in Part E) (2 weeks for palliative radiotherapy and kinase inhibitors) prior to the first dose of study therapy, or who has not recovered from the adverse events due to previous agents administered more than 4 weeks prior to the first dose of study therapy. If the subject has residual toxicity from prior treatment, toxicity must be ≤ Grade 1 or baseline, except for alopecia.

   Part A: Chemotherapy, radiation therapy, biological therapy or kinase inhibitors

   Part B, C, D and E: Radiation therapy

2. (This criterion is applicable to Part B only) Has a histological diagnosis of squamous cancer.

3. Is currently participating or has participated in a study of an investigational agent or using an investigational device within 30 days of administration of pembrolizumab.

4. Is expected to require any other form of antineoplastic therapy while on study (including maintenance therapy with another agent for NSCLC or SCLC).

5. Is on chronic systemic steroid therapy within two weeks prior to the first dose of trial treatment or on any other form of immunosuppressive medication.

6. Has a history of acute diverticulitis, intra-abdominal abscess, GI obstruction, abdominal carcinomatosis which are known risks factors for bowel perforation.

7. (This criterion is applicable to Part B, C, D and E only) Has a known history of a hematologic malignancy, primary brain tumor or sarcoma, or of another primary solid tumor, unless the subject has undergone potentially curative therapy with no evidence of that disease for 5 years.

Note: The time requirement for no evidence of disease for 5 years does not apply to the tumor for which a subject is enrolled in the study. The time requirement also does not apply to subjects who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are clinically stable for at least 8 (in Part A) or 4 (in Part B, C and D) or 2 (in Part E) weeks and, have no evidence of new or enlarging brain metastases and also are off steroids 3 days prior to dosing with study medication. Stable brain metastases by this definition should be confirmed using MRI or CT images prior to the first dose of study medication by the investigator. Subject with asymptomatic

brain metastases (ie., no neurological symptoms, norequirements for corticosteroids, and no lesion > 1.5 cm) may participate but will require regular imaging of the brain as a site of disease.

9. (This criterion is applicable to Part C only) Has pre-existing peripheral neuropathy that is ≥ Grade 2 by CTCAE version 4 criteria.

10. Previously had a hypersensitivity reaction to the study drug substance or another mAb.

11. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

12. Has prior therapy with an anti-PD-1, PD-L1, or PD-L2 agent or an antibody targeting other immuno-regulatory receptors or mechanisms.

    - Examples of such antibodies include (but are not limited to) antibodies against IDO, IL-2R, GITR, CD137, CTLA-4.

13. Has received a live-virus vaccination within 4 weeks of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

14. Has an active infection requiring systemic intravenous therapy.

15. Has interstitial lung disease detected by chest CT, or a history of pneumonitis that required oral or intravenous glucocorticoids to assist with management. Lymphangitic spread of the NSCLC is not exclusionary.

16. Is positive for Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), Hepatitis B (HBsAg reactive) or Hepatitis C [HCV RNA (qualitative) is detected].

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

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

19. Is, at the time of signing informed consent, known to be actively abusing alcohol or drug.

20. Has symptomatic ascites or pleural effusion. A subject who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.

21. Is pregnant or breast-feeding, or expecting to conceive or father children within the projected duration of the study, starting with screening visit through 120 days after the last dose of trial treatment and through 180 days after last dose of chemotherapeutic agents. Subjects who stop breast-feeding prior to initiation of trial treatment and not expecting to resume of breast-feeding will not be excluded from the study.

22. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

5.2 Trial Treatments

Trial treatments to be used in this trial are outlined below in Table 1.

Table 1 Trial Treatment

Drug, Biologic, Device, etc.	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Part A, Dose level 1 (n= 3 or 6)					
Pembrolizumab	2 mg/kg	Q2W ‡	IV infusion (30 min)	Day 1 of each cycle	Experimental
Part A, Dose level 2 (n= 3 or 6)					
MK-3475	10 mg/kg	Q2W ‡	IV infusion (30 min)	Day 1 of each cycle	Experimental
Part B*, Cohort 1 (n= 6-9)					
Pembrolizumab	200 mg	Q3W	IV infusion (30 min)	Day 1 of each cycle §	Experimental
Cisplatin	75 mg/m^2	Q3W	IV infusion †	Day 1 of each cycle	Standard of care
Pemetrexed	500 mg/m^2	Q3W	IV infusion †	Day 1 of each cycle	Standard of care
Part B*, Cohort 2 (n= 6-9)					
Pembrolizumab	200 mg	Q3W	IV infusion (30 min)	Day 1 of each cycle §	Experimental
Carboplatin	AUC of 5 mg/mL/min	Q3W	IV infusion †	Day 1 of each cycle	Standard of care
Pemetrexed	500 mg/m^2	Q3W	IV infusion †	Day 1 of each cycle	Standard of care
Part C**, Cohort 1 (n= 6-9)					
Pembrolizumab	200 mg	Q3W	IV infusion (30 min)	Day 1 of each cycle §	Experimental
Carboplatin	AUC of 6 mg/mL/min	Q3W	IV infusion †	Day 1 of each cycle	Standard of care
Paclitaxel	200 mg/m^2	Q3W	IV infusion †	Day 1 of each cycle	Standard of care

Drug, Biologic, Device, etc.	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Part C**, Cohort 2 (n= 6-9)					
Pembrolizumab	200 mg	Q3W	IV infusion (30 min)	Day 1 of each cycle §	Experimental
Carboplatin	AUC of 6 mg/mL/min	Q3W	IV infusion †	Day 1 of each cycle	Standard of care
Nab-paclitaxel	100 mg/m^2	Q1W	IV infusion †	Day 1, 8, 15 of each cycle	Standard of care
Part D***, (n=6-9)					
Pembrorizumab	200 mg	Q3W	IV infusion (30 min)	Day 1 and 22 of each cycle‖	Experimental
Ipilimumab ¶	1mg/kg	Q6W	IV infusion (90 min)	Day 1 of each cycle ‖	Experimental
Part E****, Cohort 1 (n=6-9)					
Pembrorizumab	200 mg	Q3W	IV infusion (30 min)	Day 1 of each cycle §	Experimental
Cisplatin	75 mg/ m^2	Q3W	IV infusion †	Day 1 of each cycle	Standard of care
Etoposide	100 mg/m^2	Q3W	IV infusion †	Day 1, 2, 3 of each cycle	Standard of care
Part E****, Cohort 2 (n=6-9)					
Pembrorizumab	200 mg	Q3W	IV infusion (30 min)	Day 1 of each cycle §	Experimental
Carboplatin	AUC of 5 mg/mL/min	Q3W	IV infusion †	Day 1 of each cycle	Standard of care
Etoposide	100 mg/m^2	Q3W	IV infusion †	Day 1, 2, 3 of each cycle	Standard of care
Part E****, Cohort 3 (n=3-9)					
Pembrorizumab	200 mg	Q3W	IV infusion (30 min)	Day 1 of each cycle §	Experimental
Cisplatin	75 mg/ m^2	Q3W	IV infusion †	Day 1 of each cycle	Standard of care
Etoposide	100 mg/m^2	Q3W	IV infusion †	Day 1, 2, 3 of each cycle	Standard of care
Pegfilgrastim	3.6 mg	one time	Subcutaneous Injection	Day 4 of cycle 1 † †	Concomitant medication

* In Part B, pemetrexed may be administered every 3 weeks after finishing the treatment of combination therapy for 4 cycles by investigation's judgment as clinically significant.
** In Part C, pembrolizumab will be administered every 3 weeks after finishing the treatment of combination therapy for 4 cycles.
*** In Part D, pembrolizumab and ipilimumab will be administered up to 18 cycles of ipilimumab (35 times of pembrolizumab).
**** In Part E, pembrolizumab will be administered every 3 weeks after finishing the treatment of combination therapy for 4 cycles.
† Infusion of combination regimens and pre-medications will follow local institutional practice.
‡ The doing interval is 4 weeks for Cycle 1 only
§ Pembrolizumab to be administered prior to chemotherapy.
‖ Pembrolizumab to be administered prior to ipilimumab.
¶ ipilimumab has not been approved for NSCLC.
† † Use of Pegfilgrastim after cycle 2 and later is in section 5.5.1.

5.2.1 Dose Selection/Tolerability Evaluation Rules/Definition of Dose-Limiting Toxicity/Modification

5.2.1.1 Dose Selection

In Part A, the dose amount required to prepare the pembrolizumab infusion solution will be based on the dose level (2 mg/kg or 10 mg/kg) and the subject's weight in kilograms (kg). If a subject's weight at screening does not fluctuate by more than 10%, this weight can be used to calculate dose.

In Part B, C, D and E, a fixed dose of 200 mg of pembrolizumab will be used. A dose amount required to prepare the cisplatin (75 mg/m^2), pemetrexed (500 mg/m^2), carboplatin (AUC of 5, for Part B and E, or 6, for Part C, mg/mL/min), paclitaxel (200 mg/m^2) , nab-paclitaxel (100 mg/m^2), ipilimumab (1 mg/kg) or etoposide (100 mg/m^2) infusion solution will be based on the standard practice in each site.

Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual.

(Part E Cohort 3 only) Dose of lasting G-CSF (pegfilgrastim) 3.6 mg (via subcutaneous injection) is decided by a regulatory approved dose following the local prescribing information. Preparation and administration is also following the local prescribing information.

5.2.1.2 Tolerability Evaluation Rules

As a general rule, all of the study procedures in the DLT evaluation period will be performed under hospitalization.

Part A (Monotherapy) – 3+3 design

DLTs observed during the DLT evaluation period (the first 4 weeks after initiation of study treatment) will be used to determine escalation to the next dose level and the tolerability of the dose level using a TPI (toxicity profile interval) design [29] (target DLT rate: 20%). The dose escalation/tolerability evaluation rules (Table 2) are as follows:

Dose level 1 (2 mg/kg)

- An initial cohort of 3 subjects is enrolled.
  - If 0/3 subjects develops a DLT, the doles level 1 will be considered tolerated, then escalation to the dose level 2 (10 mg/kg) will occur.
  - If 1/3 subjects develops a DLT, other 3 subjects will be enrolled at the dose level 1.
    - If ≤1/6 subjects develop a DLT then the dose level 1 is considered to be tolerated, then escalation to the dose level 2 (10 mg/kg) will occur.

- ✧ If ≥2/6 subjects develop a DLT, the dose level 1 will be considered to be not tolerated.

- ➢ If ≥2/3 subjects develop a DLT, the dose level 1 will be considered to be not tolerated.

Dose level 2 (10 mg/kg)

- An initial cohort of 3 subjects is enrolled.

  - ➢ If 0/3 subjects develops a DLT, the doles level 2 will be considered tolerated. Other 3 subjects will be enrolled at the dose level 2.

  - ➢ If 1/3 subjects develops a DLT, other 3 subjects will be enrolled at the dose level 2.

    - ✧ If ≤1/6 subjects develop a DLT then the dose level 2 is considered to be tolerated.

    - ✧ If ≥2/6 subjects develop a DLT, the dose level 2 will be considered to be not tolerated.

  - ➢ If ≥2/3 subjects develop a DLT, the dose level 2 will be considered to be not tolerated.

Table 2 Dose Escalation/Tolerability Evaluation Rules in Part A

Number of subjects treated at current dose			
Number of toxicities		3	6
	0	E	E
	1	S	E
	2	DU	D
	3	DU	DU
	4		DU
	5		DU
	6		DU
E = Escalate to the next higher dose (do not escalate from Dose level 2) S = Stay at the current dose D = De-escalate to the next lower dose (do not de-escalate from Dose level 1) DU = The current dose is unacceptably toxic, no more subjects to be treated at this dose			

Part B, C, D and E (Combination)

DLTs observed during the DLT evaluation period [the first 3 weeks after initiation of study treatment (part B, C and E), the first 6 weeks after initiation of study treatment (Part D)] will be used to determine the tolerability of the combination regimen using a TPI design (target DLT rate: 30%). The tolerability evaluation rules (Table 3) are as follows:

- Six to 9 subjects are enrolled based on TPI design in the combination regimen; (Six to 9 subjects each for Cohort 1 and Cohort 2 of part B, C and E, and 3 to 9 subjects are enrolled based on TPI design in part E cohort 3) (respectively parallel enrollment is allowed).
  - If 0/3 subjects or ≤2/6 subjects or ≤4/9 subjects develop a DLT at the combination regimen, then it is considered to be tolerated.
  - If ≥3/6 or ≥5/9 subjects develop a DLT, the regimen will be considered to be not tolerated.

Table 3 Dose Evaluation Rules in Part B, C, D and E

Number of subjects treated at current dose				
Number of toxicities		3	6	9
	0	E	E	E
	1	A	E	E
	2	DU	E	E
	3	DU	DU	E
	4		DU	E
	5		DU	DU
	6		DU	DU
	7			DU
	8			DU
	9			DU

E = Evaluable
A = Add further 3 patients
DU = The current dose is unacceptably toxic, no more subjects to be treated at this dose

5.2.1.3 Definition of Dose-Limiting Toxicity

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.0.

The occurrence of any of the following toxicities during the DLT evaluation period will be considered a DLT, if judged by the Investigator to be related to study drug administration:

1. Grade 4 neutropenia lasting >7 days.
2. Grade 3 and Grade 4 febrile neutropenia:
    - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C or a sustained temperature of ≥38 degrees C for more than one hour
    - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C or a sustained temperature of ≥38 degrees C for more than one hour, with life-threatening consequences and urgent intervention indicated.
3. Grade 4 thrombocytopenia (<25,000/mm^3)
4. Grade 4 anemia
5. Grade 4 non-hematologic toxicity (not laboratory)
6. Grade 3 non-hematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care.
7. Any Grade 3 non-hematologic laboratory value if:
    - M edical intervention is required to treat the subject, or
    - The abnormality persists for >7 days.
8. (Part D only) Missing the 2nd dose of pembrolizumab (Cycle1 Day 22) due to drug-related adverse event.

If a subject experiences a DLT in DLT evaluation period, the subject may be discontinued from the study or refer to Section 5.2.1.4 in detail.

The SPONSOR and the investigator will decide the appropriateness of the DLT, and enrollment of additional subjects in consultation with the Efficacy and Safety Evaluation Committee as needed.

5.2.1.4 Dose Modification

Pembrolizumab

Dose reduction or dose increase of pembrolizumab will not be permitted in individual subjects.

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

Table 4 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

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

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1mg/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 1-2mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
All Other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

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 5.

Table 5 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 patient's study record.

(In Part E only) If PCI which is specified in the study design is conducted, pembrolizumab dosing should be postponed during the PCI conducted period. At least 2 weeks following completion of PCI, patients will continue 200 mg pembrolizumab Q3W as maintenance therapy.

Chemotherapy regimen

(For Part B, C and E only) Dose modification of cytotoxic chemotherapy will conform to the site's standards procedures. Dose modification of chemotherapy will not be permitted in DLT evaluation period.

(For Part B only) Subject has the option, in the event of toxicity, to change the choice of platinum (cisplatin and carboplatin) administered.

Immunotherapy regimen

(For Part D only) Dose reduction or dose increase of Ipilimumab will not be permitted in individual subjects. If a toxicity is observed with pembrolizumab in combination with ipilimumab and requires a dose modification, pembrolizumab and ipilimumab should be withheld and toxicities treated as per criteria outlined in Table 4. Subjects who experience an unacceptable toxicity that is attributed to combination therapy and not pembrolizumab monotherapy in the opinion of the investigator may permanently discontinue ipilimumab and continue with pembrolizumab as monotherapy, upon improvement of toxicity as per Table 4. Ipilimumab may not be continued under any circumstances if pembrolizumab is discontinued or while pembrolizumab is held.

5.2.2 Timing of Dose Administration

Trial treatment can be administerd+/- 3 days of the targeted Day 1 for each cycle due to administrative reasons only.

The specific time of trial treatment infusion (e.g., time of the week for first administration; time of the day for each administration) should take into consideration PK sampling time points and study visit procedures.

Pembrolizumab

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

Subjects enrolled in the Parts A, B, C and E will receive pembrolizumab at the following timing:

1. Pembrolizumab will be administered on Day 1 of each cycle as a 30-minute IV infusion (25-40 min).

Subjects enrolled in the Parts D will receive pembrolizumab at the following timing:

1. Pembrolizumab will be administered on Day 1 and Day 22 of each cycle up to 35 times as a 30-minute IV infusion (25-40 min).

In Part B, C and E, pembrolizumab will be administered at least 30 minutes prior to premedication for the following chemotherapies.

Trial treatmentcan be administerd+/- 3 days of the targeted Day 1 for each cycle due to administrative reasons only.

The specific time of trial treatment infusion (e.g., time of the week for first administration; time of the day for each administration) should take into consideration PK sampling time points and study visit procedures.

Combination Regimens for Part B

All subjects should receive the appropriate pre-medications per site's standard practice.

Subjects enrolled in Cohort 1 will receive cisplatin/pemetrexed at the following timing:

1. Pemetrexed 500 mg/m^2 will be administered as an IV infusion on Day 1 of each cycle (every 3 weeks) up to 4 cycles. Subjects should also receive appropriate vitamin supplementation of vitamin B12 and folic acid.

2. Cisplatin 75 mg/m^2 will be administered as an IV infusion after Pemetrexed infusion on Day 1 of each cycle (every 3 weeks) up to 4 cycles.

