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**TITLE:**

A Phase II, Open-label, Single-arm, Multicenter Study to Evaluate Efficacy and Safety of Pembrolizumab Monotherapy in Subjects with Advanced Recurrent Ovarian Cancer (KEYNOTE -100)

**IND NUMBER:** [126,191]

**EudraCT NUMBER:** [2015-003338-29]

## TABLE OF CONTENTS

**DOCUMENT HISTORY** ..... **11**

**SUMMARY OF CHANGES** ..... **12**

**1.0 TRIAL SUMMARY** ..... **13**

**2.0 TRIAL DESIGN** ..... **14**

**2.1 Trial Design** ..... **14**

2.1.1 Overall Trial Design ..... 14

2.1.2 Trial Diagram at Individual Subject Level ..... 16

**2.2 Trial Diagram** ..... **17**

**3.0 OBJECTIVE(S) & HYPOTHESIS(ES)** ..... **18**

**3.1 Primary Objective(s) & Hypothesis(es)** ..... **18**

**3.2 Secondary Objective(s) & Hypothesis(es)** ..... **18**

**3.3 Exploratory Objectives** ..... **19**

**4.0 BACKGROUND & RATIONALE** ..... **19**

**4.1 Background** ..... **19**

4.1.1 Pharmaceutical and Therapeutic Background ..... 20

4.1.1.1 Disease Background ..... 20

4.1.1.2 Targeting PD-1 Immune Checkpoints for Cancer Treatment ..... 22

4.1.1.3 Anti-PD-1 Antibody Pembrolizumab ..... 22

4.1.2 Summary of Pembrolizumab Clinical Activities ..... 23

**4.2 Rationale** ..... **25**

4.2.1 Rationale for the Trial and Selected Subject Population ..... 25

4.2.2 Rationale for Dose Selection/Regimen/Modification ..... 26

4.2.3 Rationale for Endpoints ..... 27

4.2.3.1 Efficacy Endpoints ..... 27

4.2.3.2 Immune-related RECIST (irRECIST) ..... 28

4.2.3.3 Safety Endpoints ..... 28

4.2.3.4 Planned Biomarker Research ..... 29

4.2.3.5 Future Biomedical Research ..... 30

**4.3 Benefit/Risk ..... 31**

**5.0 METHODOLOGY ..... 31**

**5.1 Entry Criteria ..... 31**

5.1.1 Diagnosis/Condition for Entry into the Trial ..... 31

5.1.2 Subject Inclusion Criteria ..... 31

5.1.3 Subject Exclusion Criteria ..... 34

**5.2 Trial Treatment(s) ..... 35**

5.2.1 Dose Selection/Modification ..... 35

5.2.1.1 Dose Selection (Preparation) ..... 35

5.2.1.2 Dose Modification and Toxicity Management Guidelines for Pembrolizumab ..... 36

5.2.2 Timing of Dose Administration ..... 41

5.2.3 Trial Blinding/Masking ..... 42

**5.3 Randomization or Treatment Allocation ..... 42**

**5.4 Stratification ..... 42**

**5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited) ..... 42**

5.5.1 Acceptable Concomitant medications ..... 42

5.5.2 Prohibited Concomitant Medications ..... 42

**5.6 Rescue Medications & Supportive Care ..... 43**

5.6.1 Supportive Care Guidelines ..... 43

**5.7 Diet/Activity/Other Considerations ..... 44**

5.7.1 Diet ..... 44

5.7.2 Contraception ..... 44

5.7.3 Use in Pregnancy ..... 46

5.7.4 Use in Nursing Women ..... 46

**5.8 Subject Withdrawal/Discontinuation Criteria ..... 46**

5.8.1 Discontinuation of Study Therapy after Complete Response ..... 47

**5.9 Subject Replacement Strategy ..... 47**

**5.10 Beginning and End of the Trial ..... 47**

**5.11 Clinical Criteria for Early Trial Termination ..... 48**

**6.0 TRIAL FLOW CHART ..... 49**

**6.1 Initial Treatment Phase ..... 49**

**6.2 Second Course Phase (Retreatment) ..... 53**

**7.0 TRIAL PROCEDURES ..... 55**

**7.1 Trial Procedures ..... 55**

7.1.1 Administrative Procedures ..... 55

7.1.1.1 Informed Consent ..... 55

7.1.1.1.1 General Informed Consent ..... 55

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research ..... 55

7.1.1.2 Inclusion/Exclusion Criteria ..... 56

7.1.1.3 Subject Identification Card ..... 56

7.1.1.4 Medical History ..... 56

7.1.1.4.1 Ovarian Cancer Disease Details ..... 56

7.1.1.4.2 Menopausal Details ..... 56

7.1.1.5 Prior and Concomitant Medications Review ..... 56

7.1.1.5.1 Prior Medications ..... 56

7.1.1.5.2 Concomitant Medications ..... 57

7.1.1.6 Subsequent Anti-Cancer therapy Status ..... 57

7.1.1.7 Assignment of Screening Number ..... 57

7.1.1.8 Assignment of Treatment/Randomization Number ..... 57

7.1.1.9 Trial Compliance (Medication/Diet/Activity/Other) ..... 57

7.1.2 Clinical Procedures/Assessments ..... 58

7.1.2.1 Adverse Event Monitoring ..... 58

7.1.2.2 Physical Exam ..... 58

7.1.2.2.1 Full Physical Exam ..... 58

7.1.2.2.2 Directed Physical Exam ..... 58

7.1.2.3 Vital Signs ..... 58

7.1.2.4 12-Lead Electrocardiogram ..... 59

7.1.2.5 Eastern Cooperative oncology Group Performance Status ..... 59

7.1.2.6 Tumor Imaging and Assessment of Disease ..... 59

7.1.2.6.1 Screening Tumor Imaging ..... 59

7.1.2.6.2 Disease Assessments During Treatment Period ..... 60

7.1.2.6.3 Bone Scans ..... 60

7.1.2.6.4 End of Treatment and Follow-up Tumor Imaging ..... 61
7.1.2.6.5 Second Course (Retreatment) Tumor Imaging ..... 61
7.1.2.6.6 RECIST 1.1 Assessment of Disease ..... 61
7.1.2.6.7 irRECIST Assessment of Disease ..... 62
7.1.3 Laboratory Procedures/Assessments ..... 64
7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis) ..... 64
7.1.3.2 Blood for Menopausal Status ..... 66
7.1.3.3 Blood for Tumor Biomarker CA-125 ..... 66
7.1.3.4 Pharmacokinetics/Pharmacodynamic Evaluations ..... 67
7.1.3.4.1 Blood Collection for Serum Pembrolizumab Pharmacokinetics ..... 67
7.1.3.4.2 Blood Collection for Anti Drug Pembrolizumab Antibodies ..... 67
7.1.3.5 Tumor Tissue Collection ..... 67
7.1.3.6 Correlative Blood Collections- Samples for Correlative and Biomarker Analyses ..... 68
7.1.3.7 Planned Genetic Analysis Sample Collection ..... 68
7.1.3.8 Future Biomedical Research Sample Collection ..... 68
7.1.4 Other Procedures ..... 68
7.1.4.1 Withdrawal/Discontinuation ..... 68
7.1.4.1.1 Withdrawal From Future Biomedical Research ..... 68
7.1.4.2 Blinding/Unblinding ..... 69
7.1.4.3 Calibration of Critical Equipment ..... 69
7.1.5 Visit Requirements ..... 69
7.1.5.1 Screening ..... 69
7.1.5.2 Treatment Cycles ..... 70
7.1.5.2.1 Second Course Phase (Retreatment Period) ..... 70
7.1.5.3 Post-Treatment ..... 71
7.1.5.3.1 Discontinuation Visit ..... 71
7.1.5.3.2 Safety Follow-up Visit ..... 71
7.1.5.3.3 Follow-up Visits ..... 72
7.1.5.3.4 Survival Follow-up ..... 72
7.1.5.4 Survival Status ..... 72
**7.2 Assessing and Recording Adverse Events ..... 72**