Subjects enrolled in the Cohort 2 will receive carboplatin/pemetrexed at the following timing:

1. Pemetrexed 500 mg/m^2 will be administered as an IV infusion on Day 1 of each cycle (every 3 weeks) up to 4 cycles. Subjects should also receive appropriate vitamin supplementation of vitamin B12 and folic acid.

2. Carboplatin AUC of 5 mg/mL/min will be administered as an IV infusion after pemetrexed infusion on Day 1 of each cycle (every 3 weeks) up to 4 cycles.

Pemetrexed 500 mg/m^2 may be administered as an IV infusion on Day 1 of each cycle (3 weeks) with pembrolizumab after finishing the treatment of combination therapy for 4 cycles by investigation's judgment as clinically significant in both cohorts 1 and 2. Subjects should also receive appropriate vitamin supplementation of vitamin B12 and folic acid.

Combination Regimens for Part C

All subjects should receive the appropriate pre-medications per site's standard practice.

Subjects enrolled in Cohort 1 will receive carboplatin/paclitaxel at the following timing:

1. Paclitaxel 200 mg/m^2 will be administered as an IV infusion on Day 1 of each cycle (every 3 weeks) up to 4 cycles. Paclitaxel should be completely administered before initiating carboplatin dose.

2. Carboplatin AUC of 6 mg/mL/min will be administered as an IV infusion after paclitaxel infusion on Day 1 of each cycle (every 3 weeks) up to 4 cycles.

Subjects enrolled in the Cohort 2 will receive carboplatin/nab-paclitaxel at the following timing:

1. Nab-paclitaxel 100 mg/m^2 will be administered as an IV infusion on Day 1, 8 and 15 of each cycle (every 3 weeks) up to 4 cycles. Nab-paclitaxel should be completely administered before initiating carboplatin dose.

2. Carboplatin AUC of 6 mg/mL/min will be administered as an IV infusion after nab-paclitaxel infusion on Day 1 of each cycle (every 3 weeks) up to 4 cycles.

Pembrolizumab will be administered as an IV infusion on Day 1 of each cycle (3 weeks) after finishing the treatment of combination therapy for 4 cycles in both cohorts 1 and 2.

Combination Regimens for Part E

All subjects should receive the appropriate pre-medications per site's standard practice.

Subjects enrolled in Cohort 1 and 3 will receive cisplatin/etposide at the following timing:

1. Etposide 100 mg/m^2 will be administered as an IV infusion on Day 1, 2 and 3 of each cycle (every 3 weeks) up to 4 cycles. Etoposide should be completely administered before initiating cisplatin dose.

2. Cisplatin 75 mg/m^2 will be administered as an IV infusion after Etoposide infusion on Day 1 of each cycle (every 3 weeks) up to 4 cycles.

3. (Cohort 3 only) Subject who enrolled into cohort 3 should take prophylactic use of lasting G-CSF (pegfilgrastim) 3.6 mg via subcutaneous injection following the local prescribing information. A lasting G-CSF (pegfilgurastim) should administer at least 24 hours after from the end of infusion of etoposide on Cycle 1 Day 3.

Subjects enrolled in the Cohort 2 will receive carboplatin/etoposide at the following timing:

1. Etposide 100 mg/m^2 will be administered as an IV infusion on Day 1, 2 and 3 of each cycle (every 3 weeks) up to 4 cycles. Etoposide should be completely administered before initiating carboplatin dose.

2. Carboplatin AUC of 5 mg/mL/min will be administered as an IV infusion after etoposide infusion on Day 1 of each cycle (every 3 weeks) up to 4 cycles.

Pembrolizumab will be administered as an IV infusion on Day 1 of each cycle (3 weeks) after finishing the treatment of combination therapy for 4 cycles in each cohort.

(For Part C and E only) Carboplatin: AUC is using Calvert formula.

Calvert Formula

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

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

Table 6 Maximum dose of Carboplatin

AUC	Maximum dose of Carboplatin
6	900 mg
5	750 mg
4	600 mg

Combination Regimens for Part D

Subjects enrolled in Part D will receive ipilimumab at the following timing:

Ipilimumab will be administered on day 1 in each cycle as a 90-minute IV infusion Q6W up to 18 cycles. Sites should make every effort to target infusion timing to be as close to 90 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 90 minutes: 5 min/+10 min). infuse pembrolizumab first followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion.

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

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

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. Listed below are some specific restrictions for concomitant therapy or vaccination during the course of the trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the local Clinical Monitor. 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 Allowed Concomitant Medications

All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date will also be included on the CRF.

All prior/concomitant medications received within 30 days before the first dose of study mediation and 30 days after the last infusion of study medication should be recorded.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Radiotherapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with the Sponsor.

Colony-Stimulating Factors

Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF) during DLT assessment period is NOT allowed, except part E cohort 3 (See Section 5.5.2). Subject who enrolled into cohort 3 should take prophylactic use of lasting G-CSF (pegfilgrastim) (See Table 1 and section 5.2.2). Treatment use of G-CSF is allowed during treatment period. After a DLT assessment period, there is no specific limitation for use of G-CSF (investigators may follow the latest guidelines for use of Colony-Stimulating Factor).

5.5.2 Prohibited Concomitant Medication

Subjects may receive other medications that the Investigator deems to be medically necessary. The following medication will be prohibited during screening and treatment period and second course period:

- Non-protocol specified chemotherapy
- Radiation therapy

  Note: Radiotherapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with the Sponsor. In Part E, PCI which is specified in the study design is acceptable.

- Non-protocol specified Immunotherapy
- Antineoplastic biological therapy
- Investigational agents other than pembrolizumab and ipilimumab

- Live vaccines within 4 weeks prior to the first dose of trial treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection aregenerally killed virus vaccines and are allowed.

- Prophylactic use of colony-stimulating factors including G-CSF during DLT assessment period (except part E cohort 3).

- Initiation of bisphosphonate or anti-RANKL mAb after the initiation of study drug

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 study.

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

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

In Part B, C and E, subjects will receive platinum-doublet chemotherapy, in part D subjects will receive ipilimumab (details are in Table 1) in combination with pembrolizumab. For prohibited medication for the chemotherapy and ipilimumab, refer to the approved labeling.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.4, Table 4. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Table 4 in Section 5.2.1.2 for guidelines regarding dose modification and supportive care.

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) 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, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)

- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

† Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy and through 180 days after last dose of chemotherapeutic agents. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a female subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or

newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

5.7.4 Breast-feeding

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment. Subjects who stop breast-feeding prior to initiation of trial treatment and not expecting to resume of breast-feeding will be eligible for the study.

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 are 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 period will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5.3 – Discontinuation.

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.
- Documented disease progression.

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.3.4
- Unacceptable adverse experiences as described in Section 5.2.1.4
- Intercurrent illness that prevents further administration of treatment.
- Completed 24 months of treatment with pembrolizumab [In Part D, Completion of 18 cycles of ipilimumab (35 times of pembrolizumab)].

- Investigator's decision to withdraw the subject.
- The subject has a confirmed positive serum pregnancy test.
- Noncompliance with trial treatment or procedure requirements.
- The subject is lost to follow-up.
- Administrative reasons.

If a pembrolizumab treated subject attains an investigator-determined confirmed CR according to irRC (in Part A) or RECIST 1.1 (in Part B, C, D and E), has been treated for at least 6 months with pembrolizumab, and has at least two treatments with pembrolizumab beyond the date when the initial CR was declared, OR the subject has received the maximum administrations of pembrolrizumab as outlined above, investigator may consider stopping therapy with pembrolizumab (In part D, pembrolizumab + ipilimumab). Subjects who discontinue pembrolizumab (In part D, pembrolizumab + ipilimumab) and then experience radiographic disease progression according to irRC or RECIST 1.1 may be eligible for re-treatment with pembrolizumab (In part D, pembrolizumab + ipilimumab) in the Second Course Phase at the discretion of the investigator as described in Section 7.1.5.6. The subject will resume therapy at the same dose and schedule at the time of initial discontinuation. Patients who have already started the second course phase of administration before the approval of the protocol version 08, may continue the second course phase (up to 12 months) if applicable. For other patients, the second course phase is not applicable.

Note: After the approval of the protocol version 08, the final visit of this study will be a safety follow-up visit, and imaging follow-up and survival follow-up will not be performed. Participants in the follow-up phase or survival follow-up phase are completed and no further visits are required.

5.8.2 Withdrawal from the Trial

A subject must be withdrawn from the trial if the subject or subject's legally acceptable representative withdraws consent from the trial.

If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

In order for a subject to be considered evaluable for the analysis of DLT, the subject must have had a DLT in the DLT evaluation period, and had received at least 90% of the prescribed dose of pembrolizumab and the combination regimen and completed all safety evaluations in the DLT evaluation period without experiencing a DLT. A subject without a DLT will replaced if he/she did not adequately complete the evaluation period associated with the first cycle of study therapy (i.e., discontinue prematurely due to a reason unrelated to study therapy) or if that subject received <90% of the prescribed dose.

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

5.10 Beginning and End of the Trial

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

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

5.11 Clinical Criteria for Early Trial Termination

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

6.0 TRIAL FLOW CHART

6.1 Part A

Part A	Screening[1] (-28 to -1days)	Cycle 1(28 days)						Cycle 2 and Additional Cycles (14 Days)	Discontinuation Visit	Safety Follow-up	Follow-up 1	Follow-up 2
Cycle Day		1	2	3	8	15	22	1		30 days after last dose	3 months after last dose	6 months after last dose
Visit Number	1	2	3	4	5	6	7	N				
Windows (days)	-28～-1							±2		±3	±7	±7
Study Procedures												
Informed Consent	X											
Informed Consent for Future Biomedical Research (optional)	X											
Inclusion/Exclusion Criteria	X											
Demographics/Medical History/Prior Medications	X											
Height, Weight and Vital Signs[2]	X	X			X	X	X	X	X	X		
ECOG Performance Status[3]	X	X						X	X	X		
Physical Examination[3]	X	X						X	X	X		
12-lead ECG[4]	X							X	X	X		
Review Adverse Events		X----------X										
Review Concomitant Medications		X----------X										
Hematology[1, 5]	X	X			X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel[1, 5]	X	X			X	X	X	X	X	X		
Coagulation Parameters[1]	X											
Urinalysis[1, 5]	X	X			X	X	X	X	X	X		
Pregnancy Test - Urine or Serum β-HCG[6]	X											
Thyroid Function[1, 5, 7]	X							X	X	X		
Blood for Future Biomedical Research (optional)[8]		X										
Anti-pembrolizumab Antibodies[9]		X						X	X	X	X	X
Pharmacokinetics[10]		X	X	X	X	X	X	X	X	X	X	X
HIV, HBV and HCV[11]	X											
KL-6, β-D glucan[1, 12]	X											
Pulmonary Radiographic Evaluation[13]	X							X				
Tumor Imaging[14], Serum Tumor Markers[1, 14]	X							X				

Part A	Screening[1] (-28 to -1days)	Cycle 1(28 days)						Cycle 2 and Additional Cycles (14 Days)	Discontinuation Visit	Safety Follow-up	Follow-up 1	Follow-up 2
Cycle Day		**1**	**2**	**3**	**8**	**15**	**22**	**1**		**30 days after last dose**	**3 months after last dose**	**6 months after last dose**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**N**				
Administer pembrolizumab		X						X				
Archival Tumor Tissues/ Fresh tumor biopsy (optional)[15] (additional consent required)	X											

Part A	Screening[1] (-28 to -1days)	Cycle 1(28 days)						Cycle 2 and Additional Cycles (14 Days)	Discontinuation Visit	Safety Follow-up	Follow-up 1	Follow-up 2
Cycle Day		1	2	3	8	15	22	1		30 days after last dose	3 months after last dose	6 months after last dose
Visit Number	1	2	3	4	5	6	7	N				

1. Laboratory tests (hematology, serum chemistry and urinalysis, etc.) for screening should be performed within 14 days prior to the first dose of trial treatment.
2. Vital signs include temperature, pulse (in a sitting position), respiratory rate and blood pressure (in a sitting position). Weight and vital signs will be measured at predose in every cycle and the scheduled time point in Cycle 1. Height will be measured at screening visit. only
3. These procedures will be conducted at predose.
4. Electrocardiogram (12-lead ECG) should be performed at screening, predose in every other cycle, discontinuation visit, and safety follow-up visit.
5. See Table 7 for list of laboratory tests. Laboratory tests may be collected up to 48 hours prior to dosing in every cycle and the scheduled time point in Cycle 1.
6. For women of reproductive potential, a urine/serum pregnancy test will be performed within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
7. FT3, FT4, TSH; at screening, at predose in every cycle, discontinuation visit, and safety follow-up visit.
8. Signing the informed consent for future biomedical research (FBR) samples is optional. Informed consent for future biomedical research (FBR) samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on allocated subjects only, or at a later date as soon as the informed consent is obtained. See Section 12.2 for guidance regarding the collection and management of specimens for FBR.
9. Blood for anti-pembrolizumab antibodies should be collected within 24 hours prior to start of infusion in Cycle 1 and Cycle 2 then in every other subsequent cycles (during the first 12 months of study therapy), at discontinuation visit and at safety follow-up visit. Every effort should be made to collect additional blood samples for anti-pembrolizumab antibodies after discontinuation visit for up to 6 months from the last dose of pembrolizumab or until start of a new anti-cancer therapy, whichever occurs first.
10. The time points for blood sampling for serum concentrations of pembrolizumab are as follows.
    Cycle 1 Day 1: pre-dose (-60 min to 0), post-dose (to +30 min), 6 (±30 min), 24 , 48, 168, 336, and 504 (±2 hr for 24 to 504 hr) after completion of MK-3475 infusion.
    Cycle 2 and additional Cycles (during the first 12 months of study therapy) Every other cycle Day 1: pre-dose (-60 min to 0), post-dose (to +30 min) after completion of pembrolizumab infusion.
    Discontinuation, safety follow-up Visit and follow-up visit 1 and 2: Every effort should be made to collect additional blood samples for serum concentration of pembrolizumab after Discontinuation Visit for up to 6 months from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first.
11. Include HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies. If results of these test obtained within 3 months before screening are available, they can be used even before consent is obtained.
12. KL-6 and β–D glucan will be measured for pulmonary evaluation at screening and thereafter if a subject develops suspected pneumonitis, an additional test will be performed as needed by investigator's judgment.
13. A chest CT performed for tumor imaging will be used for pulmonary radiographic evaluation.
14. Tumor imaging (CT or MRI) will be performed within 28 days prior to enrollment. In Part A, tumor imaging should be performed every 6 calendar weeks (42 days ±7 days) after the first dose of study treatment in treatment period. Tumor imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. Tumor response on trial will be assessed using irRC and RECIST ver.1.1 by the study site. Standard tumor markers (as appropriate for a given tumor type) will be collected at screening (within 14 days prior to the first dose of study treatment), and at the same timing as tumor imaging thereafter.
15. Collection of archival/fresh tumor tissue for purpose of PD-L1 expression analysis. Access to archival/fresh tumor tissue is highly desirable but not mandatory. Written subject consent is required for collection of tumor tissue. Specific instructions for tissue collection and shipment are provided in the Procedures Manual. If the subject signs the FBR consent, an aliquot of the tissue specimens will be designated for FBR. In addition, any leftover archival/fresh tissue specimens at the end of the main study that would ordinarily be discarded will be retained for FBR providing the subject has signed the FBR consent.

6.2 Combination Therapy

6.2.1 Part B and C- treatment phase

Part B and C	Screening[1] (-28 to -1days)	Cycle 1(21 days)					Cycle 2 and Additional Cycles (21 Days)			Discontinuation Visit[20]
Cycle Day		1	2	5	8	15	1	8	15	
Visit Number	1	2	3	4	5	6	N	N+1	N+2	
Windows (days)[2]	-28～-1						±3	±1	±1	
Study Procedures										
Informed Consent	X									
Informed Consent for Future Biomedical Research (optional)	X									
Inclusion/Exclusion Criteria	X									
Subject Identification Card	X									
Demographics/Medical History/Prior Medications	X									
Height, Weight and Vital Signs[4, 5]	X	X			X	X	X	X[23]	X[23]	X
SpO_2[5]	X	X			X	X	X	X[23]	X[23]	X
ECOG Performance Status[5]	X	X					X			X
Physical Examination[5]	X	X					X			X
12-lead ECG[6]	X						X[6]			
Review Adverse Events		X----------								----------X[21]
Review Concomitant Medications		X----------								----------X
Hematology[3, 7]	X	X			X	X	X	X[23]	X[23]	X
Comprehensive Serum Chemistry Panel[3, 7]	X	X			X	X	X			X
Coagulation Parameters[3, 7]	X									
Urinalysis[3, 7]	X	X			X	X	X			X
Pregnancy Test - Urine or Serum β-HCG[8]	X									
Thyroid Function[3, 7, 9]	X						X			X
Blood for Genetics[10]		X								
Anti-pembrolizumab Antibodies[11]		X					X			X
Pharmacokinetics[12]		X	X	X		X	X			X
HIV, HBV and HCV[13]	X									
KL-6, SP-D[3, 14]	X	X			X	X	X			X
β-D glucan[3, 14]	X									
Pulmonary Radiographic Evaluation[15]	X						X			
Tumor Imaging[16], Serum Tumor Markers[3, 16]	X						X			
Administer pembrolizumab		X					X			
Administer Chemotherapy (except for nab-paclitaxel)[17]		X					X			

Part B and C	Screening[1], (-28 to -1days)	Cycle 1(21 days)					Cycle 2 and Additional Cycles (21 Days)			Discontinuation Visit[20]
Cycle Day		1	2	5	8	15	1	8	15	
Visit Number	1	2	3	4	5	6	N	N+1	N+2	
Windows (days)[2]	-28～-1						±3	±1	±1	
Administer nab-paclitaxel[17, 22]		X			X	X	X	X	X	
Archival Tumor Tissues/ Fresh tumor biopsy [18]	X									
Blood for Correlative Studies (DNA and RNA) [19]		X					X			X
Biomarker Samples (Plasma and Serum) [19]		X								

1. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21-days). If treatment cycles are adjusted all procedures except imaging will be completed according to the Cycle number and not weeks on treatment; imaging will be performed every 6 calendar weeks (± 7days) after the first dose for the first 24 weeks, and every 9 calendar weeks (± 7 days) from the date of imaging assessment at the week 24 regardless of any treatment delays.
2. In general, the window for each visit is +/- 3 days unless otherwise specified.
3. Laboratory tests (hematology, serum chemistry and urinalysis, etc.) for screening should be performed within 14 days prior to the first dose of trial treatment.
4. Vital signs include temperature, pulse (in a sitting position), respiratory rate and blood pressure (in a sitting position). Weight and vital signs will be measured at predose in every cycle and the scheduled time point in Cycle 1. Height will be measured at screening visit. only
5. These procedures will be conducted at pre-dose.
6. Electrocardiogram (12-lead ECG) should be performed at screening and end of cycle 1 (pre-dose of cycle 2). An additional measurement will be performed as needed by investigator's judgment.
7. See Table 7 for list of laboratory tests. Laboratory tests may be collected up to 48 hours prior to dosing in every cycle and the scheduled time point in Cycle 1.
8. For women of reproductive potential, a urine/serum pregnancy test will be performed within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
9. FT3, FT4, TSH; at screening, at pre-dose in every cycle, discontinuation visit, and safety follow-up visit.
10. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
11. Blood for anti-MK-3475 antibodies should be collected within 24 hours prior to start of infusion in Cycle 1, 2, 4, 6, 8 and every 4 cycles thereafter, at discontinuation visit and at safety follow-up visit. Every effort should be made to collect additional blood samples for anti-MK-3475 antibodies after discontinuation visit for up to 6 months from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first. See 7.1.3.2 in detail.
12. The time points for blood sampling for serum concentrations of MK-3475 are as follows. See 7.1.3.2 in detail.
    Cycle 1 Day 1: pre-dose (-24hr to 0hr), post-dose (to +30 min), 24hr, 96hr (96hr is preferable, although 72hr or 120hr is also acceptable, ±2 hr) and 336hr (±24 hr) after completion of MK-3475 infusion.
    Cycle 2, 4, 6, 8 and every 4 cycles thereafter: pre-dose (-24 hr to 0)
    Cycle 8: post-dose (to +30min) after completion of MK-3475 infusion.
    Discontinuation, safety follow-up Visit and follow-up visit 1 and 2: Every effort should be made to collect additional blood samples for serum concentration of MK-3475 after Discontinuation Visit for up to 6 months from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first.
13. Include HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies. If results of these test obtained within 3 months before screening are available, they can be used even before consent is obtained.
14. KL-6, SP-D and β–D glucan will be measured for pulmonary evaluation. If a subject develops suspected pneumonitis, an additional test will be performed as needed by investigator's judgment.
15. A chest CT performed for tumor imaging will be used for pulmonary radiographic evaluation.
16. Tumor imaging (CT or MRI) will be performed within 28 days prior to enrollment. In Part B and C, tumor imaging should be performed every 6 calendar weeks (± 7days) for the first 24 weeks, and every 9 calendar weeks (63 days ±7 days) from the date of imaging assessment at the week 24. Tumor imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of MK-3475/chemotherapy cycle frequencies. The same imaging technique should be used in a subject as was used earlier in this trial. Tumor response on trial will be assessed using irRECIST by the study site. Local reading (investigator assessment with site radiology reading) will be used to for subject management; In Part B and C, sponsor will collect radiological assessments for retrospective analysis by a central vendor. The processes for image collection and transmission to the central vendor are in the Investigator Imaging Operations Manual (IIOM). Standard tumor markers (as appropriate for a given tumor type) will be collected at screening (within 14 days prior to the first dose of study treatment), and at the same timing as tumor imaging thereafter.
17. Subjects will receive platinum-doublet chemotherapy [cisplatin/pemetrexed (cohort 1) or carboplatin/pemetrexed (cohort 2) for Part B, and carboplatin/paclitaxel (cohort 1) or carboplatin/nab-paclitaxel (cohort 2) for Part C] in combination with MK-3475 for 4 cycles. Subjects may receive MK-3475 Q3W as maintenance therapy (for Part B

only, in combination with pemetrexed) once the first 4 cycles of the platinum containing (either carboplatin/pemetrexed or cisplatin/pemetrexed for Part B, and either carboplatin/paclitaxel or carboplatin/nab-paclitaxel for Part C) doublet have completed.

18. Collection of archival/fresh tumor tissue for purpose of PD-L1 expression analysis is mandatory for part B and C. EGFR/ALK testing is performed at central laboratory if the site is unable to provide this source document (Part B only). Specific instructions for tissue collection and shipment are provided in section 7.1.3.6 and the Procedures Manual. If the subject signs the FBR consent, an aliquot of the tissue specimens will be designated for FBR. In addition, any leftover archival/fresh tissue specimens at the end of the main study that would ordinarily be discarded will be retained for FBR providing the subject has signed the FBR consent.
19. Whole blood samples for correlative studies (DNA and RNA) should be collected pre-dose on Day 1 of cycle 1, Cycle 2, and Cycle 3, and again at treatment discontinuation. Whole blood for Biomarker Samples (plasma and serum) to be collected pre-dose on Day 1 of Cycle 1 only. See Procedure Manual.
20. The Discontinuation Visit should occur at the time study drug 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.
21. Once a subject discontinues study treatment, report all SAEs (related and unrelated to trial treatment) occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs that are considered related to trial treatment.
22. Dosing for nab-paclitaxel is on Day 1, Day 8 and Day 15 of each Q3W cycle.
23. If a subject receives nab-paclitaxel, hematology tests/weight and vital signs, and SpO_2 are performed/measured before each dose of nab-paclitaxel on Day 8 and Day 15 of each Q3W cycle.

6.2.2 Part D- treatment phase

Part D	Screening (-28 to -1days)	Cycle 1 (42 days)		Cycle 2 to 18 Cycles (42 Days)		Discontinuation Visit[19]
Cycle Day [1]		1	22	1	22	
Visit Number	1	2	3	N	N+1	
Windows (days) [2]	-28～-1		±3	±3	±3	
Study Procedures						
Informed Consent	X					
Informed Consent for Future Biomedical Research (optional)	X					
Inclusion/Exclusion Criteria	X					
Subject Identification Card	X					
Demographics/Medical History/Prior Medications	X					
Height, Weight and Vital Signs[4, 5]	X	X	X	X	X	X
SpO_2[5]	X	X	X	X	X	X
ECOG Performance Status[5]	X	X	X	X	X	X
Physical Examination[5]	X	X	X	X	X	X
12-lead ECG[6]	X[6]			X[6]		
Review Adverse Events		X----------				----------X[20]
Review Concomitant Medications		X----------				----------X
Hematology[3, 7]	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel[3, 7]	X	X	X	X	X	X
Coagulation Parameters[3]	X					
Urinalysis[3, 7]	X	X	X	X	X	X
Pregnancy Test - Urine or Serum β-HCG[8]	X					
Thyroid Function[3, 9]	X		X	X	X	X
adrenocorticotropic hormone (ACTH) level [3,22]	X			X		X
Blood for Genetics[10]		X				
Anti-MK-3475 Antibodies[11]		X	X		X	X
Pharmacokinetics[12]		X	X		X	X
HIV, HBV and HCV[13]	X					
KL-6, SP-D[3, 14]	X	X	X	X	X	X
β-D glucan[3, 14]	X					
Pulmonary Radiographic Evaluation[15]	X			X	X	
Tumor Imaging[16], Serum Tumor Markers[3, 16]	X			X	X	
Administer MK-3475		X	X	X	X	
Administer Ipilimumab[21]		X		X		
Archival Tumor Tissues/ Fresh tumor biopsy (optional)[17]	X					
Blood for Correlative Studies (DNA and RNA) [18]		X		X		X
Biomarker Samples (Plasma and Serum) [18]		X				

1. In general, assessments/procedures are to be performed on Day 1 and Day 22 prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 6 weeks (42-days). If treatment cycles are adjusted, all procedures except imaging will be completed according to the cycle number and not weeks on treatment; imaging will be performed every 6 calendar weeks (± 7days) after the first dose for the first 24 weeks, and every 9 calendar weeks (± 7 days) from the date of imaging assessment at the week 24 thereafter regardless of any treatment delays.
2. In general, the window for each visit is +/- 3 days unless otherwise specified.
3. Laboratory tests (hematology, serum chemistry and urinalysis, etc.) for screening should be performed within 14 days prior to the first dose of trial treatment.
4. Vital signs include temperature, pulse (in a sitting position), respiratory rate and blood pressure (in a sitting position). Weight and vital signs will be measured at pre-dose in Day 1 and Day 22 of each cycle. Height will be measured at screening visit. only
5. These procedures will be conducted at pre-dose.
6. Electrocardiogram (12-lead ECG) should be performed at screening and end of cycle 1 (pre-dose of cycle 2). An additional measurement will be performed as needed by investigator's judgment.
7. See Table 7 for list of laboratory tests. Laboratory tests may be collected up to 48 hours prior to dosing of Day 1 and Day 22 in every cycle.
8. For women of reproductive potential, a urine/serum pregnancy test will be performed within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
9. FT3, FT4, TSH; at screening, up to 48 hours prior to pre-dose in day 22 of cycle 1, at pre-dose in day 1 and day 22 of cycle 2 to 18 and discontinuation visit.
10. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
11. Blood for anti-MK-3475 antibodies should be collected within 24 hours prior to start of infusion in Day 1 of Cycle 1, Day 22 of Cycle 1, Day 22 of Cycle 2, Day 22 of Cycle 3, Day 22 of Cycle 4 and Day 22 of every 2 cycles thereafter, and at discontinuation visit and at safety follow-up visit. Every effort should be made to collect additional blood samples for anti-MK-3475 antibodies after discontinuation visit for up to 6 months from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first. See 7.1.3.2 in detail.
12. The time points for blood sampling for serum concentrations of MK-3475 are as follows. See 7.1.3.2 in detail.

    Cycle 1 Day 1: pre-dose (-24hr to 0hr), post-dose (to +30 min), 24hr, 96hr (96hr is preferable, although 72hr or 120hr is also acceptable, ±2 hr) and 336hr (± 24 hr) after completion of MK-3475 infusion.
    Day 22 of Cycle 1, Day 22 of Cycle 2, Day 22 of cycle 3, Day 22 of Cycle 4 and Day 22 of every 2 cycles thereafter: predose (-24 hr to 0)
    Day 22 of Cycle 4: post-dose (to +30min) after completion of MK-3475 infusion.
    Discontinuation, safety follow-up Visit and follow-up visit 1 and 2: Every effort should be made to collect additional blood samples for serum concentration of MK-3475 after Discontinuation Visit for up to 6 months from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first.
13. Include HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies. If results of these test obtained within 3 months before screening are available, they can be used even before consent is obtained.
14. KL-6, SP-D and β–D glucan will be measured for pulmonary evaluation. If a subject develops suspected pneumonitis, an additional test will be performed as needed by investigator's judgment.
15. A chest CT performed for tumor imaging will be used for pulmonary radiographic evaluation.
16. Tumor imaging (CT or MRI) will be performed within 28 days prior to enrollment. The tumor imaging should be performed every 6 calendar weeks (± 7days) for the first 24 weeks, and every 9 calendar weeks (63 days ±7 days) from the date of imaging assessment at the week 24 thereafter. Tumor imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab/ipilimumab cycle frequencies. The same imaging technique should be used in a subject as was used earlier in this trial. Tumor response on trial will be assessed using irRECIST by the study site. Local reading (investigator assessment with site radiology reading) will be used to for subject management; In Part D, sponsor will collect radiological assessments, but retrospective analysis by a central vendor will not be conducted. Standard tumor markers (as appropriate for a given tumor type) will be collected at screening (within 14 days prior to the first dose of study treatment), and at the same timing as tumor imaging thereafter.

17. Collection of archival/fresh tumor tissue for purpose of PD-L1 expression analysis is optional. Specific instructions for tissue collection and shipment are provided in section 7.1.3.6 and the Procedures Manual. If the subject signs the FBR consent, an aliquot of the tissue specimens will be designated for FBR. In addition, any leftover archival/fresh tissue specimens at the end of the main study that would ordinarily be discarded will be retained for FBR providing the subject has signed the FBR consent.
18. Whole blood samples for correlative studies (DNA and RNA) should be collected pre-dose on Day 1 of cycle 1, Day 1 of Cycle 2, and Day 1 of Cycle 3, and again at treatment discontinuation. Whole blood for Biomarker Samples (plasma and serum) to be collected pre-dose on Day 1 of Cycle 1 only. See Procedure Manual in detail.
19. The Discontinuation Visit should occur at the time study drug 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.
20. Once a subject discontinues study treatment, report all SAEs (related and unrelated to trial treatment) occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs that are considered related to trial treatment.
21. Ipilimumab will be administered at Day 1 in every cycle up to Cycle 18.
22. ACTH will be measured at screening, up to 48 hours prior to pre-dose of Day 1 of Cycle 2 to Cycle 18 and discontinuation visit. An additional test will be performed as needed by investigator's judgment.

6.2.3 Part E- treatment phase

Part E	Screening (-28 to -1days)	Cycle 1(21 days)							Cycle 2 and Additional Cycles (21 Days)			Discontinuation Visit[20]
Cycle Day[1]		1	2	3	4	5	8	15	1	2	3	
Visit Number	1	2	3	4	5	6	7	8	N	N+1	N+2	
Windows (days)[2]	-28～-1								±3			
Study Procedures												
Informed Consent	X											
Informed Consent for Future Biomedical Research (optional)	X											
Inclusion/Exclusion Criteria	X											
Subject Identification Card	X											
Demographics/Medical History/Prior Medications	X											
Height, Weight and Vital Signs[4, 5]	X	X	X	X			X	X	X	X[22]	X[22]	X
SpO_2[5]	X	X	X	X			X	X	X	X[22]	X[22]	X
ECOG Performance Status[5]	X	X							X			X
Physical Examination[5]	X	X	X	X					X	X[22]	X[22]	X
12-lead ECG[6]	X[6]								X[6]			
Review Adverse Events		X----------										----------X[21]
Review Concomitant Medications		X----------										----------X
Hematology[3, 7]	X	X					X	X	X			X
Comprehensive Serum Chemistry Panel[3, 7]	X	X					X	X	X			X
Coagulation Parameters[3]	X											
Urinalysis[3, 7]	X	X					X	X	X			X
Pregnancy Test - Urine or Serum β-HCG[8]	X											
Thyroid Function[3, 7, 9]	X								X			X
Blood for Genetics[10]		X										
Anti-pembrolizumab Antibodies[11]		X							X			X
Pharmacokinetics[12]		X	X			X		X	X			X
HIV, HBV and HCV[13]	X											
KL-6, SP-D[3, 14]	X	X					X	X	X			X
β-D glucan[3, 14]	X											
Pulmonary Radiographic Evaluation[15]	X								X			

Part E	Screening (-28 to -1days)	Cycle 1(21 days)							Cycle 2 and Additional Cycles (21 Days)			Discontinuation Visit[20]
Cycle Day[1]		1	2	3	4	5	8	15	1	2	3	
Visit Number	1	2	3	4	5	6	7	8	N	N+1	N+2	
Windows (days)[2]	-28～-1								±3			
Study Procedures												
Tumor Imaging[16], Serum Tumor Markers[3, 16]	X								X			
Administer pembrolizumab		X							X			
Administer Cisplatin or Carboplatin[17]		X							X			
Administer Etoposide[17]		X	X	X					X	X	X	
Administer lasting G-CSF (pegfilgrastim)[23]					X							
Archival Tumor Tissues/ Fresh tumor biopsy (optional) [18]	X											
Blood for Correlative Studies (DNA and RNA) [19]		X							X			X
Biomarker Samples (Plasma and Serum) [19]		X										

1. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21-days). If treatment cycles are adjusted all procedures except imaging will be completed according to the Cycle number and not weeks on treatment; imaging will be performed every 6 calendar weeks (± 7days) after the first dose for the first 24 weeks, and every 9 calendar weeks (± 7 days) from the date of imaging assessment at the week 24 regardless of any treatment delays.
2. In general, the window for each visit is +/- 3 days unless otherwise specified.
3. Laboratory tests (hematology, serum chemistry and urinalysis, etc.) for screening should be performed within 14 days prior to the first dose of trial treatment.
4. Height will be measured at screening visit only. Vital signs include temperature, pulse (in a sitting position), respiratory rate and blood pressure (in a sitting position). Weight and vital signs will be measured at pre-dose in every cycle and the scheduled time point in Cycle 1. In addition, weight and vital signs will be measured before dosing etoposide on Day 2 and 3 of each cycle.
5. These procedures will be conducted at pre-dose.
6. Electrocardiogram (12-lead ECG) should be performed at screening and end of cycle 1 (pre-dose of cycle 2). An additional measurement will be performed as needed by investigator's judgment.
7. See Table 7 for list of laboratory tests. Laboratory tests may be collected up to 48 hours prior to dosing in every cycle and the scheduled time point in Cycle 1.
8. For women of reproductive potential, a urine/serum pregnancy test will be performed within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
9. FT3, FT4, TSH; at screening, at pre-dose in every cycle, discontinuation visit, and safety follow-up visit.
10. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
11. Blood for anti-pembrolizumab antibodies should be collected within 24 hours prior to start of infusion in Cycle 1, 2 4, 6, 8 and every 4 cycles thereafter, at discontinuation visit and at safety follow-up visit. Every effort should be made to collect additional blood samples for anti-pembrolizumab antibodies after discontinuation visit for up to 6 months from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first. See 7.1.3.2 in detail.
12. The time points for blood sampling for serum concentrations of pembrolizumab are as follows. See 7.1.3.2 in detail.
    Cycle 1 Day 1: pre-dose (-24hr to 0hr), post-dose (to +30 min), 24hr (±2 hr), 96hr (96hr is preferable, although 72hr or 120hr is also acceptable, ±2 hr) and 336hr (±24 hr) after completion of pembrolizumab infusion.
    Cycle 2, 4, 6, 8 and every 4 cycles thereafter: pre-dose (-24 hr to 0)
    Cycle 8: post-dose (to +30 min) after completion of pembrolizumab infusion.
    Discontinuation, safety follow-up Visit and follow-up visit 1 and 2: Every effort should be made to collect additional blood samples for serum concentration of pembrolizumab after Discontinuation Visit for up to 6 months from the last dose of pembrolizumab or until start of a new anti-cancer therapy, whichever occurs first.
13. Include HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies. If results of these test obtained within 3 months before screening are available, they can be used even before consent is obtained.
14. KL-6, SP-D and β–D glucan will be measured for pulmonary evaluation. If a subject develops suspected pneumonitis, an additional test will be performed as needed by investigator's judgment.
15. A chest CT performed for tumor imaging will be used for pulmonary radiographic evaluation.
16. Tumor imaging (CT or MRI) will be performed within 28 days prior to enrollment, the tumor imaging should be performed every 6 calendar weeks (± 7days) for the first 24 weeks, and every 9 calendar weeks (63 days ±7 days) from the date of imaging assessment at the week 24. Tumor imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab/chemotherapy cycle frequencies. The same imaging technique should be used in a subject as was used earlier in this trial. Tumor response on trial will be assessed using irRECIST by the study site. Local reading (investigator assessment with site radiology reading) will be used to for subject management; Sponsor will collect radiological assessments, but retrospective analysis by a central vendor will not be conducted. Standard tumor markers (as appropriate for a given tumor type) will be collected at screening (within 14 days prior to the first dose of study treatment), and at the same timing as tumor imaging thereafter.

17. Subjects will receive platinum-doublet chemotherapy [cisplatin/etoposide (cohort 1) or carboplatin/etoposide (cohort 2)] in combination with pembrolizumab for 4 cycles. Subjects may receive pembrolizumab Q3W as maintenance therapy once the first 4 cycles of the platinum containing doublet have completed.
18. Collection of archival/fresh tumor tissue for purpose of PD-L1 expression analysis is optional. Specific instructions for tissue collection and shipment are provided in section 7.1.3.6 and the Procedures Manual. If the subject signs the FBR consent, an aliquot of the tissue specimens will be designated for FBR. In addition, any leftover archival/fresh tissue specimens at the end of the main study that would ordinarily be discarded will be retained for FBR providing the subject has signed the FBR consent.
19. Whole blood samples for correlative studies (DNA and RNA) should be collected pre-dose on Day 1 of cycle 1, Cycle 2, and Cycle 3, and again at treatment discontinuation. Whole blood for Biomarker Samples (plasma and serum) to be collected pre-dose on Day 1 of Cycle 1 only. See Procedure Manual.
20. The Discontinuation Visit should occur at the time study drug 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.
21. Once a subject discontinues study treatment, report all SAEs (related and unrelated to trial treatment) occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs that are considered related to trial treatment.
22. If a subject receives etoposide, Physical Examination, weight, vital signs, and SpO_2 are performed/measured before each dose of etoposide on Day 2 and Day 3 of each Q3W cycle
23. (Cohort 3 only) Subject who enrolled into cohort 3 should take prophylactic use of lasting G-CSF (pegfilgrastim) 3.6 mg via subcutaneous injection following the local prescribing information. A lasting G-CSF (pegfilgurastim) should administer at least 24 hours after from the end of infusion of etoposide on Cycle 1 Day 3.

6.2.4 Follow-up phase-Part B, C, D and E

After the approval of the protocol version 08, the final visit of this study will be a safety follow-up visit, and imaging follow-up and survival follow-up will not be performed. Participants in the follow-up phase or survival follow-up phase will discontinue the study and no further visits are required.

post- treatment follow-up period	
Visit	Safety Follow-up Visit [1]
Time from Last Dose of Trial Treatment	30 Days
Scheduling Window	± 3 days
Administrative Procedures	
Review Medications	X
Subsequent antineoplastic therapy Status	X
Review Adverse Events [2]	X
ECOG Performance Status	X
Physical Examination	X
Vital Signs and Weight [3]	X
SpO_2	X
12-Lead ECG	X[6]
Tumor Imaging	X[5]
CBC with Differential [5]	X
Comprehensive Serum Chemistry Panel [5]	X
adrenocorticotropic hormone (ACTH) level[7]	X
KL-6, SP-D[5]	X
FT3, FT4 and TSH [5]	X

1. All subjects will conduct the procedures at Safety Follow-Up Visit. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first.
2. Record all AEs and ECIs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) occurring within 90 days of the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anti-cancer treatment, whichever comes first. After this time, report only SAEs that are considered related to trial treatment.
3. Vital signs to include temperature, pulse (in a sitting position), respiratory rate, blood pressure (in a sitting position) and weight.
4. The same imaging technique should be used in a subject as was used earlier in the trial. If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at Safety Follow-up Visit isn't mandatory.
5. See Section 7.1.3 for list of laboratory tests.
6. 12-lead ECG will be performed as needed by investigator's judgment.

6.2.5 Part B, C and E- Second Course phase and Follow-up phase

Patients who have already started the second course phase of administration before the approval of the protocol version 08, may continue the second course phase (up to 12 months) if applicable. For other patients, the second course phase is not applicable.

	Second Course Phase[1]											**Follow-up for second course phase**
Treatment Cycle / Scheduled Time	1	2	3	4	5	6	7	8	9	10 and beyond	Discontinuation Visit	Safety Follow-up Visit [17]
Scheduling Window (Days**):**[2]		± 3	± 3	± 3	±3	±3	±3	±3	±3	±3		30 Days ± 3 days from last dose
Eligibility Criteria[3]	X											
Concomitant Medications[4]	X	X	X	X	X	X	X	X	X	X	X	
Trial Treatment Administration	X	X	X	X	X	X	X	X	X	X		
Review Adverse Events [5, 6]	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[7, 9]	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs and Weight [8, 9]	X	X	X	X	X	X	X	X	X	X	X	X
SpO_2[9]	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status [9]	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test - Urine or Serum β-HCG [10]	X											
PT/INR and aPTT [11]	X[12]											
CBC with Differential[13]	X[12]	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel[13]	X[12]	X	X	X	X	X	X	X	X	X	X	X
KL-6, SP-D[13]	X[12]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[13,14]	X[12]				X				X	X	X	X
FT3, FT4 and TSH [13, 14]	X[12]	X				X				X	X	X
Tumor Imaging [15, 16]	X			X			X			X	X	X
Subsequent antineoplastic therapy Status												X

1. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. If treatment cycles are delayed all procedures except imaging will be completed according to the Cycle number and not weeks on treatment. Imaging will be performed every 9 weeks (63 ± 7 days) from the first dose of trial treatment regardless of any treatment delays.
2. In general, the window for each visit is ± 3 days unless otherwise specified.
3. Review Secord Course Phase eligibility criteria in Section 7.1.5.6 prior to administering the first dose of trial treatment.
4. Concomitant Medications - Enter new medications started during the trial through the Safety Follow-up Visit for treatment phase. After the Safety Follow-up Visit record all medications taken for SAEs as defined in Section 7.2.
5. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
6. All AEs of unknown etiology associated with trial treatment exposure should be evaluated In the follow-up phase, record all AEs and ECIs occurring within 30 days after the last dose of trial treatment or until the initiation of the new therapy for cancer. Report all SAEs (related and unrelated to trial treatment) occurring within 90 days of the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anti-cancer treatment, whichever comes first. After this time, report only SAEs that are considered related to trial treatment.
7. Perform physical examinations at pre-dose on the day of the study treatment visit.
8. Vital signs to include temperature, pulse (in a sitting position), respiratory rate, weight and blood pressure (in a sitting position).
9. These procedures will be conducted at pre-dose.
10. For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first Second Course dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
11. Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
12. Laboratory tests for determining eligibility for Second Course Phase are to be performed within 10 days prior to the first dose. See Section 7.1.3 for details regarding laboratory tests.
13. After the cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests.
14. Thyroid function tests should be performed every 4 cycles after Cycle 10. Urinalysis tests should be performed at pre-dose of Day 1 in every 4 cycle after cycle 9.
15. The Second Course Cycle 1 scan may have been performed up to 28 days prior to the first dose of trial treatment in the Second Course Phase. Imaging will be performed every 9 weeks (63 ± 7 days) after the first dose of Second Course Phase trial treatment or more frequently if clinically indicated. The timing of imaging should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to for subject management; in part B and C, sponsor will collect radiological assessments for retrospective analysis by a central vendor. In Part E, sponsor will collect radiological assessments, but retrospective analysis by a central vendor will not be conducted. The processes for image collection and transmission to the central vendor are in the Investigator Imaging Operations Manual (IIOM).
16. After the first documentation of progression (if the subject is clinically stable) or responses per RECIST 1.1, confirmatory imaging may be performed as early as 28 days later; alternately, the scan performed at the next scheduled time point (e.g. every 63 ±7 days) may be used as confirmation
17. All subjects will conduct the procedures at Safety Follow-Up Visit. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first.

6.2.6 Part D- Second Course phase and Follow-up phase

Patients who have already started the second course phase of administration before the approval of the protocol version 08, may continue the second course phase (up to 12 months) if applicable. For other patients, the second course phase is not applicable.

	Second Course Phase					**Follow-up for second course phase**
Treatment Cycle / Scheduled Time[1]	Cycle 1 (42 Days)		Cycle 2 to 9 Cycles (42 Days)		Discontinuation Visit	Safety Follow-up Visit [18]
Cycle Day	1	22	1	22		
Scheduling Window (Days**):**[2]		± 3	± 3	± 3		30 Days ± 3 days from last dose
Eligibility Criteria[3]	X					
Concomitant Medications[4]	X	X	X	X	X	
Administer pembrolizumab	X	X	X	X		
Administer Ipilimumab[120]	X		X			
Review Adverse Events [5, 6]	X	X	X	X	X	X
Physical Examination[7, 9]	X	X	X	X	X	X
Vital Signs and Weight [8, 9]	X	X	X	X	X	X
SpO_2[9]	X	X	X	X	X	X
ECOG Performance Status [9]	X	X	X	X	X	X
Pregnancy Test - Urine or Serum β-HCG [10]	X					
PT/INR and aPTT [11]	X[12]					
CBC with Differential[13]	X[12]	X	X	X	X	X
Comprehensive Serum Chemistry Panel[13]	X[12]	X	X	X	X	X
KL-6, SP-D[13]	X[12]	X	X	X	X	X
Urinalysis[13,14]	X[12]		X[14]		X	X
FT3, FT4 and TSH [13,15]	X[12]		X[15]		X	X
adrenocorticotropic hormone (ACTH) level [19]	X[12]		X		X	X
Tumor Imaging [16, 17]	X		X	X	X	X
Subsequent antineoplastic therapy Status						X

1. In general, assessments/procedures are to be performed on Day 1 and Day 22 prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 6 weeks (42-days). If treatment cycles are delayed all procedures except imaging will be completed according to the Cycle number and not weeks on treatment. Imaging will be performed every 9 weeks (63 ± 7 days) from the first dose of trial treatment regardless of any treatment delays.
2. In general, the window for each visit is ± 3 days unless otherwise specified.
3. Review Secord Course Phase eligibility criteria in Section 7.1.5.6 prior to administering the first dose of trial treatment.
4. Concomitant Medications - Enter new medications started during the trial through the Safety Follow-up Visit for treatment phase. After the Safety Follow-up Visit record all medications taken for SAEs as defined in Section 7.2.
5. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
6. All AEs of unknown etiology associated with trial treatment exposure should be evaluated In the follow-up phase, record all AEs and ECIs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) occurring within 90 days of the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anti-cancer treatment, whichever comes first. After this time, report only SAEs that are considered related to trial treatment.
7. Perform physical examinations at pre-dose on the day of the study treatment visit.
8. Vital signs to include temperature, pulse (in a sitting position), respiratory rate, weight and blood pressure (in a sitting position).
9. These procedures will be conducted at pre-dose.
10. For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first Second Course dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
11. Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
12. Laboratory tests for determining eligibility for Second Course Phase are to be performed within 10 days prior to the first dose. See Section 7.1.3 for details regarding laboratory tests.
13. After the cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests.
14. Urinalysis tests should be performed at pre-dose of Day 1 in every 2 cycle after cycle 1
15. Thyroid function tests should be performed at pre-dose of Day 1 in cycle 1, cycle 2 and every 2 cycles thereafter.
16. The Second Course Cycle 1 scan may have been performed up to 28 days prior to the first dose of trial treatment in the Second Course Phase. Imaging will be performed every 9 weeks (63 ± 7 days) after the first dose of Second Course Phase trial treatment or more frequently if clinically indicated. The timing of imaging should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to for subject management; Sponsor will collect radiological assessments, but retrospective analysis by a central vendor will not be conducted.
17. After the first documentation of progression (if the subject is clinically stable) or responses per RECIST 1.1, confirmatory imaging may be performed as early as 28 days later; alternately, thre scan performed at the next scheduled time point (e.g. every 63 ±7 days) may be used as confirmation
18. All subjects will conduct the procedures at Safety Follow-Up Visit. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first.
19. ACTH will be measured at pre-dose of Day 1 of each cycle, discontinuation visit and safety follow up visit. An additional test will be performed as needed by investigator's judgment.
20. Ipilimumab will be administered at Day 1 in every cycle up to Cycle 9.

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 must obtain documented consent from each potential subject prior to participating in a clinical trial or Future Biomedical Research.

The 2nd cycle and thereafter are positioned as the continuation administration study. Consent should be obtained again from the subjects in writing before starting the 2nd cycle (Part A).

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. 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. Record any prior cancer other than the current cancer evaluated in this study even if diagnosed greater than 10 years prior to screening visit. History of the current cancer will be recorded separately and not listed as Medical History (See Section 7.1.1.7.1).

7.1.1.5 Demographics

Demographics (including smoking history, cancer-related gene mutation/translocation status, expression of cancer-related gene products, and cancer-related viral infection, etc.) will be obtained by the investigator or qualified designee.

7.1.1.5.1 Molecular Testing

Site must be able to provide documentation of subject's tumor EGFR mutation and ALK translocation status (Part B and D only). If the site is unable to provide this source documentation, then the Sponsor will offer this molecular testing of the tumor (Part B only). Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

7.1.1.6 Prior and Concomitant Medications Review

7.1.1.6.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before starting the trial therapy. In addition, record all treatments for a prior cancer other than the current cancer even if taken greater than 30 days prior to starting the trial therapy. Prior treatments for the current cancer will be recorded separately and not listed as a prior medication (See Section 7.1.1.7.2).

7.1.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial from start of study treatment through the 30-day safety follow-up visit. After the safety follow-up visit record all medications related to reportable SAEs as defined in Section 7.2.

7.1.1.7 Solid Tumor and NSCLC/SCLC Disease Details and Prior Treatments

7.1.1.7.1 Disease Details

The investigator or qualified designee will obtain prior and current solid tumor and NSCLC/SCLC disease details.

7.1.1.7.2 Prior Treatment

The investigator or qualified designee will review all prior treatments for current solid tumor and NSCLC/SCLC including systemic treatments, radiation and surgeries.

7.1.1.8 Subsequent Antineoplastic Therapy Status

The Investigator or qualified designee will review all new antineoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new antineoplastic therapy within 30 days after the last dose of trial treatment, the “30-day Safety Follow-up visit” must occur before the first dose of the new therapy. Once new antineoplastic therapy has been initiated the subject will move into survival follow-up. After the approval of the protocol version 08, the final visit of this study will be a safety follow-up visit 30 days after the last dose, and survival follow-up will not be performed. Participants in the follow-up phase or survival follow-up phase will discontinue the study and no further visits are required.

7.1.1.9 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.

7.1.1.10 Assignment of Randomization Number

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

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

7.1.1.11 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.

The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual.

Cisplatin, pemetrexed, carboplatin, paclitaxel, nab-paclitaxel, etoposide and ipilimumab will be prepared and administered as per the approved product label.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event Monitoring

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

An immune related adverse event (irAE) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event immune related. Immunological, serological and histological (biopsy) data should be used to support the diagnosis of an immune-related toxicity. Certain irAEs should also be reported to the Sponsor.