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor ..... 73
7.2.2 Reporting of Pregnancy and Lactation to the Sponsor ..... 74
7.2.3 Immediate Reporting of Adverse Events to the Sponsor ..... 74
7.2.3.1 Serious Adverse Events ..... 74
7.2.3.2 Events of Clinical Interest ..... 75
7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting ..... 76
7.2.4 Evaluating Adverse Events ..... 76
7.2.5 Sponsor Responsibility for Reporting Adverse Events ..... 79
**7.3 TRIAL GOVERNANCE AND OVERSIGHT ..... 79**
7.3.1 Scientific Advisory Committee ..... 79

**8.0 STATISTICAL ANALYSIS PLAN ..... 79**
**8.1 Statistical Analysis Plan Summary ..... 79**
**8.2 Responsibility for Analyses/In-House Blinding ..... 80**
**8.3 Hypotheses/Estimation ..... 80**
**8.4 Analysis Endpoints ..... 81**
8.4.1 Efficacy Endpoints ..... 81
8.4.2 Safety Endpoints ..... 81
**8.5 Analysis Populations ..... 81**
8.5.1 Efficacy Analysis Populations ..... 81
8.5.2 Safety Analysis Populations ..... 82
**8.6 Statistical Methods ..... 82**
8.6.1 Statistical Methods for Efficacy Analyses ..... 82
8.6.2 Statistical Methods for Safety Analyses ..... 84
8.6.3 Demographic and Baseline Characteristics ..... 84
**8.7 Interim Analyses ..... 84**
**8.8 Multiplicity ..... 84**
**8.9 Sample Size and Power Calculations ..... 85**
**8.10 Subgroup Analyses and Effect of Baseline Factors ..... 86**
**8.11 Compliance (Medication Adherence) ..... 86**
**8.12 Extent of Exposure ..... 86**

**9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES ..... 86**
**9.1 Investigational Product ..... 86**
**9.2 Packaging and Labeling Information ..... 87**
**9.3 Clinical Supplies Disclosure ..... 87**
**9.4 Storage and Handling Requirements ..... 87**
**9.5 Discard/Destruction/Returns and Reconciliation ..... 87**
**9.6 Standard Policies ..... 88**
**10.0 ADMINISTRATIVE AND REGULATORY DETAILS ..... 88**
**10.1 Confidentiality ..... 88**
10.1.1 Confidentiality of Data ..... 88
10.1.2 Confidentiality of Subject Records ..... 88
10.1.3 Confidentiality of Investigator Information ..... 88
10.1.4 Confidentiality of IRB/IEC Information ..... 89
**10.2 Compliance with Financial Disclosure Requirements ..... 89**
**10.3 Compliance with Law, Audit and Debarment ..... 89**
**10.4 Compliance with Trial Registration and Results Posting Requirements ..... 91**
**10.5 Quality Management System ..... 91**
**10.6 Data Management ..... 92**
**10.7 Publications ..... 92**
**11.0 LIST OF REFERENCES ..... 94**
**12.0 APPENDICES ..... 98**
**12.1 Merck Code of Conduct for Clinical Trials ..... 98**
**12.2 Collection and Management of Specimens for Future Biomedical Research ..... 100**
**12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff ..... 104**
**12.4 ECOG Performance Status ..... 115**
**12.5 Common Terminology Criteria for Adverse Events ..... 116**
**12.6 Abbreviations ..... 117**
**13.0 SIGNATURES ..... 119**

**13.1 Sponsor's Representative ..... 119**
**13.2 Investigator ..... 119**

## LIST OF TABLES

Table 1 Adequate Organ Function Laboratory Values ..... 33
Table 2 Trial Treatment ..... 35
Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab ..... 37
Table 4 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines ..... 40
Table 5 irRECIST Imaging and Treatment after First Radiologic Evidence of PD ..... 64
Table 6 Laboratory Tests ..... 65
Table 7 Evaluating Adverse Events ..... 77
Table 8 Analysis Strategy for Key Efficacy Endpoints ..... 83
Table 9 Two-sided 95% Confidence Interval of ORR in All Comer ..... 85
Table 10 Two-sided 95% Confidence Interval for ORR in PD-L1$_H$ ..... 86
Table 11 Product Descriptions ..... 87

## LIST OF FIGURES

Figure 1 Overall Study Design ..... 17
Figure 2 Trial Diagram at Subject Level ..... 17
Figure 3 Swim Lane Plot of Tumor ..... 25

## DOCUMENT HISTORY

| Document | Date of Issue | Overall Rationale |
|---|---|---|
| 3475-100-02 | 27-JAN-2020 | Added standard extension study language |
| 3475-100-01 | 07-DEC-2017 | Expanded on cutpoint language to provide maximum flexibility to perform additional data analysis, updated language related to PK, revised guidelines for irAEs |
| 3475-100-00 | 13-NOV-2015 | Original protocol |

## SUMMARY OF CHANGES

**PRIMARY REASON(S) FOR THIS AMENDMENT:**

| Section Number (s) | Section Title(s) | Description of Change (s) | Rationale |
|---|---|---|---|
| 1.0 | Trial Summary | Added standard extension study language | To transition study into the pembrolizumab rollover |
| 5.10 | Beginning and End of the Trial | Added standard extension study language | To transition study into the pembrolizumab rollover |

**ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:**

| Section Number (s) | Section Title (s) | Description of Change (s) | Rationale |
|---|---|---|---|
| Multiple sections | Multiple sections | Minor typographical corrections | Correct minor typographical errors for clarity and consistency |

## 1.0 TRIAL SUMMARY

| | |
|---|---|
| Abbreviated Title | A Phase II Study of Pembrolizumab Monotherapy in Subjects with Advanced Recurrent Ovarian Cancer |
| Trial Phase | II |
| Clinical Indication | Advanced recurrent ovarian cancer (ROC) |
| Trial Type | Interventional |
| Type of control | No treatment control |
| Route of administration | Intravenous |
| Trial Blinding | Unblinded Open-label |
| Treatment Groups | Cohort A will enroll subjects with ROC who have received 0-2 prior lines for treating ROC (i.e., 1-3 total prior lines counting the front line) and with a platinum-free interval or treatment-free interval of 3 to 12 months based on the last regimen received.<br>Cohort B will enroll subject with ROC who have received 3 to 5 prior lines for treating ROC (i.e., 4-6 total prior lines counting the front line) and with a platinum-free interval or treatment-free interval ≥3 months based on the last regimen received.<br>In both cohorts, subjects will be treated with pembrolizumab monotherapy 200 mg every 3 weeks. |
| Number of trial subjects | Approximately 325 subjects will be enrolled. |
| Estimated duration of trial | The Sponsor estimates that the trial will require approximately 48 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit, inclusive of overall survival (OS) follow-up period. The overall survival period will last for 3 years after the final subject has been enrolled. |
| Duration of Participation | Each subject will participate in the trial from the time the subject signs the Informed Consent Form through the final protocol- specified contact.<br>The study includes three study periods: the Screening Period, the Study Treatment Period, and a Disease/ Survival Follow-up Period.<br>Screening Period: The Screening procedures should be completed within 28 days of the planned first dose. However, certain screening tests such as clinical laboratory tests must be performed within a shorter time period of the planned first dose, as specified in the Trial Flow Chart in Section 6 of the protocol.<br>Treatment Period: Each eligible subject will receive pembrolizumab monotherapy, the study treatment, at 200mg Q3W intravenously. Subject will continue treatment until disease progression is confirmed by the site per immune related Response Evaluation Criteria in Solid Tumors (irRECIST), unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, noncompliance with trial treatment or procedures requirements or administrative reasons requiring cessation of treatment, or until the subject has received 35 administrations of pembrolizumab (approximately 2 years). Subjects who have obtained a complete response (CR) prior to 24 months may stop study treatment at the discretion of his/her investigator.<br>Subjects who stop trial treatment after receiving 35 administrations of |

| | |
|---|---|
| | pembrolizumab (approximately 2 years) for reasons other than disease progression or intolerability, or subjects who attain a CR and stop trial treatment may be eligible for up to 17 additional administrations of pembrolizumab (approximately one year) upon experiencing disease progression (Section 7.1.5.2.1). The subject can be retreated only if the subject meets the criteria for retreatment and the trial is ongoing.<br>Disease/Survival Follow-up Period: After discontinuation of the study treatment, each subject will be followed for 30 days for AE monitoring (serious adverse events will be collected for 90 days after the trial treatment or 30 days after the end of treatment if the subject initiates new anti-cancer therapy, whichever is earlier). After the end of treatment, each subject will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 7.2 of the protocol.<br>Imaging-based disease assessment and serum CA 125 will be performed every 9 weeks within the first 54 weeks, and every 12 weeks thereafter until disease progression, death, withdrawal of consent or until study has achieved its primary objectives, whichever comes first. Subjects who discontinue study treatment for reasons other than disease progression, will have post-treatment follow-up for disease status until disease progression is confirmed by the site per irRECIST, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for OS until death, withdrawal of consent, or the end of the study.<br>Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study. |

| | |
|---|---|
| Randomization Ratio | N/A |

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

## 2.0 TRIAL DESIGN

### 2.1 Trial Design

#### 2.1.1 Overall Trial Design

This is a Phase 2, open-label, single-arm, two-cohort, multi-center study to evaluate efficacy and safety of pembrolizumab monotherapy 200 mg every 3 weeks (Q3W) in subjects with advanced epithelial ovarian cancer (EOC), fallopian tube cancer, or primary peritoneal cancer (will collectively refer as advanced EOC) who have demonstrated recurrent disease following the primary or interval cytoreductive/debulking surgery and the standard front line platinum–based combination therapy. The study will enroll the following 2 cohorts of subjects with recurrent ovarian cancer (ROC):

- Cohort A will enroll ROC subjects who have received 0 to 2 prior lines for treating ROC (i.e., 1 to 3 total prior lines counting the front line) and must have a platinum-free interval (PFI) or a treatment-free interval (TFI) of 3 to 12 months based on the last regimen received.

- Cohort B will enroll ROC subjects who have received 3 to 5 prior lines for treating ROC (i.e., 4 to 6 total prior lines counting the front line) and must have a PFI or TFI ≥3 months based on the last regimen received. Refer to Section 5.1.for definition of PFI and TFI and detailed inclusion and exclusion criteria for each Cohort. The trial will be conducted in conformance with Good Clinical Practices (GCP).

The study has 4 primary objectives. Primary objectives (1) and (2) are designated for Cohort A. Primary objectives (3) and (4) are designated for Cohort B.

Primary objective (1) is to evaluate objective response rate (ORR) in the first 180 enrolled subjects who fulfill the eligibility criteria for Cohort A. This group is designated as Cohort A-All Comer group. Within Cohort A-All Comer group, a minimum of 75 subjects will be enrolled for the subgroup with a PFI or TFI of 3 to <6 months and the subgroup with a PFI or TFI of 6 to 12 months. The primary analysis of ORR will be based on the assessment by a central imaging vendor (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, in Section 11.0.

Primary objective (2) is to evaluate ORR in subjects who fulfill the eligibility criteria for Cohort A and with higher expression of program cell death-ligand protein 1 (PD-L1) in tumor tissue samples. It is expected that higher PD-L1 expression in tumor tissue will be associated with better clinical responses to pembrolizumab (refer to Section 4 for background and rationale). In order to achieve this primary objective, a PD-L1 expression cutpoint will first be established with a goal to enrich the population for better clinical benefit. The cutpoint will be determined during the planned interim analysis using the clinical efficacy data and PD-L1 expression data from the first 100 enrolled Cohort A subjects. This data set is designated as the "training set" (refer to Section 8.7 on the approach for determining the PD-L1 cutpoint). In order to confirm the association of higher PD-L1 expression with increased clinical activity by pembrolizumab treatment, another 150 subjects who fulfill eligibility criteria for Cohort A will be enrolled, which is designated as the "confirmation set". Cohort A will therefore, enroll a total of 250 subjects. Based on the established PD-L1 cutpoint from the training set, subjects in the confirmation set will be assigned into the subgroup with PD-L1 expression above or equal to the cutpoint (i.e., Cohort A PD-$L1_H$) or the subgroup with PD-L1 expression below the cutpoint (i.e., Cohort A PD-$L1_L$). Enrollment into Cohort A will not be interrupted for interim analysis. However, in order to ensure data integrity, samples from the "confirmation set" will not be assessed for PD-L1 expression until the cutpoint has been established and the assay has been confirmed. Based on the prevalence data regarding higher PD-L1 expression, the total enrollment of Cohort A may be increased to up to 280 to ensure a minimum of 60 subjects from the confirmation set (see below) will have PD-L1 expression above the expected cutpoint.

Approximately 75 subjects will be enrolled into Cohort B regardless of PD-L1 expression status. Primary objective (3) is to evaluate ORR in all enrolled subjects who fulfill the eligibility criteria for Cohort B. This group is designated as Cohort B-All Comer group. Primary objective (4) is to evaluate ORR in subjects enrolled into Cohort B who have tumor tissue PD-L1 expression above the clinical cutpoint established from the Cohort A training set. The population supporting primary objective (4) is designated as Cohort B PD-$L1_H$ group. Tumor tissue samples from Cohort B will not be evaluated until a cutpoint has been established from Cohort A training set.