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

7.1.2.2 Physical Exam

The investigator or qualified designee will perform a complete physical exam at screening, prior to the administration of trial treatment (including Day 22 of each cycle in part D), discontinuation visit, safety follow-up visit and follow up visit 1 and 2. In addition, in Part E, the investigator or qualified designee will perform a complete physical exam before dosing etoposide on Day 2 and 3 of each cycle. Clinically significant abnormal findings at screening should be recorded as medical history. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Height, Weight, and Vital Signs

The investigator or qualified designee will take weight and vital signs at screening, Cycle 1 Day 1 (pre-dose), Day 8, Day 15, Day 22 (Part A and Part D), and pre-dose of trial treatment in every cycle (including Day 22 of each cycle in Part D), discontinuation visit, and safety follow-up visit. In addition, in Part E, the investigator or qualified designee will take weight and vital signs before dosing etoposide on Day 2 and 3 of each cycle.

- Height (screening visit only)
- Weight
    - If a subject's weight at screening does not fluctuate by more than 10%, this weight can be used to calculate dose.
- Vital signs
    - Temperature
    - Pulse (in a sitting position)
    - Respiratory rate
    - Blood pressure (in a sitting position)

7.1.2.4 12-lead ECG

A standard 12-lead ECG will be performed using local standard procedures.

Part A: at screening, pre-dose in every other cycle, discontinuation visit, and safety follow-up visit.

Part B, C, D and E: at screening and end of cycle 1 (pre-dose of cycle 2). An additional measurement will be performed as needed by investigator's judgment.

Clinically significant abnormal findings at screening should be recorded as medical history. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG status (see Section 12.4) at screening, prior to the Day 1 administration of trial treatment in every cycle (part A, B, C and E), prior to the Day 1 and Day 22 administration of trial treatment in every cycle (part D), discontinuation visit, safety follow-up visit, and Follow up visit 1 and 2..

7.1.2.6 Pulse Oximetry (SpO_2)

Pulse oximetry (SpO_2) will be performed using local standard procedures once at screening, prior to the administration of each dose of trial treatment (including Day 22 of every cycle in Part D), at discontinuation visit, at safety follow-up visit, at Follow-up Visit 1 and at Follow-up visit 2.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Procedure manual.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry, Urinalysis and Other)

Laboratory tests for hematology, chemistry, urinalysis and others are specified in Table 7.

Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Adrenocorticotropic hormone (ACTH) level*	Blood	PT (INR)
Hemoglobin	Albumin	Glucose	aPTT
Platelet count	Alkaline phosphatase	Protein	Free triiodothyronine (T3)
WBC (total and differential)	Alanine aminotransferase (ALT)	Specific gravity	Free thyroxine (T4)
Red blood cell count	Aspartate aminotransferase (AST)	Microscopic exam, if abnormal results are noted	Thyroid stimulating hormone (TSH)
Absolute neutrophil Count	Lactate dehydrogenase (LDH)		Serum/Urine β-human chorionic gonadotropin (β-hCG)
Absolute lymphocyte count	CRP		HIV antibody
	Creatinine or calculated creatinine clearance (CrCl)		HBsAg
	Uric acid		HCV RNA
	Calcium		KL-6
	Chloride		SP-D
	Glucose		β-D glucan
	Phosphorus		

Hematology	Chemistry	Urinalysis	Other
	Potassium		
	Sodium		
	Magnesium		
	Total bilirubin		
	Direct and indirect Bilirubin		
	Total protein		
	Blood urea nitrogen		
	Total cholesterol		
	Triglycerides		
* ACTH; Part D only			

Laboratory tests (hematology, serum chemistry, urinalysis, coagulation parameters, thyroid function, KL-6, SP-D and β-D glucan) for screening should be performed within 14 days prior to the first dose of trial treatment. Laboratory tests (hematology, serum chemistry, urinalysis, thyroid function, KL-6 and SP-D) may be collected up to 48 hours prior to dosing [if a subject receives nab-paclitaxel, laboratory tests on Day 8 and Day 15 of each Q3W cycle is required only for hematology. If a subject participates in Part D includes laboratory tests (except ACTH) on Day 22 of each cycle (refer to 6.2.2 in detail).] in every cycle and the scheduled time point in Cycle 1. The investigator or qualified designee must review the result and confirm acceptability of continuation of trial treatment at pre-dose in every cycle.

PT/INR and aPTT will be collected as coagulation parameters.

TSH, FT3, and FT4 will be measured for thyroid function test.

Testing for HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies will be performed at screening. If results of these tests obtained within 3 months before screening are available, they can be used even before consent is obtained.

For women of reproductive potential, a urine/serum pregnancy test will be performed within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

KL-6 and SP-D is a lung-specific marker for pneumonitis [30, 31]. β-D glucan is a marker for fungus infectious disease [32], and is used for the differential diagnosis for pneumonitis. KL-6, SP-D and β-D glucan will be measured at screening and prior to dosing in every cycle(In Part D, Day 1 and Day 22 in each cycle) (only for KL-6 and SP-D), and if a subject develops suspected pneumonitis, an additional test will be performed as needed by investigator's judgment.

(Part D only) ACTH will be measured at screening, pre-dose of Day 1 of Cycle 2 to Cycle 18, discontinuation visit and Safety Follow-up Visit. An additional test will be performed as needed by investigator's judgment.

7.1.3.2 Pharmacokinetic / Anti-pembrolizumab Antibodies /Evaluations

To further evaluate pembrolizumab immunogenicity and pembrolizumab exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of anti-drug antibodies (ADA) and PK are currently planned as shown in Section 7.1.3.2.1 and 7.1.3.2.2. If ongoing ADA and PK results continue to be consistent with existing ADA and PK data from other pembrolizumab clinical trials, it may be decided to discontinue or reduce further sample collection in this study, which will be communicated by administrative memo.

7.1.3.2.1 Blood Collection for Serum Pharmacokinetics of MK-3475

Serum samples for pharmacokinetics will be obtained at the following points. 3.5 mL blood will be collected at each point. Every effort should be made to collect additional blood samples for pharmacokinetics after the discontinuation visit for up to 6 months from the last dose of pembrolizumab or until start of a new anti-cancer therapy, whichever occurs first. Serum samples for pharmacokinetic measurements will be discontinued after the completion of discontinuation visit after the final dose after approval of the protocol version 08. Serum sample preparation, storage and shipment instructions for serum samples will be provided in the Procedure Manual.

Table 8 Sampling Points for Pharmacokinetics in Part A

Sampling Point	Time window
Cycle 1	
Pre-dose (Day 1)	Within 60 min prior to start of infusion
30 mins after completion of infusion (Day 1)	Within 30 min after completion of infusion
6 hours after completion of infusion (Day 1)	±30 min
24 hours after completion of infusion (Day 2)	±2 hours
48 hours after completion of infusion (Day 3)	±2 hours
168 hours after completion of infusion (Day 8)	±2 hours
336 hours after completion of infusion (Day 15)	±2 hours
504 hours after completion of infusion (Day 22)	±2 hours
Cycle 2 and the additional Cycles during the first 12 months of study therapy	
Pre-dose (Day 1) in every other cycle	Within 60 min prior to start of infusion
Post-dose (Day 1) in every other cycle	Within 30 min after completion of infusion
Discontinuation	
Safety follow-up visit	
30 days after the last dose	±3 days
Fol1ow-up visit 1	
3 months after the last dose	±7 days
Follow-up visit 2	
6 months after the last dose	±7 days

Table 9 Sampling Points for Pharmacokinetics in Part B, C and E

Sampling Point	Time window
Cycle 1	
Pre-dose (Day 1)	Within 24 hours prior to start of infusion
30 minutes after completion of infusion (Day 1)	Within 30 min after completion of infusion
24 hours after completion of infusion (Day 2)	±2 hours
96 hours after completion of infusion (Day 5) (72 or 120 hours is acceptable)	±2 hours
336 hours after completion of infusion (Day 15)	±24 hours
Cycle 2	
Pre-dose (Day 1)	Within 24 hours prior to start of infusion
Cycle 4	
Pre-dose (Day 1)	Within 24 hours prior to start of infusion
Cycle 6	
Pre-dose (Day 1)	Within 24 hours prior to start of infusion
Cycle 8 and every 4 cycles thereafter	
Pre-dose (Day 1)	Within 24 hours prior to start of infusion
30 minutes after completion of infusion (Cycle 8 Day 1 only)	Within 30 minutes after completion of infusion
Discontinuation	

Table 10 Sampling Points for Pharmacokinetics in Part D

Sampling Point	Time window
Cycle 1	
Pre-dose (Day 1)	Within 24 hours prior to start of infusion
30 minutes after completion of infusion (Day 1)	Within 30 minutes after completion of infusion
24 hours after completion of infusion (Day 2)	±2 hours
96 hours after completion of infusion (Day 5)(72 or 120 hours is acceptable)	±2 hours
336 hours after completion of infusion (Day 15)	±24 hours
Pre-dose (Day 22)	±24 hours
Cycle 2	
Pre-dose (Day 22)	±24 hours
Cycle 3	
Pre-dose (Day 22)	±24 hours
Cycle 4	
Pre-dose (Day 22)	±24 hours
30 minutes after completion of infusion (Day22)	Within 30 minutes after completion of infusion
Every 2 cycle thereafter	
Pre-dose (Day 22)	±24 hours
Discontinuation	

7.1.3.2.2 Blood Collection for Serum Anti-pembrolizumab Antibodies

Serum samples for serum anti-pembrolizumab antibodies will be obtained at the following points. 5 mL blood will be collected at each point. Every effort should be made to collect additional blood samples for anti-pembrolizumab antibodies after the discontinuation visit for up to 6 months from the last dose of pembrolizumab or until start of a new anti-cancer therapy, whichever occurs first. Blood samples collection for anti-pembrolizumab antibodies measurements will be discontinued after the completion of discontinuation visit after approval of the protocol version 08. Serum sample preparation, storage and shipment instructions for serum samples will be provided in the Procedure Manual.

Table 11 Sampling Points for Anti-pembrolizumab Antibodies in Part A

Sampling Point	Time window
Cycle 1	
Pre-dose on Day 1	Within 24 hours prior to start of infusion
Cycle 2 and the additional Cycles during the first 12 months of study therapy	
Pre-dose on Day 1 in every other cycle	Within 24 hours prior to start of infusion
Discontinuation	
Safety follow-up visit	
30 days after the last dose	±3 days
Follow-up visit 1	
3 months after the last dose	±7 days
Follow-up visit 2	
6 months after the last dose	±7 days

Table 12 Sampling Points for Anti-pembrolizumab Antibodies in Part B, C, and E

Sampling Point	Time window
Cycle 1	
Pre-dose (Day 1)	Within 24 hours prior to start of infusion
Cycle 2	
Pre-dose (Day 1)	Within 24 hours prior to start of infusion
Cycle 4	
Pre-dose (Day 1)	Within 24 hours prior to start of infusion
Cycle 6	
Pre-dose (Day 1)	Within 24 hours prior to start of infusion
Cycle 8 and every 4 cycles thereafter	
Pre-dose (Day 1)	Within 24 hours prior to start of infusion
Discontinuation	

Table 13 Sampling Points for Anti-pembrolizumab Antibodies in Part D

Sampling Point	Time window
Cycle 1	
Pre-dose (Day 1)	Within 24 hours prior to start of infusion
Pre-dose (Day 22)	Within 24 hours prior to start of infusion
Cycle 2	
Pre-dose (Day 22)	Within 24 hours prior to start of infusion
Cycle 3	
Pre-dose (Day 22)	Within 24 hours prior to start of infusion
Cycle 4	
Pre-dose (Day 22)	Within 24 hours prior to start of infusion
Every 2 cycle thereafter	
Pre-dose (Day 22)	Within 24 hours prior to start of infusion
Discontinuation	

7.1.3.3 Tumor Marker

Standard tumor markers (as appropriate for a given tumor type) will be collected within 14 days prior to the first dose of study treatment, and at the same timing as tumor imaging thereafter.

7.1.3.4 Tumor Imaging and Assessment of Disease (irRC and irRECSIT)

The tumor imaging (CT or MRI) for screening should be performed within 28 days prior to the first dose of trial treatment in Part A, B, C, D and E. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. The same imaging technique must be used for a subject throughout the study.

In Part A, tumor imaging should be performed every 6 calendar weeks (42 days±7 days) after the first dose of study treatment in treatment period. In Part B, C, D and E, tumor imaging should be performed every 6 calendar weeks (± 7days) for the first 24 weeks, and every 9 calendar weeks (± 7 days) from the date of imaging assessment at the week 24. Tumor imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab (ipilimumab in part D) cycle frequencies. Tumor response by the study sites will be assessed using irRC (see Section 12.6) and RECIST ver. 1.1 (see Section 12.5) in Part A, and irRECIST in Part B, C, D and E. In irRECIST, after initial PD based on RECIST 1.1 is identified, a subject may continue treatment if clinically stable, at the discretion of the investigator. An additional imaging ≥4 week later is needed to confirm PD. If PD is not confirmed, treatment can continue. Please see below and Section 12.5.1 for more precise instruction.

After the first documentation of progression per irRC (Part A) or RECIST 1.1 (Part B, C, D and E), it is at the discretion of the investigator to keep a clinically stable subject on trial treatment or to stop trial treatment until repeat imaging performed at least 4 weeks later

confirms progression using irRECIST. When feasible, subjects should not be discontinued until progression is confirmed per irRC (Part A) or irRECIST (Part B, C, D and E).

NOTE: If a subject with confirmed the first radiographic progression based on irRC (Part A) or RECIST 1.1 (Part B, C, D and E) 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. Clinical Stability is defined as:

1) Absence of symptoms and signs indicating clinical significant progression of disease (including worsening of laboratory values) indicating disease progression.

2) No decline in ECOG performance status.

3) Absence of rapid progression of disease or progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

4) Absence of rapid progression of disease

Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If progression is confirmed at the subsequent scan, then the subject will be discontinued from trial treatment unless, if in the opinion of the investigator, the subject is deriving clinical benefit and upon consultation with the Sponsor. If progression is not confirmed at the subsequent scan, then the subject should resume/continue trial treatment and have their next scan according to the every 6 week (42 ± 7 days, in Part A) or every 6 calendar weeks (63 ± 7 days) for the first 24 weeks, and every 9 calendar weeks (63 days ±7 days) from the date of imaging assessment at the week 24 thereafter (in Part B, C, D and E) schedule.

Regarding imaging and treatment determinations after the first radiological evidence of progression, see Table 14.

Table 14 Imaging and Treatment Determinations After First Radiological Evidence of PD (based on irRC in Part A or RECIST 1.1 in Part B, C, D and E)

Imaging and Treatment Determinations After First Radiological Evidence of PD				
	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible.	Discontinue treatment
Repeat scan confirms PD	No additional imaging required if Investigator does not see benefit. If Investigator sees benefit, continue regularly scheduled imaging assessments	May continue treatment if Investigator considers subject deriving clinical benefit	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule outlined in the protocol

In Part B, C, D and E, subjects who discontinued study treatment due to other than disease progression should be obtained imaging every 6 calendar weeks (± 7days) after the first dose for the first 24 weeks, and every 9 calendar weeks (± 7 days) from the date of imaging assessment at the week 24 by radiologic imaging to monitor disease status until the subject experiences disease progression or initiation of a new therapy for cancer. After the approval of the protocol version 08, all follow-up including imaging follow-up will be discontinued after the completion of the 30 days follow-up visit.

Subjects who move into the Second Course Phase will continue to have scans performed every 9 weeks (63 ± 7 days) after the first dose of Second Course Phase trial treatment for Year 1 and every 12 weeks (84 ± 7 days) thereafter.

Central imaging vendor will receive radiographic images for tumor volumetric analysis (in Part A) and RECIST 1.1 (in Part B and C). However, images taken after July 20, 2019 need not be submitted to the central vendor.

7.1.3.5 Pulmonary Radiographic Evaluation for pembrolizumab-Induced Pneumonitis

Pulmonary radiographic imaging is used in a diagnosis of pembrolizumab-induced pneumonitis. A chest CT performed for tumor imaging may be used for pulmonary radiographic evaluation. For a subject with suspected pneumonitis based on respiratory symptoms, other clinical findings or laboratory findings, a chest CT should be performed immediately. If a finding on pneumonitis is observed, the subject should be followed every month with chest imaging to monitor the pneumonitis.

Pulmonary radiographic evaluation will be performed according to the table in Section 6.0. The investigator or sub-investigator will judge whether the variation after the study drug administration is an adverse experience or not and record it in the Case Report Form.

Additionally, an independent radiologist will review chest CTs of all subjects for pulmonary radiographic evaluation. For that purpose, the chest CT imaging will be submitted to the SPONSOR. However, images taken after July 20, 2019 need not be submitted.

In Part C, D and E, the sponsor will confirm the eligibility for exclusion criteria 15 in section 5.1.3 before randomization. After obtaining consent by the subject, the site staff will send the screening scan to the sponsor. Refer to the Procedures manual for details.

7.1.3.6 Tumor Tissue Collection

Part A

Tumor tissue from an archival tissue sample or fresh biopsy of a tumor lesion not previously irradiated will be used for PD-L1expression analysis by IHC. A fine needle aspirate or cytological specimen will not be acceptable. If the subject signs the Future Biomedical Research (FBR) consent, an aliquot of the tissue biopsies will be designated for FBR.

Part B, C, D and E

Tumor tissue for biomarker analysis from formalin fixed paraffin embedded tumor tissue sample or newly obtained formalin fixed biopsy of a tumor lesion not previously irradiated must be provided in the form of a tissue block or unstained slides and received by the central vendor for PD-L1 expression analysis by IHC (mandatory for part B and C. optional for part D and E). Fine needle aspirates, Endobronchial Ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) or cell blocks are not acceptable. Needle or excisional biopsies, or resected tissue is required. Newly obtained formalin fixed specimens are encouraged. Note that if a tumor biopsy of a target lesion is obtained during eligibility assessment, it is preferred to obtain a new baseline scan.

Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. Older biopsy material or surgical specimens may be used to assess EGFR mutation status and ALK translocation status, if not already known when the subject signs informed consent (Part B and D only).

7.1.3.7 Blood Collection for Correlative Studies and Biomarker Samples

Details regarding time points for blood collection are outlined in the Trial Flow Chart – Section 6.2.1, 6.2.2 and 6.2.3.

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

7.1.3.8 Planned Genetic Analysis Sample Collection

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

7.1.3.9 Future Biomedical Research

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

Part A

- Blood for genomics use
- An aliquot of the Fresh Tumor Biopsy and/or Archival Tumor Tissue collected from the main study.
- Leftover Fresh Tumor Biopsy and/or Archival Tumor Tissue from the main study.

Part B, C, D and E

- Leftover DNA for future research
- Leftover Fresh Tumor Biopsy and/or Archival Tumor Tissue from the main study.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

The investigator or trial coordinator must notify the Sponsor when a subject has been discontinued/withdrawn from the trial. If a subject discontinues for any reason at any time during the course of the trial, the subject may be asked to return to the clinic (or be contacted) for a post-trial visit (approximately 14 days after the last dose of trial drug is performed to have the applicable procedures conducted. However, the investigator may decide to perform the post-trial procedures at the time of discontinuation or as soon as possible after discontinuation. If the post-trial visit occurs prior to 14 days after the last dose of trial drug is performed, the investigator should perform a follow-up phone call at 14 days post the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit. 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.

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 writing to 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.

7.1.4.1.2 Lost to Follow-up

If a subject fails to return to the clinic for a required study visit and/or if the site is unable to contact the subject, the following procedures are to be performed:

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the subject at each missed visit (e.g. phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.

- Note: A subject is not considered lost to follow up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Domiciling

In principle, subjects will be hospitalized for DLT evaluation period.

7.1.5 Visit Requirements

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

7.1.5.1 Screening

UP to 28 days prior to first dose of trial treatment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

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

- Laboratory tests (hematology, serum chemistry, urinalysis, coagulation parameters, thyroid function test, KL-6, SP-D and β-D glucan) for screening should be performed within 14 days prior to the first dose of trial treatment.

- Standard tumor markers (as appropriate for a given tumor type) will be collected within 14 days prior to the first dose of study treatment.

- For women of reproductive potential, a urine/serum pregnancy test will 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 will be required.

- If results of HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies test obtained within 3 months before screening are available, they can be used even before consent is obtained.

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 repeating a screening test if performed within the specified time frame and the results meet the inclusion/exclusion criteria.

7.1.5.2 Treatment Period

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures. Subject will be received study treatment until the subject meets 5.8 Discontinuation criteria.

7.1.5.3 Discontinuation

If a subject discontinues trial treatment, procedures for discontinuation will be conducted.

7.1.5.4 Follow-up phase

7.1.5.4.1 Mandatory Safety Follow-Up Visit

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

7.1.5.4.2 Observation visit

Subjects who discontinue trial treatment for a reason other than disease progression during Treatment Phase or Second Couse Phase will move into the Observation Phase. The subject should continue the tumor imaging every 6 calendar weeks (± 7days) for the first 24 weeks, and every 9 calendar weeks (± 7 days) from the date of imaging assessment at the week 24 thereafter (Part B, C, D and E) to monitor disease status until radiologic progression. Once the subject stops the imaging assessments and then initiates a new antineoplastic therapy, the subject moves into the survival follow-up phase. After the approval of the protocol version 08, all follow-up including imaging follow-up will be discontinued after the completion of the 30 days of follow-up visit.

7.1.5.4.3 Follow-Up Visit 1 and 2

Subjects who completed the safety follow-up visit will move to follow-up visit 1 and 2 to collect serum samples for pharmacokinetics and anti-pembrolizumab antibodies. Follow-up visit 1 and 2 will be conducted 3 months and 6 months after the last dose of trial treatment, respectively, or until beginning of a new antineoplastic treatment, whichever comes first. After the approval of the protocol version 08, all follow-up, including serum or blood sample collection for pharmacokinetic or anti-MK-3475 antibody assessment, will be discontinued after the 30 days follow-up visit.

7.1.5.5 Survival Follow-up (Part B, C, D and E)

Once a subject experiences PD or initiates new antineoplastic therapy, the subject moves to survival follow-up phase and followed by telephone every 2 months from the last contact in the study for survival. Post-study treatments and the subject's response to them will also be collected. The Sponsor may request survival status to be assessed and its respective entry into the database at additional time points during the course of the study (ex. around the projected analysis). After approval of the protocol version 08, the final visit of this trial will be a safety follow-up visit and no follow-up for survival will be conducted. Participants in the follow-up phase or survival follow-up phase will discontinue the study and no further visits are required.

7.1.5.6 Second Course Phase (Part B, C, D and E only)

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures. Patients may be eligible to receive MK-3475 only (in part D, MK-3475 +ipilimumab) in the Second Course Phase of

this study for up to 12 months if the subject meet the following conditions. Patients who have already started the second course phase of administration before the approval of the protocol version 08, may continue in the second course phase (up to 12 months) is applicable. For other patients, the second course phase is not applicable.

- Stopped their initial treatment with pembrolizumab(in part D, pembrolizumab +ipilimumab) after attaining an investigator determined confirmed CR according to RECIST 1.1, were treated for at least six months with pembrolizumab, and received at least two treatments with pembrolizumab beyond the date when the initial CR was declared. A CR by RECIST 1.1 means that all target lesions have resolved, all non-target lesions have disappeared, and no new lesions have been identified. These findings must be confirmed on subsequent imaging at least 4 weeks later for the call of CR by RECIST 1.1 to be appropriate. So the subject will have no evidence of metastatic cancer in order for the subject and his/her physician to consider the subject's participation in this Second Course Phase.

OR

- Had SD, PR or CR and stopped pembrolizumab treatment after 24 months (In Part D, 35 times) of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression after stopping their initial treatment with pembrolizumab (in part D, pembrolizumab +ipilimumab)

- Did not receive any-cancer treatment since the last dose of pembrolizumab (in part D, pembrolizumab+ ipilimumab)

- Continues to meet inclusion criteria 3, 4, 7 to 9.

- Does not meet exclusion criteria 4, 5, 11, 13 to 20

Subjects who receive pembrolizumab plus ipilimumab may be eligible to receive up to 17 additional trial treatments of pembrolizumab plus 9 cycles of ipilimumab in the Second Course Phase; subjects will receive the treatment regimen that was assigned at the last administration in initial treatment (i.e., if ipilimumab was discontinued early in initial treatment at the investigator's discretion and the subject continued on pembrolizumab monotherapy for any length of time, they would only be eligible for monotherapy pembrolizumab in Second Course Phase). Additionally, investigators may choose to administer pembrolizumab only for the Second Course Phase treatment and forego the ipilimumab for the entire Second Course Phase even if the 18 course of ipilimumab and pembrolizumab is completed..

An objective response or progression of disease that occurs during the Second Course Phase for a subject will not be counted as an event for the primary analysis of either endpoint in this trial.

7.1.5.7 Critical Procedures Based on Trial Objectives: Timing of Procedure

For this trial, the blood sample for MK-3475 is the critical procedure.

At any post-dose time points, the blood sample for MK-3475 needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Trial procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the trial with joint agreement of the investigator and the Sponsor Clinical Monitor.

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

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events

will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for study therapy: five times the pembrolizumab and three times the ipilimumab dose or more than 20 % of the chemotherapy regimen. No specific information is available on the treatment of overdose of study therapy. In the event of overdose, study therapy 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 adverse event occurring at any dose or during any use of Sponsor's product that:

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

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

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

Refer to Table 15 for additional details regarding each of the above criteria.

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

2. 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.

3. 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.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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

7.2.4 Evaluating Adverse Events

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

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

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 15 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); 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 test drug	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR 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 Efficacy and Safety Evaluation Committee

The Efficacy and Safety Evaluation Committee (ESEC) will be established for the purpose of evaluating the safety information of this study from the specialist and objective viewpoints to ensure the safety of subjects.

The details of the ESEC are prescribed by separate instructions.

7.3.2 Independent Pulmonary Radiographic Adviser

An independent pulmonary radiographic adviser will review pulmonary radiographic changes and its features using chest CT imaging.

The details of the independent pulmonary radiographic adviser are prescribed by separate instructions.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

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

The primary purpose of this study is to evaluate the safety and tolerability of pembrolizumab alone in subjects with advanced solid tumors and in combination with platinum-doublet chemotherapy in subjects with advanced NSCLC or ED-SCLC, or in combination with immunotherapy in subjects with advanced NSCLC.

DLT will be tabulated. Summary statistics for frequency, duration, grade, and time to onset of first DLT in each dose level will be provided. Adverse events will be summarized by tabulating the number (%) of subjects experiencing at least one adverse event within each system organ class and within each preferred term. Additionally, ECOG performance status, laboratory tests, vital signs, physical examinations, chest CT imaging, and 12-lead ECGs parameters will be summarized for each dose level/ cohort.

Summary statistics will be provided by dose levels/ cohort for the pharmacokinetic parameters ($AUC_{0\text{-}28days}$, C_{max}, T_{max}, C_{trough}, $t_{1/2}$, etc.) of pembrolizumab. Response categories for target and non-target lesions for subjects with advanced solid tumors or NSCLC/ED-SCLC (complete response, partial response, progressive disease, and stable disease) will be

tabulated across the various doses levels/ cohort. Exploratory analysis will be provided on the correlation between PD-L1 expression levels and tumor response.

There will be totally approximately 84 subjects [9-12 for Part A , 12-18 each for Part B, C and E (cohort 1 and 2), 6-9 for part D, 3-9 for Part E cohort 3] enrolled in this study for safety and tolerability assessment.

8.2 Statistical Analysis Plan

There are no plans to issue a separate Statistical Analysis Plan (SAP) for this trial. If, after the trial has begun, important changes are made that affect principal features of the primary or key secondary analyses, then the protocol will be amended, as appropriate (consistent with ICH Guideline E-9). Any other changes made to the planned analyses after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the trial. Post hoc exploratory analyses will be clearly identified in the CSR.

8.2.1 Responsibility for Analyses

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

This trial is being conducted as an open-label trial (i.e. subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned).

8.2.2 Trial Objectives

See Section 3.0 for primary objectives.

8.2.3 Variables/Time Points of Interest

8.2.3.1 Safety Endpoints

Safety and tolerability will be assessed by a clinical review of all relevant adverse experiences and monitoring variables relates to complete blood count, chemistry panel, urinalysis, 12-lead ECG, pulmonary radiographic findings, vital signs, physical examinations and ECOG performance status.

Primary Endpoints

The primary endpoint in this study is the incidence of DLTs observed in the DLT evaluation period in Japanese subjects according to the “Guideline for clinical evaluation method of anti-malignant tumor agents [27]”.

Other Major Variables

- Vital signs
- Physical examination
- ECOG performance status
- 12-lead ECG
- Pulmonary radiographic findings
- Adverse events
- CBC with differential
- Serum chemistry
- Urinalysis

All toxicities will be graded and recorded according to the NCI-CTCAE version 4.0.

8.2.3.2 Efficacy Endpoints

- Overall Response Rate (ORR): defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR).
- Duration of Overall Response (DOR): defined as the time from first documented evidence of CR or PR until disease progression or death.
- Progression–free survival (PFS): defined as the time from allocation to the first documented disease progression or death due to any cause, whichever occurs first.
- Overall Survival (OS): defined as the time from allocation to death due to any cause.
- Correlation between PD-L1 expression levels and tumor response

The immune related Response Criteria (irRC, in Part A), irRECIST (Part B, C, D and E), the RECIST ver.1.1, and tumor volumetric analysis (Part A) will be applied for evaluation of tumor response.

8.2.3.3 Pharmacokinetic Endpoints

- Pharmacokinetic parameters of pembrolizumab ($AUC_{0\text{-}28days}$, C_{max}, T_{max}, C_{trough}, $t_{1/2}$, etc.)
- In part B, C, D and E, pharmacokinetic parameters of pembrolizumab (Cmax, Tmax, Ctrough, etc.)

8.2.3.4 Immunogenicity Endpoints

- Anti-pembrolizumab antibody

8.2.4 Analysis Populations

8.2.4.1 Safety Analysis Populations

The All Treated Set (ATS) population will be used for the analysis of safety data in this trial. The ATS population consists of all allocated subjects who received at least one dose of treatment dose. Subjects will be included in the dose level corresponding to the treatment dose they actually received for the analysis of safety data using the ATS population.

At least one laboratory, 12-lead ECG or vital sign measurement obtained subsequent to at least one dose of treatment dose is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.2.4.2 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this trial. The FAS population is a subset of all allocated subjects with subjects excluded for the following reasons:

- Failure to receive at least one dose of treatment dose

The pharmacokinetics analyses will be based on subjects who have evaluable PK measurements at baseline and at least once during treatment. No explicit imputation was made for missing data.

8.2.5 Statistical Methods

The following analysis is applied to both Part A, B, C, D and E.

8.2.5.1 Safety Analyses

Frequencies of DLTs during the DLT evaluation period [the first 4 weeks (Part A) or 3 weeks (Part B, C and E) or 6 weeks (Part D) after initiation of study treatment] will be summarized by tabulating by Part (by dose level in Part A and by cohort in Part B, C and E). Tables of summary statistics (mean, standard deviation, median, and range) for time to onset and duration of the first grade DLT AEs will be provided. Laboratory assessments will be summarized. Adverse events will be summarized by tabulating the number (%) of subjects experiencing at least one adverse event within each system organ class and within each preferred term. Complete blood count, chemistry panel, urinalysis, pulmonary radiographic change findings, adverse events, electrocardiogram, vital signs, physical examination and ECOG PS will be summarized.

8.2.5.2 Pharmacokinetics Analyses

In part A, summary statistics (mean, standard deviation, and range) will be provided for pharmacokinetics measures ($AUC_{0\text{-}28days}$, C_{max}, T_{max}, C_{trough}, $t_{1/2}$, etc.) of MK-3475 and appropriate plots will be generated on pharmacokinetic profiles. In part B, C, D and E, summary statistics (mean, standard deviation, and range) will be provided for pharmacokinetics measures (Cmax, Tmax, Ctrough, etc.) of pembrolizumab and appropriate plots will be generated on pharmacokinetic profiles. A population pharmacokinetic analysis will be conducted using the serum concentration of pembrolizumab obtained in the study as needed.

8.2.5.3 Efficacy Analyses

Overall objective response rate and its 95% confidence interval using the exact method will be provided. Response categories for target and non-target lesions for subjects with advanced solid tumors or NSCLC/ED-SCLC (complete response, partial response, progressive disease, and stable disease), PFS and OS will be tabulated across the various doses levels/cohorts. Response duration will be summarized descriptively using Kaplan-Meier method.

An exploratory analysis of a potential correlation between PD-L1 expression levels and tumor response will be performed as appropriate.

8.2.6 Multiplicity

Since the primary objective of this trial is to estimate safety and tolerability of pembrolizumab alone in subjects with advanced solid tumors and in combination with platinum-doublet chemotherapy or immunotherapy in subjects with advanced NSCLC/ED-SCLC, no formal statistical hypothesis is tested. Therefore, no adjustment for multiplicity is needed.

8.2.7 Sample Size and Power Calculation

The primary objective for the study is to evaluate the tolerability and safety profile of pembrolizumab alone in subjects with advanced solid tumors and in combination with platinum-doublet chemotherapy or immunotherapy in subjects with advanced NSCLC/ED-SCLC**.** The primary endpoints for the study are DLT rate. A TPI (toxicity profile interval) design suggested by Ji et al [29] targeting a 20% DLT rate for Part A and 30% for Part B, C, D and E will be employed in safety assessment. Dose escalation/tolerability evaluation rules for Part A and Part B, C, D and E were described in 5.2.1.2. For DLT evaluation, 3 to 6 subjects for each dose level in Part A and 3 to 9 subjects for each part/cohort are required in Part B, C, D and E. The total number of evaluable subjects is approximately 84 [9-12 for Part A, 12-18 each for Part B, C and Part E (cohort 1 and 2), 6-9 for Part D, 3-9 for Part E cohort 3].

With 6 subjects, the probability of no more than 2 subject developing DLTs will be about 90.1% and 74.4% for assumed DLT rate 20% and 30% respectively.

8.2.8 Interim Analysis

No interim analysis is planned.

8.2.9 Accounting for Missing Data

Analyses will be based on subjects with data available. No explicit imputations will be made.

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.

Table 16 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
MK-3475 50 mg *	Lyophilized Powder for Infusion	Provided by the Sponsor
MK-3475 100 mg/4 mL *	Solution for Injection	Provided by the Sponsor
Ipirimumab 50 mg/10 mL	Solution for Injection	Provided by the Sponsor
* MK-3475 50 mg and/or 100 mg/4 mL will be provided to the site.		

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. Every attempt will be made to source these supplies from a single lot/batch number. The trial site will be responsible for recording the lot number, manufacturer and expiry date 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.

In Part A, subjects will receive open label pembrolizumab vials every 4 weeks at Cycle 1 and every 2 weeks at Cycle 2 and subsequent. In Part B, C, D and E, subjects will receive open label vials of pembrolizumab every 3 weeks. In Part D, subjects will receive open label vials of ipilimumab every 6 weeks.