As part of the inclusion criteria, all subjects must provide a tumor tissue sample collected either from a recent biopsy or prior cytoreductive surgery in order to be enrolled. Part of the tumor tissue sample will be submitted to a designated central laboratory for assessing PD-L1 expression via an immunohistochemistry (IHC) assay. PD-L1 positivity is determined using the combined positive score, which is defined as the percent PD-L1 positive cells counting tumor cells, immune-infiltrating cells and cells from adjacent stroma relative to total tumor cells. Details will be provided in a separate document.

Clinical cut-off for interim analysis will be at least 4 months after the one-hundredth Cohort A subject has been enrolled to allow adequate clinical follow up. For each designated study population (i.e., Cohort A-All Comer, Cohort A PD-$L1_{H,}$ or Cohort B), the clinical cut-off for the final analysis of the primary endpoint ORR will be at least 8 months after the last subject for each population has been enrolled. The final clinical cut-off for the study (i.e., study completion) will be 3 years after the last subject is enrolled for final overall survival (OS) analysis. Refer to Sections 3.2 and 3.3 for details regarding secondary and exploratory study objectives, and Figure 1 in Section 2.2 for illustration of the overall study design.

### 2.1.2 Trial Diagram at Individual Subject Level

This section applies to all subjects who have enrolled to the study. The study includes a 28-day Screening Period, a Study Treatment Period and a Disease/Survival Follow-up Period. Subjects must have measurable disease per RECIST 1.1, as confirmed by the BICR, and must have provided adequate tumor tissue samples in order to be eligible. After an eligible subject is enrolled, the subject will receive pembrolizumab monotherapy 200 mg Q3W via intravenous (IV) infusion until confirmed disease progression as assessed by the investigator, unacceptable toxicity, death, withdrawal of consent, or having received 35 administrations (approximately 2 years) of pembrolizumab treatment without disease progression. In order to prevent premature study treatment discontinuation due to pseudoprogression, immune-related RECIST (irRECIST) will be used for confirmation of disease progression (refer to Section 7.1.2.6.7 for details). Decisions regarding stopping pembrolizumab after a confirmed complete response (CR) and guidelines on retreatment are detailed in Section 7.1.5.2.1.

During study treatment period, subject will have clinic visits Q3W for safety assessments and pembrolizumab infusion. Imaging-based disease assessments will occur every 9 weeks (Q9W) from study entry until Week 54 and every 12 weeks (Q12W) thereafter until disease progression is determined by the investigator per irRECIST, subject's death, withdrawal of consent, initiation of a new anti-cancer therapy, study completion or early termination. Cancer antigen 125 (CA125) will be collected at baseline and at the time of each imaging assessment, However, CA125 should not be used by the investigator to determine disease progression in this study. The trial diagram at subject level is depicted in Figure 2 in Section 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.

.

## 2.2 Trial Diagram

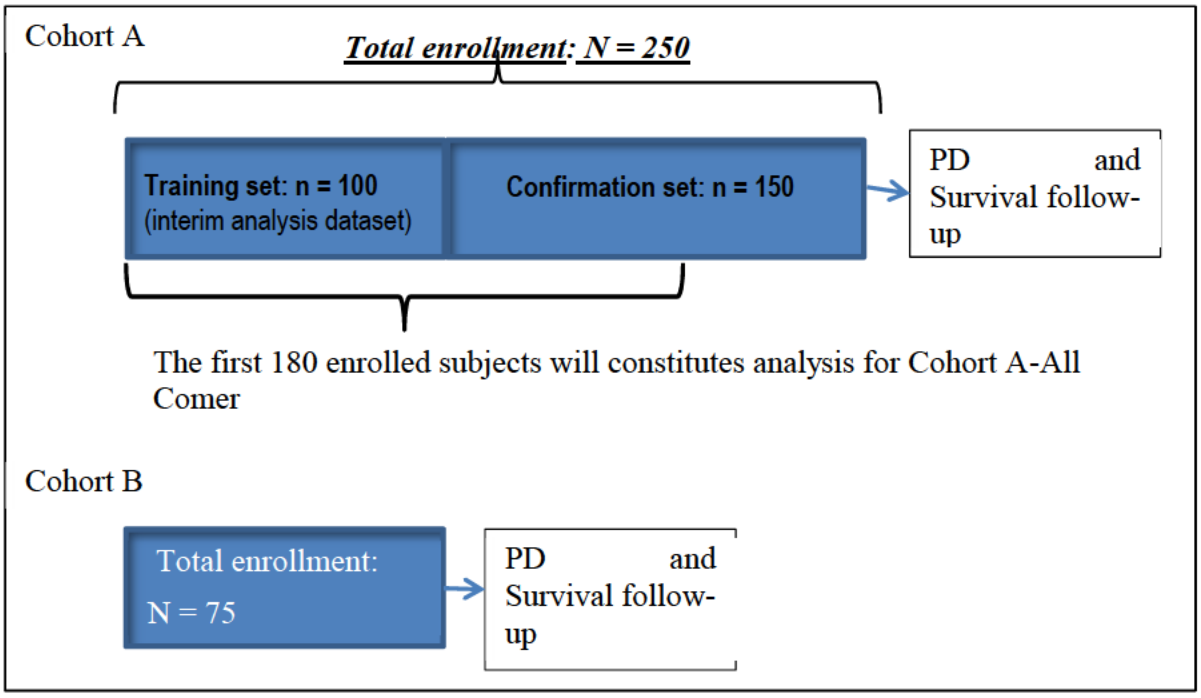


Figure 1 Overall Study Design

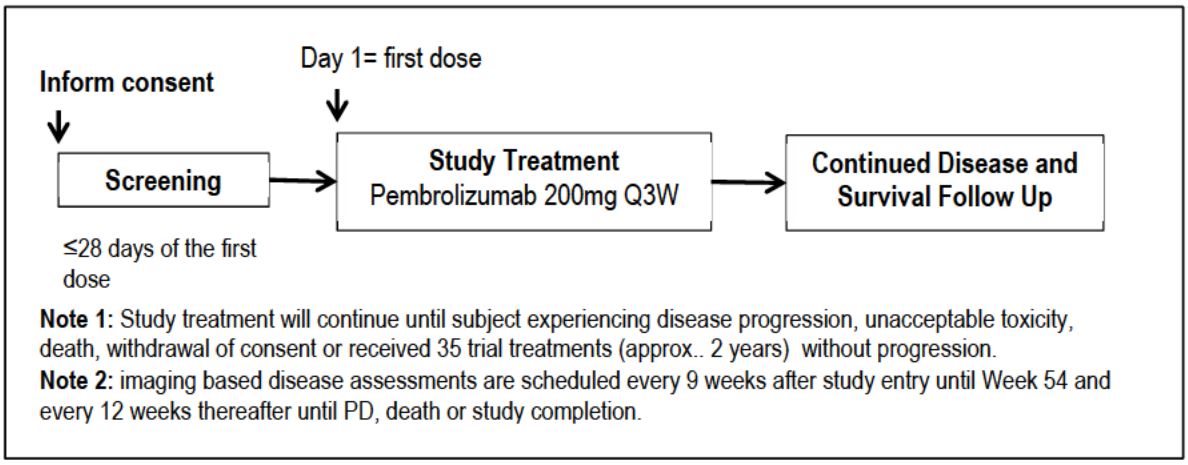


Figure 2 Trial Diagram at Subject Level

## 3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

### 3.1 Primary Objective(s) & Hypothesis(es)

In subjects with advanced ROC:

1) **Objective:** To evaluate clinical anti-tumor activity of pembrolizumab monotherapy based on ORR as assessed by BICR per RECIST 1.1 in Cohort A-All Comer group as defined in Section 2.1
2) **Objective:** To evaluate clinical anti-tumor activity of pembrolizumab monotherapy based on ORR as assessed by BICR per RECIST 1.1 in Cohort A-PD-$L1_H$ subgroup, as defined in Section 2.1, using a PD-L1 expression cutpoint established in the training set.
3) **Objectiv**e: To evaluate clinical anti-tumor activity of pembrolizumab monotherapy based on ORR as assessed by BICR per RECIST 1.1 in Cohort B-All Comer group as defined in Section 2.1
4) **Objective:** To evaluate clinical anti-tumor activity of pembrolizumab monotherapy based on ORR as assessed by BICR per RECIST 1.1 in Cohort B PD-$L1_H$ subgroup, as defined in Section 2.1, using a PD-L1 expression cutpoint established in the training set from Cohort A

The primary objectives will focus on estimation of ORR, and no formal hypothesis testing is planned. If the operating characteristics associated with a single biomarker cutpoint are not sufficiently optimized, up to 2 biomarker cutpoints may be carried forward for efficacy endpoint analyses (see Section 8.6.1).

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

In subjects with advanced ROC:

1) **Objective**: To evaluate duration of response (DOR), disease control rate (DCR) and progression-free survival (PFS) as assessed by BICR per RECIST 1.1 in Cohort A-All Comer group, Cohort A-PD-$L1_H$ subgroup, Cohort B-All Comer group, Cohort B-PD-$L1_H$ subgroup respectively, after treated with pembrolizumab monotherapy. PFS rate at 6, 12, and 18 months will also be evaluated.
2) **Objective**: To evaluate ORR, DOR, DCR, and PFS as assessed by investigator per RECIST1.1 in Cohort A-All Comer group, Cohort A-PD-$L1_H$ subgroup, Cohort B-All Comer group, Cohort B-PD-$L1_H$ subgroup, respectively, after treated with pembrolizumab monotherapy
3) **Objective**: To evaluate ORR, DOR, DCR and PFS as assessed by BICR and by investigator per RECIST 1.1, in Cohort A-All Comer subgroup with PFI/TFI ≥3 to 6 months and the subgroup with PFI/TFI >6 to 12 months, respectively, after treated with pembrolizumab monotherapy.
4) **Objective**: To evaluate OS in Cohort A-All Comer group, Cohort A-PD-$L1_H$ subgroup, Cohort A-All Comer subgroup with PFI/TFI ≥3 to 6 months and the

subgroup with PFI/TFI >6 to 12 months, Cohort B-All Comer group, Cohort B-PD-L1$_H$ subgroup, after treated with pembrolizumab monotherapy.

5) **Objective:** To evaluate and characterize the tolerability and safety profile of the entire study population and by cohorts and subgroups, respectively, after treated with pembrolizumab monotherapy.

No formal hypotheses will be tested for secondary objectives.

### 3.3 Exploratory Objectives

1) To evaluate ORR, DOR, PFS as assessed by BICR per irRECIST 1.1.
2) To evaluate ORR, DOR, PFS as assessed by investigator per Gynecologic Cancer InterGroup (GCIG) criteria [2].
3) To characterize tumor microenvironment for immune-related features such as immune-related messenger RNA expression signatures, presence of tumor-infiltrating lymphocytes (TILs), PD-L1/ program cell death-ligand protein 2 (PD-L2) expression; and to characterize genetic changes/aberrations and mutational burdens within tumor tissues.
4) To assess correlations of the biomarkers and the clinical activity observed in the overall study population and various subgroups following pembrolizumab treatment.
5) Additional translational research may include T-cell clonality, neoantigen expression, presence and changes in circulating tumor markers such as circulating tumor DNA, serum microRNA and protein changes at screening and following pembrolizumab treatment, and evaluation of pharmacokinetics of pembrolizumab.
6) Variation across the human genome may be analyzed for association with clinical efficacy and/or safety data collected in this study.

For definitions of endpoints, refer to Section 8.4.1.

## 4.0 BACKGROUND & RATIONALE

### 4.1 Background

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

### 4.1.1 Pharmaceutical and Therapeutic Background

#### 4.1.1.1 Disease Background

***Epidemiology and Histologic Categorization of Ovarian Cancer***

Ovarian cancer is the most lethal gynecologic cancer and the fifth-leading cause of cancer death among women in the United States (US). In the US, the estimated number of new cases and deaths from ovarian cancer in 2014 was 21,980 and 14,270, respectively. Due to lack of tumor-specific signs and symptoms and effective screening tests for early detection, over 70% of ovarian cancer patients are first diagnosed at advanced stages. Based on the US data from 2003 to 2009, at initially diagnosis, 61% had distant metastasis, 18% had regional disease and only 21% had localized disease. The overall 5-year survival rate of ovarian cancer was approximately 44% counting all stages; the 5-year survival rate in patients with distant metastasis was only 27% [3].

Epithelial ovarian cancer accounts for >90% of the ovarian cancer and has been recognized as a group of heterogeneous diseases with distinct histopathologic features, genetic alterations and clinical behaviors. Five main EOC subtypes have recently been designated by The International Federation of Gynecology and Obstetrics: high-grade serious carcinoma ([HGSC], accounts for ~70% EOC), endometrioid carcinoma (~10% EOC), clear cell carcinoma (~10% EOC), mucinous carcinoma (~3% EOC), low-grade serous carcinoma (5% EOC), and those that are unclassifiable [4; 5]. Primary peritoneal carcinoma and fallopian tube carcinoma have typically been managed and studied together with EOC as they share similar clinic-pathologic characteristics with HGSC.

***Current Standard Treatment and Area with Unmet Medical Need***

The standard primary treatments for advanced EOC include primary cytoreductive/debulking surgery followed by postoperative front line (i.e., adjuvant) systemic treatment with carboplatin and paclitaxel Q3W IV for 6 cycles. However, weekly paclitaxel has also been frequently used to replace Q3W paclitaxel. In suitable cases, postoperative chemotherapy, usually cisplatin plus paclitaxel, can be delivered via intraperitoneal (IP) route. In cases with bulky diseases that are initially non-operable, neoadjuvant therapy can be given prior to cytoreductive surgery (i.e., interval cytoreductive surgery) then followed by standard platinum/taxane-based chemotherapy [6; 7].