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 to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

1) name, address, telephone number and e-mail address;

2) hospital or clinic address and telephone number;

3) curriculum vitae or other summary of qualifications and credentials; and

4) other professional documentation.

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

investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The sponsor 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 discarding trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

Detailed information regarding Data Management procedures for this protocol will be provided by the Sponsor.

10.7 Publications

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

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

the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimen(s) collected in this trial as outlined in Section 7.1.3.9 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug. Future Biomedical Research specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug 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, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

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

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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

4. Confidential Subject Information for Future Biomedical Research

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

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

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

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

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

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

5. Biorepository Specimen Usage

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

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be

returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These

data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

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

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

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

10. Gender, Ethnicity and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

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

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results

obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

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

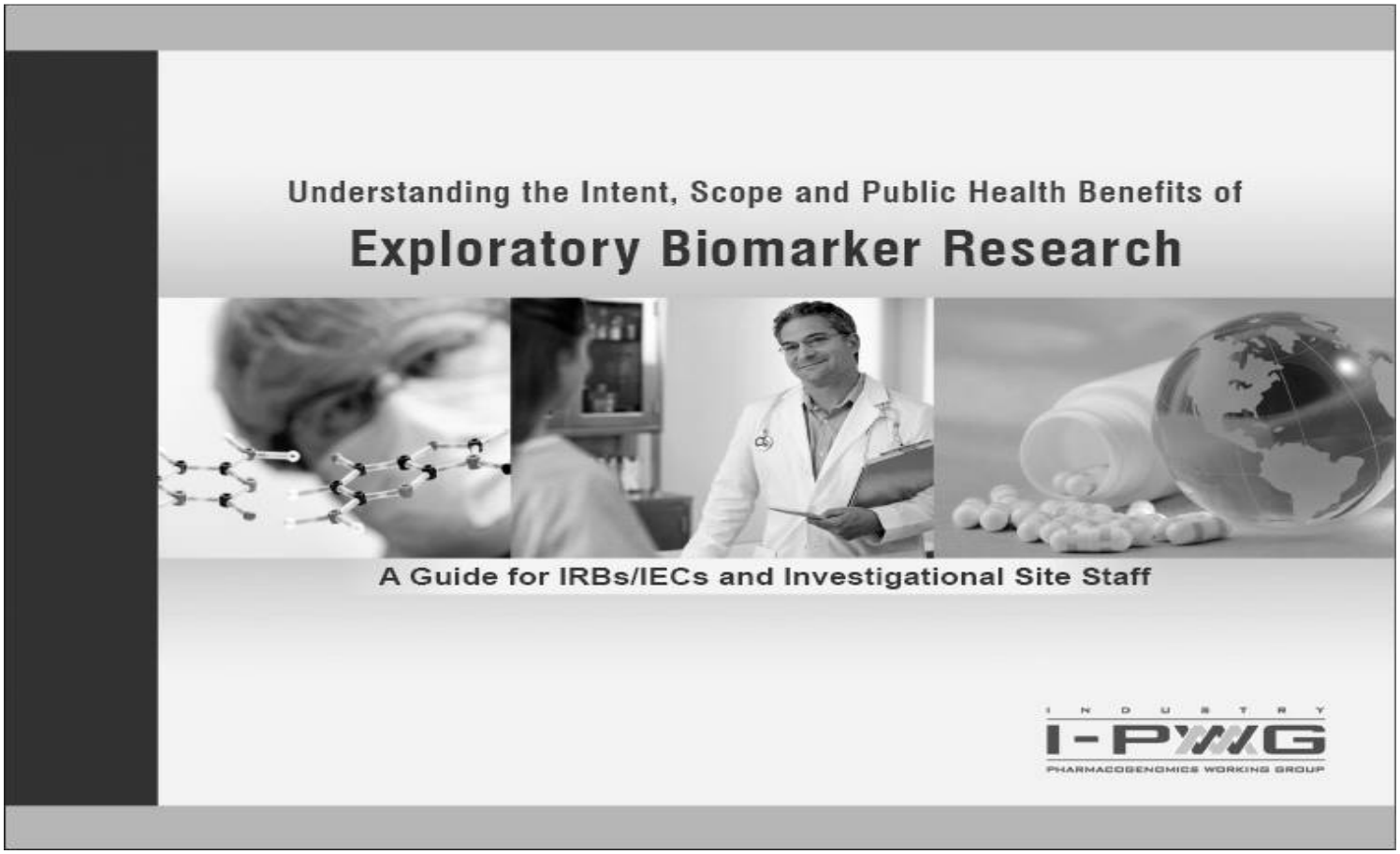
13. Questions

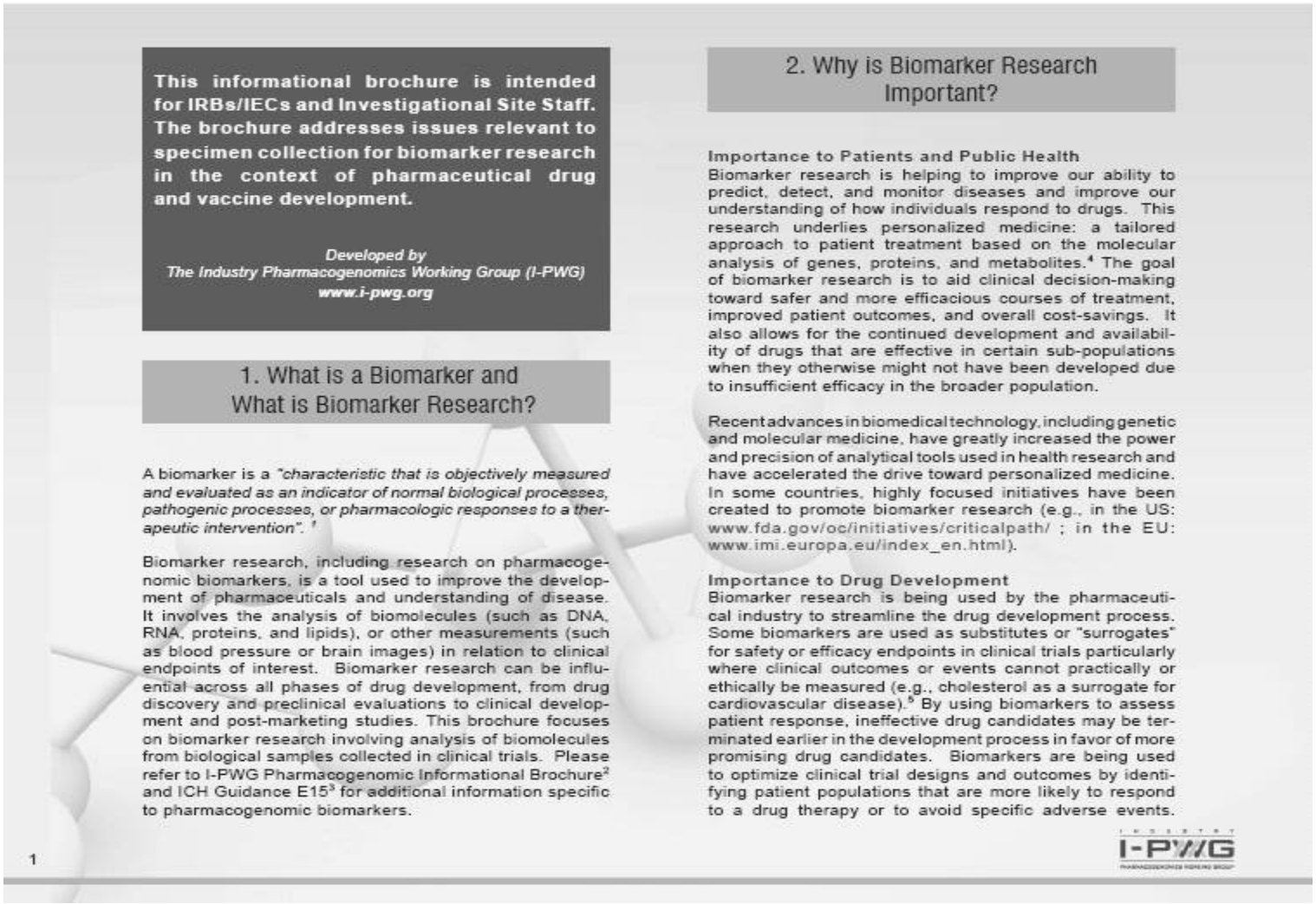
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. References

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

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





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

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

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

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

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

2. Why is Biomarker Research Important?

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

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

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

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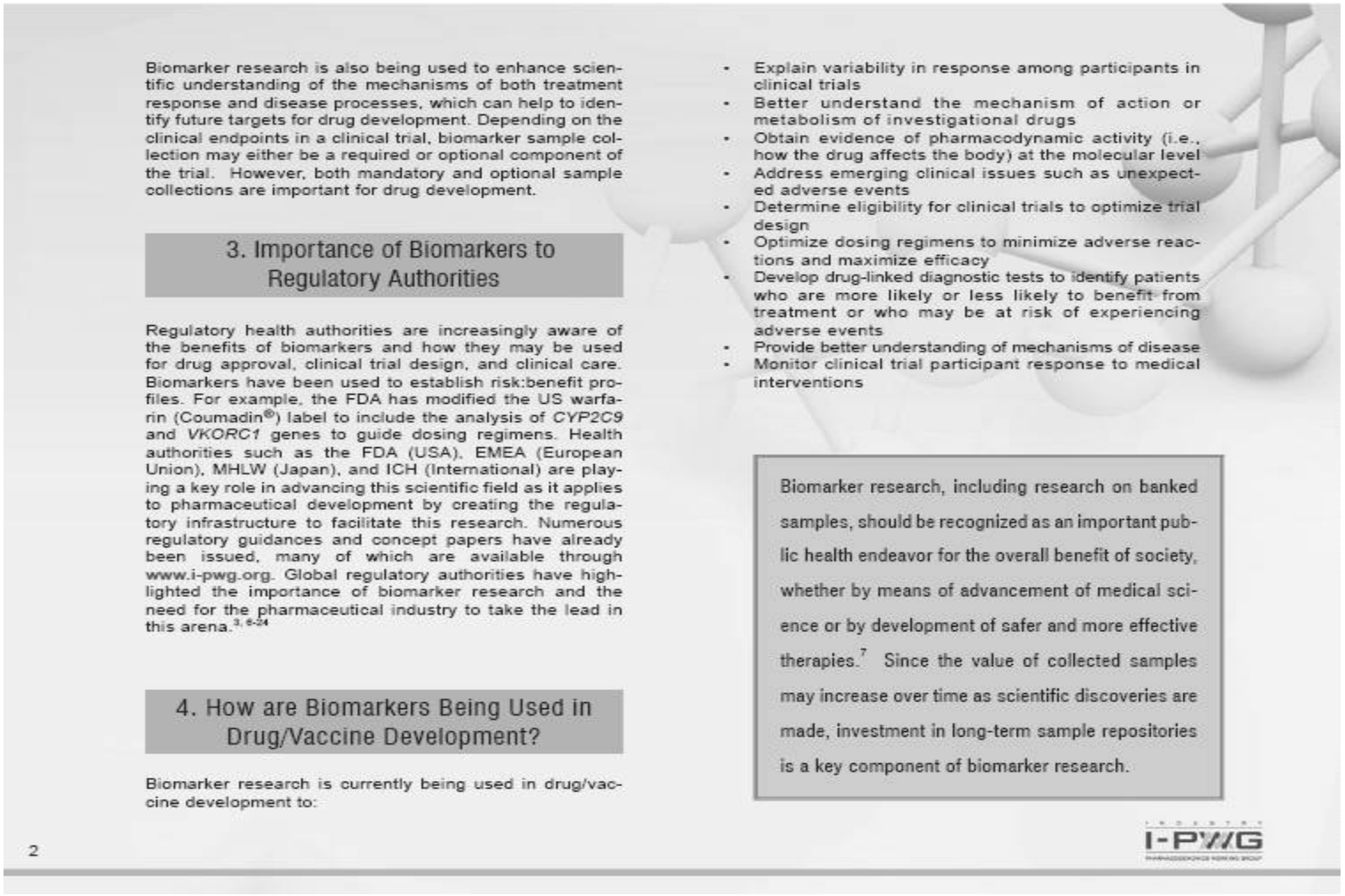
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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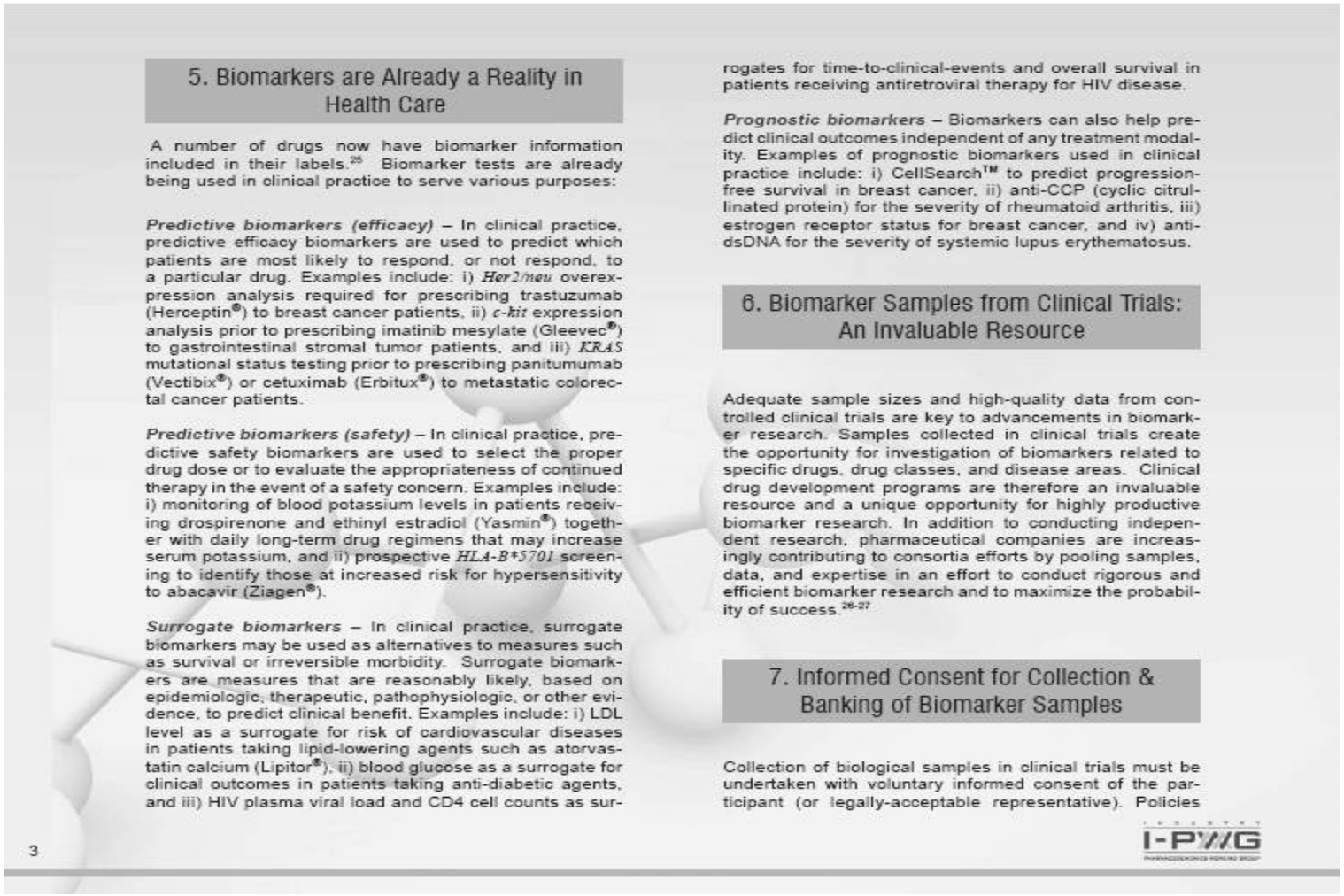