The goal of cytoreductive surgery is to achieve resection of all visible tumors and the goal of postoperative first line chemotherapy are: 1) to help achieving complete remission in those with residual disease, and 2) to prevent disease recurrence for those with complete tumor resection. However, after these primary treatments, only a small proportion of patients will achieve long-term disease-free and survival status. In a meta-analysis performed by du Bois et al [8] on data from 3 randomized trials following the standard primary treatment with surgery and platinum-taxane based chemotherapy (N=3126), only 24% of patients were recurrent free after a median follow up time of 53.9 months and the remaining 76% had disease recurred or progressed. The overall 5-year PFS and OS rate was 22.6% and 39.0%, respectively. Based on time to recurrence (TTR) since the last dose of platinum treatment, 22% recurred 0 to 6 months, 22.5% recurred 6 to 12 months, and 31.6% recurred >12 months. By 12 months, the 12-month survival rate was 30.6%, 55.1%, and 66.1% in the

group with TTR to -6 months, TTR 6 to 12 months, and TTR >12 months, respectively; the 24-month survival rate was 13.8%, 24.4%, and 34.9% in these 3 groups, respectively. This data showed an overall poor prognosis for patients with recurrent disease especially in those with a short TTR.

At present, ROC is considered not curable with the available choices of therapies and is an area of highly unmet medical need.

Selection of treatment for ROC should take into consideration several factors including: sensitivity to first-line platinum-based therapy, as measured by PFI, prior toxicity, comorbidity, age, and performance status. Platinum-free interval, which is defined as the period from the cessation of the primary platinum-based chemotherapy to disease recurrence or progression, has been recognized as an important surrogate for prognosis and predicting response to chemotherapy. Based on PFI, ROC can be divided into the following subgroups: platinum-sensitive (PFI >12 months), partially platinum-sensitive (PFI of 6 to 12 months), platinum-resistant (PFI >1 to <6 months), and platinum-refractory (PFI ≤4 weeks or progression on treatment) according to the consensus achieved by the GCIG in 2010 [9].

Based on the current National Comprehensive Cancer Network and European Society for Medical Oncology guidelines, patients with platinum-resistant ROC can be treated with either single-agent chemotherapy such as gemcitabine, pegylated liposomal doxorubicin (PLD), weekly paclitaxel, topotecan, and docetaxel, or bevacizumab in combination with gemcitabine or weekly paclitaxel or topotecan. These single agents had shown similar clinical efficacy with a response rate around 15% to 20%, median PFS of 3 to 5 months and median OS of 10 to 12 months [10; 11]. Bevacizumab plus single-agent chemotherapy showed an improved PFS compared to single-agent chemotherapy alone (6.7 versus 3.4 months, hazard ratio [HR]: 0.48, p <0.001) and an improved response rate (27.3% versus 11.8%) via a randomized Phase 3 trial, AURELIA [12]. However, the study didn't demonstrate OS benefit; and based on the Kaplan-Meier (KM) curve, less than 20% of subjects in the bevacizumab chemotherapy arm remained progression-free by 12 months, and even less in the single-agent chemotherapy arm. Platinum-resistant ROC, hence, is an area with high unmet medical need for novel therapies that can deliver durable clinical benefit.

Partially platinum-sensitive ROC (i.e., PFI >6 to 12 months), which used to be classified as part of the platinum-sensitive group, has been considered a challenging group to manage [13; 14]. Even though the recommended treatment for partially platinum-sensitive ROC remains the same as those for platinum-sensitive ROC (i.e., re-treated with a platinum-containing doublet), the partially platinum-sensitive group has significantly reduced clinical benefit compared to those with PFI >12 months. For example, in a review of 583 ROC patients from 6 Phase 2-3 clinical trials by Pujade-Lauraine et. al. [15] on the impact of TFI, on clinical response to salvage therapy, patients with TFI of 3 to 12 months showed an ORR of 35% compared to an ORR of 52% in the group with TFI of 12 to 18 months. Median time to progression and OS in the group with TFI of 3 to 12 months was much shorter (174 days and 393 days, respectively) compared to the group with TFI of 12 to 18 months (275 days and 657 days, respectively). In the Phase 3 trial CALYPSO [16] that compared carboplatin plus PLD (CD) versus carboplatin plus paclitaxel (CP), Overall survival was significantly longer in subjects with TFI ≥12 months versus subjects with TFI 6 to 12 months based on multivariate analysis (HR = 0.5; 95% confidence interval [CI] 0.43, 0.59; p<0.001). In the CALYPSO trial, median PFS in the partial platinum-sensitive subpopulation was 9.4 months

for the CD arm and 8.8 months for the CP arm; ORR was 39% in the CD arm and 45% in the CP arm. However, when taking a closer look at the KM PFS curve for partial platinum-sensitive subgroup in this study, less than 20% patients in the CP arm and a little over 20% in the CD arm remained progression-free at 12 months [17].

In a meta-analysis by Hanker et al [18] charterizing impact of second to sixth line of therapy on survival of relapsed ovarian cancer, data of n=1620 patients from 3 large randomized Phase 3 trials investigating primary therapy was included. The results showed that median PFS after the first, second, third, fourth and fifth relapse was 10.2 [95% CI 9.6 to 10.7], 6.4 (5.9 to 7.0), 5.6 (4.8 to 6.2), 4.4 (3.7 to 4.9) and 4.1 (3.0 to 5.1) months, respectively. Median OS after the first, second, third, fourth and fifth relapse was 17.6 (95% CI 16.4 to 18.6), 11.3 (10.4 to 12.9), 8.9 (7.8 to 9.9), 6.2 (5.1 to 7.7) and 5.0 (3.8 to 10.4) months, respectively. The overall clinical benefit greatly reduced with increased lines of therapy.

In addition to reduced clinical benefit and lack of long-lasting clinical activities from the existing therapies in this group, toxicities from prior or planned platinum doublets further limit the utility of these treatments in this subgroup [13]. Novel therapies with durable clinical efficacy and better safety profile are highly needed for the treatment of partially platinum-sensitive as well as platinum-resistant ROC.

#### 4.1.1.2 Targeting PD-1 Immune Checkpoints for Cancer Treatment

Adaptive immune system plays a major role in controlling and eradicating cancer via a process called cancer immunosurveillance. Cytotoxic T lymphocytes cells (CTLs, also called CD8+ or effector T-cells), which are central to responses within the adaptive immunity, can be activated and execute cell killing function upon recognizing tumor-specific or tumor-associated antigens presented by antigen-presenting cells [19; 20; 21].

T-cell activation is tightly controlled by co-stimulatory and co-inhibitory signals, which are triggered by the interactions between T-cell receptors and their ligands. The inhibitory pathways, also called immune checkpoints, are crucial for maintaining self-tolerance and minimizing collateral tissue damage in the event of immune response to pathogens. PD-1 is a member of the extended CD28/CTLA4 family of T-cell regulators. PD-1-mediated immune checkpoint plays a key role in controlling effector T-cell activities within peripheral tissues, including tumors. Binding of PD-1 to PD-L1 and/or PD-L2 will trigger downstream signaling inside T-cells leading to decreased cytokine production such as IL-2 and interferon γ, inhibition of cell proliferation, reduced T-cell effector function and survival [19; 22; 23, 24].

Human cancer can exploit immune checkpoint pathways to escape immunosurveillance. Restoration of endogenous anti-cancer immunity by immune checkpoint blockade has thus become an attractive strategy of cancer immunotherapy. The success in the clinical development of immune checkpoint inhibitors, in particular the PD-L1 inhibitors, has significantly changed the landscape of cancer treatment [20; 21; 25; 22; 26; 27].

#### 4.1.1.3 Anti-PD-1 Antibody Pembrolizumab

Pembrolizumab (also referred to as MK-3475) is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-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. As of January 2015, pembrolizumab safety and clinical activities have been evaluated in approximately 8,000 patients across multiple tumor types via Merck-sponsored clinical trials and the melanoma Expanded Access Program. Pembrolizumab was generally well tolerated. In September 2014, pembrolizumab monotherapy received an accelerated approval by the Food and Drug Administration for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and a BRAF inhibitor if BRAF V600 mutation positive, with a recommended dose of 2mg/kg Q3W [28]. Refer to pembrolizumab clinical investigator brochure and the US label for details regarding pembrolizumab preclinical and clinical pharmacology studies as well as clinical safety.

### 4.1.2 Summary of Pembrolizumab Clinical Activities

***Pembrolizumab clinical activity in advanced melanoma***

In study Keynote 001 (KN001), the Phase 1 first time in human study, pembrolizumab was evaluated in a cohort of 135 subjects with advanced melanoma who were either treatment-naïve (31%) or had progressed from prior ipilimumab (69%), at a dosage of 2 mg/kg Q3W, 10 mg/kg every 2 week (Q2W), or 10 mg/kg Q3W. The study showed an ORR of 38% (95% CI: 25% to 44%) in the overall population. Response was durable in the majority of subjects; median DOR was not reached with median follow up of 11 months [29]. In an expansion cohort, 173 subjects with advanced melanoma who had progressed from prior ipilimumab were randomly assigned to receive pembrolizumab 2mg/kg Q3W or 10mg/kg Q3W. Similar efficacy results were observed in the 2 arms: ORR was 26% in each arm; DCR was 51% and 50%, respectively. With a median follow-up of 8 months, 88% of responders were still ongoing at the clinical cut-off. Even though most responses were observed at the first scan, initial response could occur as late as 11 months and CR could occur as late as 16 months [30].

Clinical efficacy of pembrolizumab in advanced melanoma was further demonstrated via 2 large randomized trials. In study Keynote 002 (KN002) (N=540), efficacy and safety of pembrolizumab 2mg/kg Q3W or 10mg/kg Q3W were compared with chemotherapy in subjects refractory to ipilimumab. PFS (6-months PFS rate) was significantly improved in the 2 pembrolizumab arms compared with the chemotherapy arms. Overall response rate per independent review was 21% in the pembrolizumab 2 mg/kg Q3W arm, 25% in the 10 mg/kg Q3W arm compared to 4% in the chemotherapy arm ($P<0.0001$ for both comparisons). At the time of analysis, median DOR in the pembrolizumab arms was not reached; responses were ongoing in 92% and 87% of responders in the 2 pembrolizumab arms, respectively, versus 63% in the chemotherapy arm. There was no statistically significant difference in efficacy parameters between the 2 pembrolizumab arms [31].

In Phase 3 Study Keynote 006 (KN006) (N=834), unresectable advanced melanoma population), subjects that received pembrolizumab (10mg/kg Q2W or 10mg/kg Q3W) showed statistically significant and clinically meaningful improvement compared to those that received ipilimumab in estimated 6-months PFS rate (47.3%, 46.4% and 26.5%, respectively), one-year OS rate (74.1%, 68.4% and 58.2%, respectively), and ORR (33.7%, 32.9% and 11.9%, respectively). At the time of analysis, median OS was not reached in any treatment group. Responses were ongoing in 89.4% and 96.7% of the Q2W and Q3W

pembrolizumab-treated groups, respectively and in 87.9% of ipilimumab-treated patients after a median follow-up of 7.9 months [32].

***Pembrolizumab clinical activity in advanced NSCLC***

In study KN001, clinical efficacy and safety were evaluated in 495 subjects with advanced non-small cell lung cancer (NSCLC) after receiving pembrolizumab treatment at 2 mg/kg Q3W, 10mg/kg Q3W, or 10mg/kg Q2W dose, respectively. The study also evaluated the association between PD-L1 expression in tumor tissue samples and the clinical efficacy by assigning 182 subjects to the training set and 313 subjects to the validation set. In the overall population (N=495), ORR was 19.4% (95% CI, 16.0 to 23.2); median DOR was 12.5 months. In the validation data set, ORR was 45.2% (95% CI, 33.5 to 57.3) in subjects with ≥50% of tumor cells positive for PD-L1 expression (n=73); ORR was 16.5% (95% CI, 9.9 to 25.1) in patients with 1% to 49% tumor cells positive (n=103) and 10.7% (95% CI, 2.3 to 28.2) in patients with <1% tumor cells positive (n=28) for PD-L1 expression. This data indicates a potential for PD-L1 to be used as a patient enrichment biomarker for better clinical efficacy [33].

***Pembrolizumab clinical activity in other advanced cancers***

Study Keynote 012 (KN012) is an ongoing non-randomized multi-cohort Phase 1b study evaluated safety and clinical activities of pembrolizumab 10mg/kg Q2W in subjects with advanced solid tumors that have positive PD-L1 expression either in tumor cells or stroma cells. Most of these subjects were heavily pretreated. Subjects with advanced gastric cancer, head and neck cancer, urothelial track cancer and triple negative breast cancer were enrolled. An ORR of 31% was observed in subjects with advanced gastric cancers (N=39) [34]; an ORR of 27.6% (95% CI, 12.7 to 47.2%) was observed in subjects with advanced urothelial tract cancer (N=33) [35]; an ORR of 24.8% (95% CI, 17.3 to 33.6%) was observed in subjects with advanced head and neck cancer (N=132) [36]. Impressive responses have also been reported by Nanda, et. al., in triple negative breast cancer at the 2014 San Antonio Breast Cancer Symposium [37]. In all these cohorts, durable responses were observed in those who responded including some durable stable diseases. Higher PD-L1 expression seemed to associate with higher response.