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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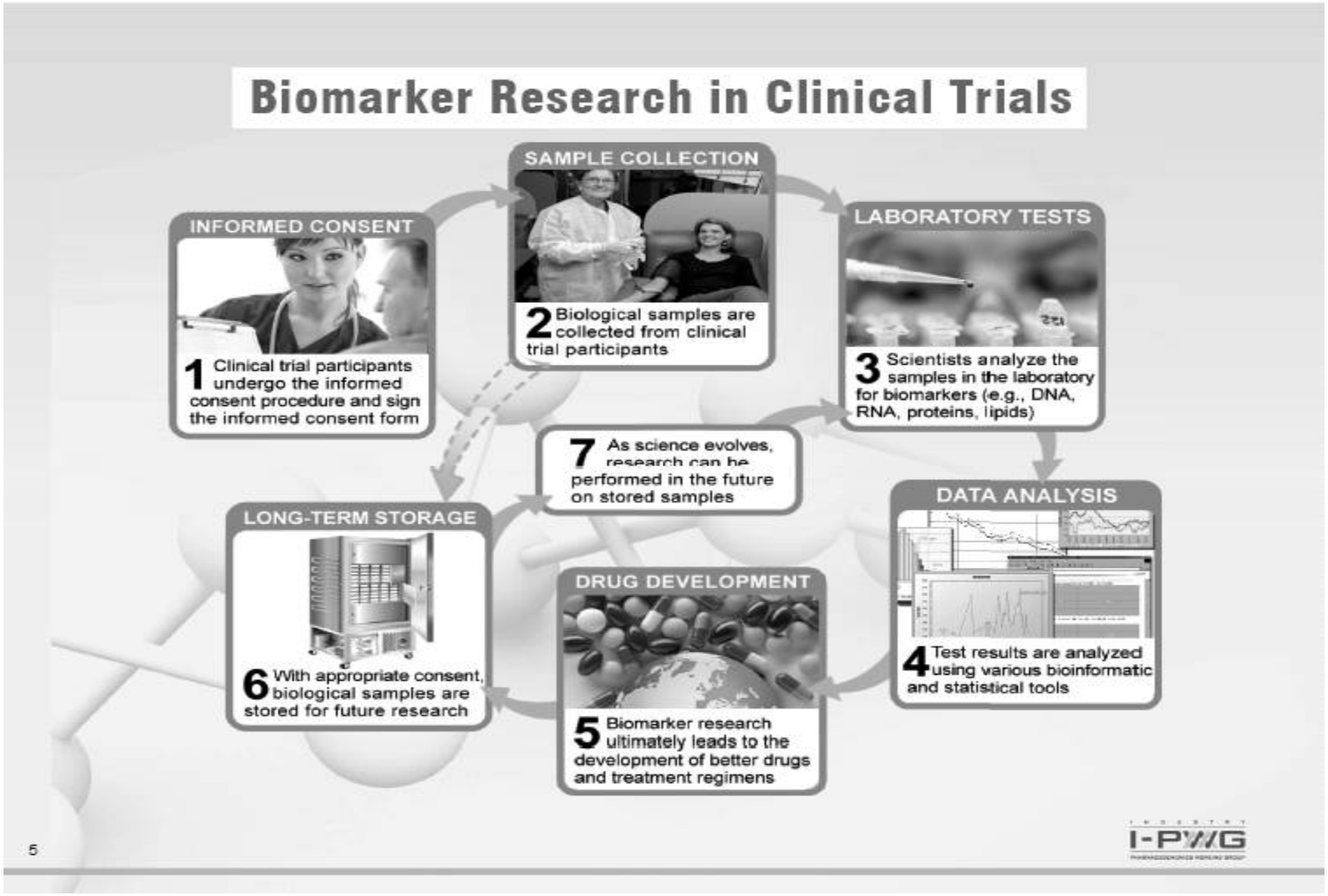
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the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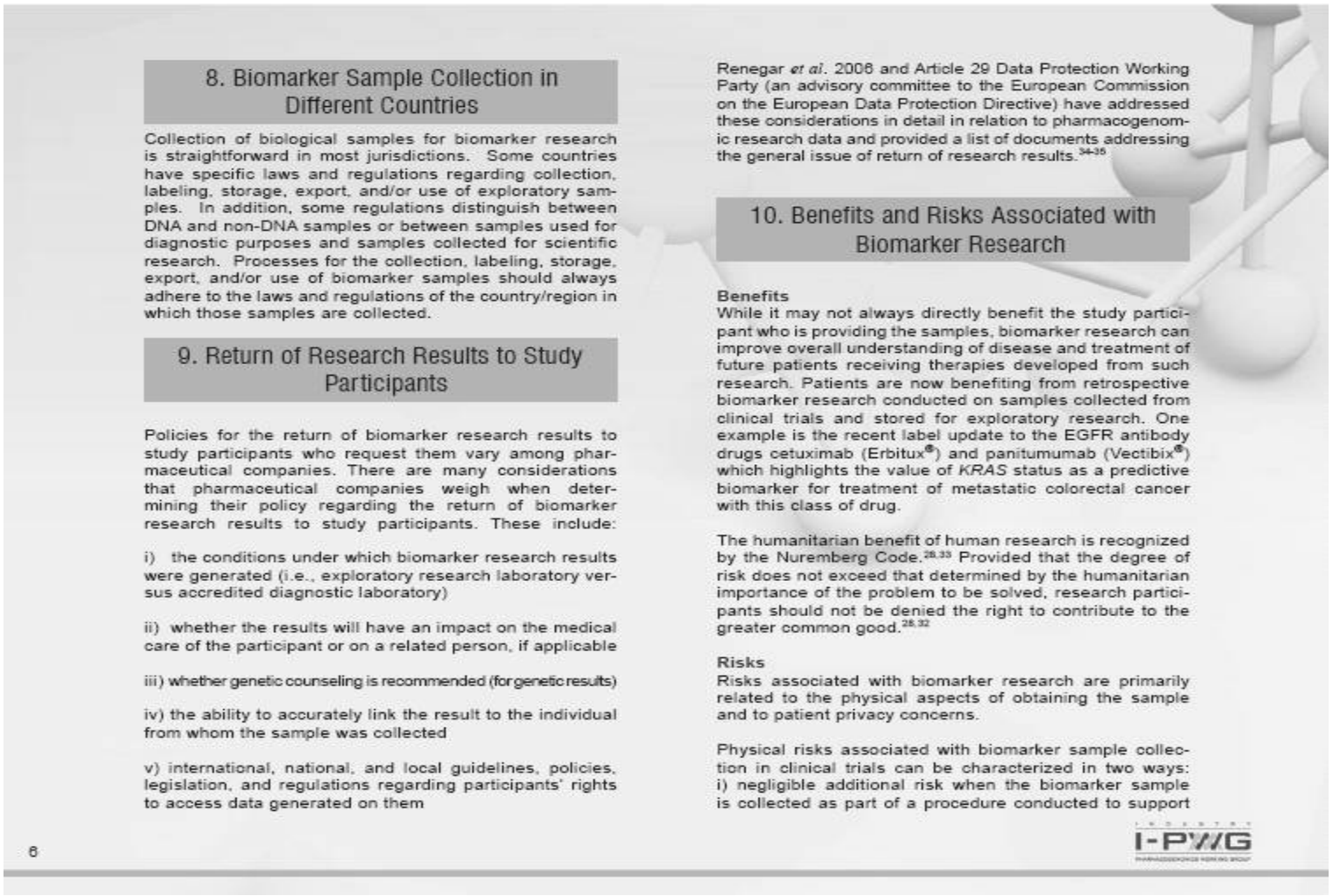

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

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

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

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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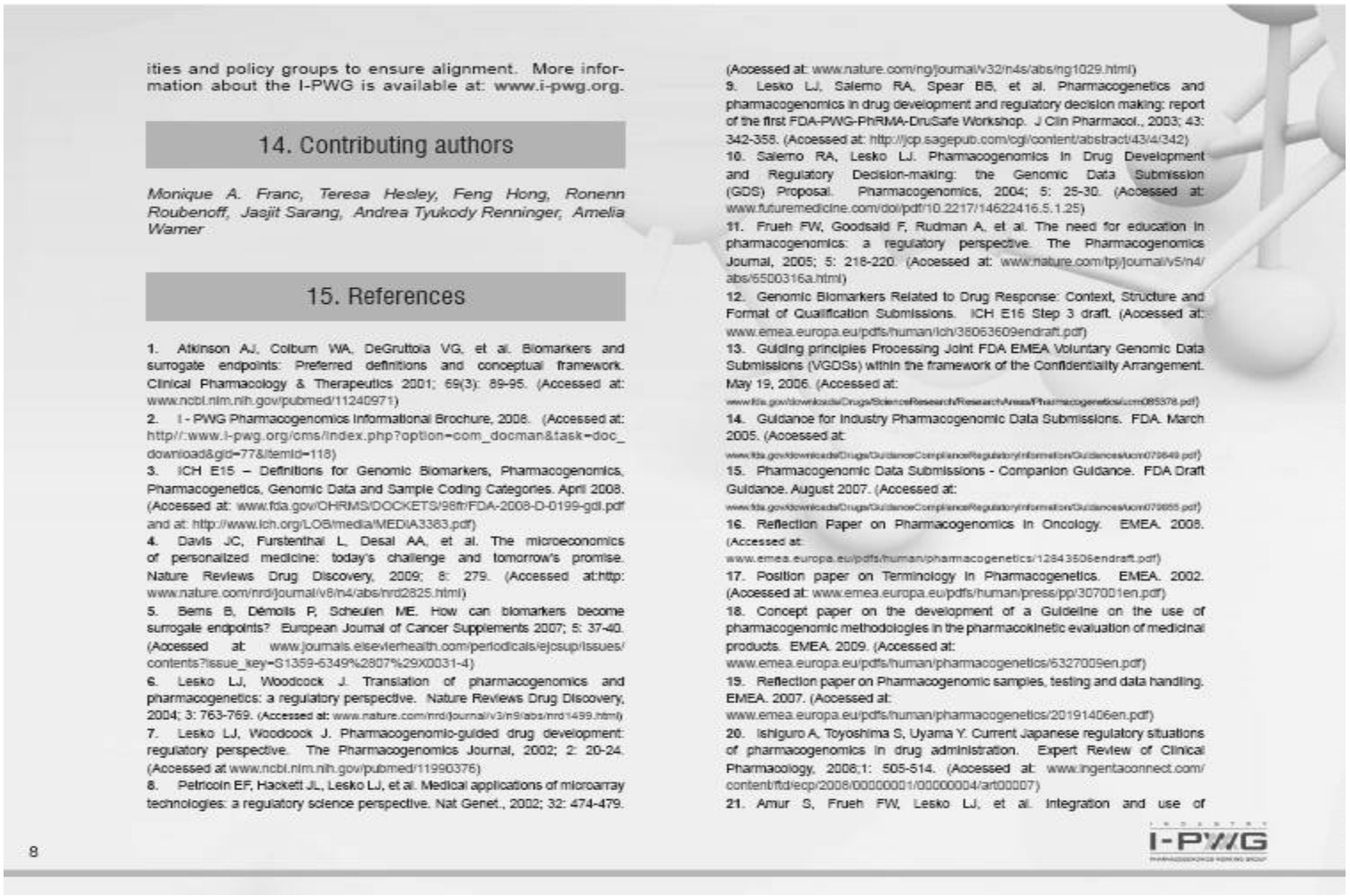

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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

15. References

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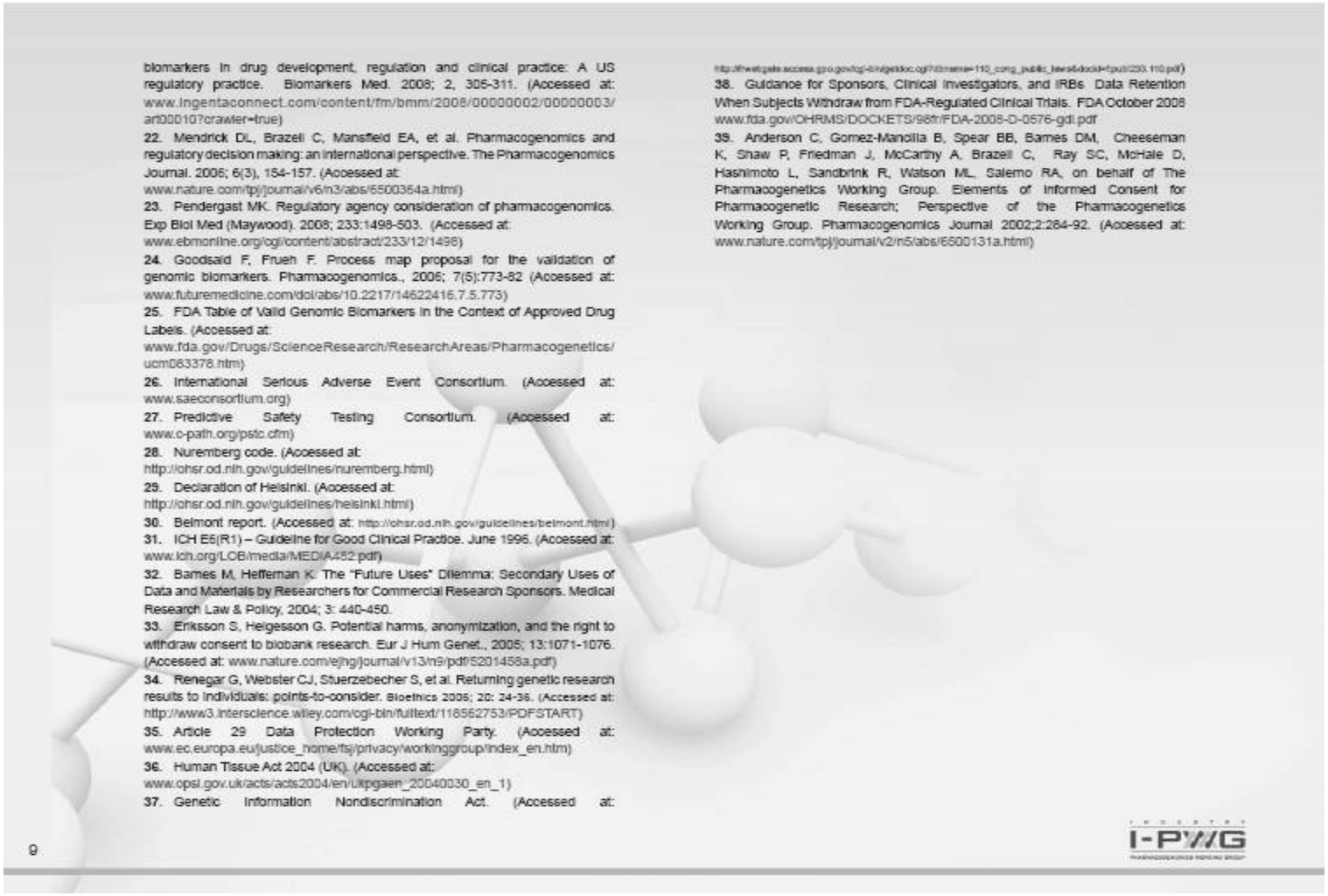

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12.4 ECOG Performance Status

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

12.5 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

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

REFERENCE

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

In addition, volumetric analysis will be used for response assessment (so-called enhanced RECIST).

12.5.1 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 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 central imaging vendor review will be evaluated retrospectively in part B and C.

When feasible, subjects should not be discontinued until progression is confirmed by the local site investigator/radiology assessment. This allowance to continue treatment despite initial radiologic progressive disease (PD) takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

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

In subjects who have shown initial evidence of radiological PD by RECIST 1.1 as verified by central imaging vendor, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained (using irRECIST for subject management, see Table 14. This clinical judgment decision by the site investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment and tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

1) Absence of symptoms and signs indicating clinical significant progression of disease (including worsening of laboratory values) indicating disease progression.

2) No decline in ECOG performance status.

3) Absence of rapid progression of disease or progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

4) Absence of rapid progression of disease

Any subjects deemed clinically unstable should be discontinued from trial treatment and is not required to have repeat imaging for PD confirmation.

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

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

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

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

Scenarios where PD is confirmed at repeat imaging if ANY of the following occur by irRECIST:

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

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

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

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

12.6 Immune Related Response Criteria

For all patients who experience disease progression on study, the date noted for of disease progression is the time of the scan where it is originally detected, and not the following date of the confirmatory scan.

Definitions of measurable and non-measurable disease

Measurable disease: Neoplastic masses that can be precisely measured in 2 in-plane perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 10 mm or 2 times the axial slice thickness, whichever is greater. Lymph nodes must have a short-axis line-length of ≥ 15 mm. Malignant lymph nodes must be measurable in 2 perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 15 mm or 2 times the axial slice thickness. The quantitative endpoint will be defined as the product of the longest diameter with its longest perpendicular.

Non-measurable disease: Non-measurable lesions are those that are not suitable for quantitative assessment over time. These include:

1. Neoplastic masses that are too small to measure, because their longest uninterrupted diameter or longest perpendicular are less than 10 mm or two times the axial slice thickness.

2. Neoplastic masses whose boundaries cannot be distinguished. This includes masses which cannot be demarcated from surrounding tissue because of inadequate contrast, masses with overly complex morphology, or those with highly heterogeneous tissue composition.

3. Other types of lesions that are confidently felt to represent neoplastic tissue, but difficult to quantify in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill defined abdominal masses, etc.

For irRC, only target lesions selected at baseline and measurable new lesions are taken into account.

At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all **index lesions** (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥ 5 X 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total time-point **tumor burden**.

Overall response using irRC:

- Complete Response (irCR): Complete disappearance of all tumor lesions (whether measureable or not, and no new lesions). CR must be confirmed by repeated, consecutive assessments made no less than 4 weeks from the date first documented.
- Partial Response (irPR): Decrease in SPD of 50% or greater by a consecutive assessment at least 4 weeks after first documentation.
- Stable Disease (irSD): Failure to meet criteria for irCR or irPR, in absence of irPD.
- Progressive Disease (irPD): At least 25% increase in SPD relative to nadir (minimum recorded tumor burden) Confirmation by a repeat, consecutive assessment no less than 4 weeks from the data first documented.

Please note other key differences between irRC and the original WHO criteria:

- New measurable lesions will be incorporated into the SPD
- New non measurable lesions do not define progression but preclude irCR
- Non-index lesions contribute to defining irCR (complete disappearance required).

*REFERENCE

IrRC for the current protocol is adopted from the following reference:

Wolchok, JD, Hoos, A, O'Day S, et al., Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clinical Cancer Research, 2009 Dec 1;15(23):7412-20. Epub 2009 Nov 24.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	SIGNATURE	DATE
_____	_____	_____

13.2 Investigator

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

TYPED NAME	SIGNATURE	DATE
_____	_____	_____