***Pembrolizumab clinical activity in advanced ovarian cancer***

Study Keynote 028 (KN028) is an ongoing Phase 1b open-label, non-randomized multi-cohort study evaluating clinical activity of pembrolizumab monotherapy 10mg/kg Q2W in advanced solid tumors. A cohort of 26 subjects with advanced ovarian cancer that have failed prior chemotherapies was included. All enrolled subjects had positive PD-L1 expression, which was defined as ≥1% of cells in tumor nests or PD-L1+ bands in stroma as determined by a prototype IHC assay at a central laboratory. Twenty-six ovarian cancer subjects were enrolled. Mean (standard deviation) age was 58.1 (7.5) years; 57.7% were white. 84.6% received prior therapies for recurrent/metastatic disease (38.5% received ≥5 therapies), and 50% received prior adjuvant therapies. The best overall (confirmed) response was 11.5% (n=3/26, 95% CI: 2.4, 30.2); 1 subject achieved CR and 2 subjects experienced partial response (PR). Six out of 26 subjects (23.1%) achieved stable disease (SD). As of clinical cut-off of 04-AUG-2015, the 3 responders and 1 subject with SD were still on pembrolizumab treatment without progression: 1 subject was still ongoing for >46 weeks and 3 were still ongoing for >52 weeks. Another subject with SD showed

progression at 48 weeks. In a retrospective analysis, subjects were separated into 2 subgroups based on TFI between the last dose of their last anti-cancer regimen and the first dose of pembrolizumab. In the subgroup with TFI of less than 3 months (n=15), there were 3 SDs, including the ongoing SD, with no responders; in the subgroup with TFI ≥3 months (n=11), there were 3 responders and 3 SDs including the SD that progressed at 48 weeks. Figure 3 is a swimmer plot showing tumor response changes from baseline over time in the ovarian cohort.

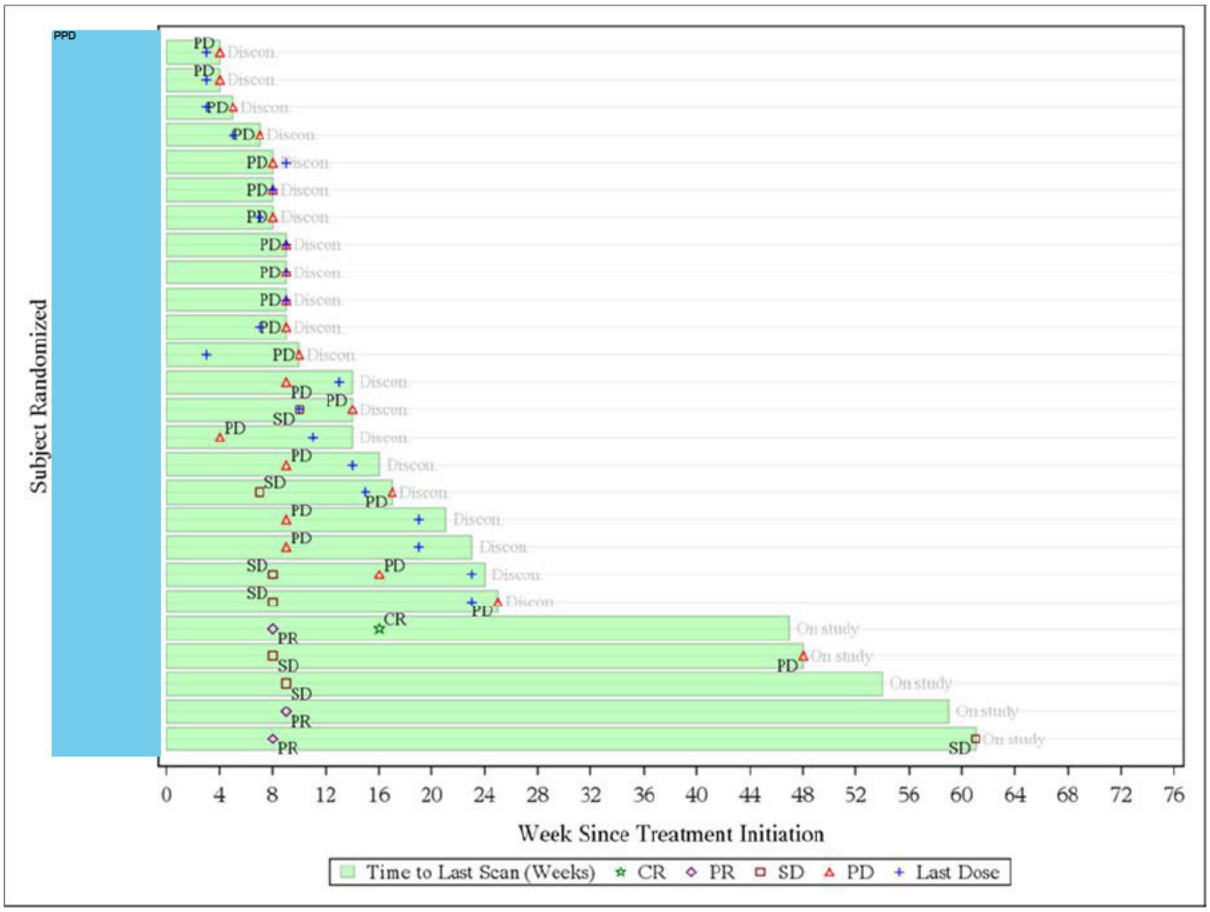


Figure 3 Swim Lane Plot of Tumor

Based on data seen to date, clinical activities generated by pembrolizumab seem to show the following unique characteristics: 1) broad clinical activities have been observed across multiple tumor types; 2) tumor responses tend to be durable; 3) tumor PD-L1 expression level seems to have an association with increased clinical activity. These observations are consistent with clinical activities observed in other PD-1 checkpoint inhibitors [38].

## 4.2 Rationale

### 4.2.1 Rationale for the Trial and Selected Subject Population

In this study, we will evaluate efficacy and safety of pembrolizumab monotherapy in subjects with ROC who have received up to 5 prior lines of treatment for ROC (i.e., 1 to 6 total prior lines counting front line). The study population is separated into 2 cohorts based on the

number of lines of prior treatments. Even though over 70% to 80% of patients will be in remission following the primary treatment, majority of them will relapse within 3 years. Currently, there are no curative treatments available for ROC; therefore, this is an area of high unmet medical need. Patients with ROC can response to platinum-based or non platinum-based therapies with varied response rate; however, the responses are mostly short-lived, especially in the setting with a PFI/TFI within 12 months. Even though some patients will receive multiple lines of treatments, they will eventually develop refractory and die. Treatment-related toxicities can be overwhelming especially for those who receive combination chemotherapy therapy. In addition to extending survival and delaying symptomatic disease progression, the goal of treatment in this setting also includes to improve quality of life. Novel agents that can deliver, curative or long-lasting anti-cancer effect with good tolerability are highly needed in this setting.

PD-1/PD-L1 immune checkpoint inhibitors like pembrolizumab have shown high anti-cancer activity in a wide range of solid tumors as well as hematologic malignancies. Unprecedented durable clinical activities have been observed in various advanced cancer indications such as melanoma, NSCLC, etc. Pembrolizumab has shown preliminary clinical activity in a small cohort of advanced ovarian cancer patients in Study KN028. Most subjects were heavily pretreated and became chemorefractory. Even though the observed response rate is relatively low (11.8%), however, 3 subjects with PR and 1 subject with stable disease were still on pembrolizumab treatment for >48 weeks without progressive disease (3 have passed 52 weeks) as of 04-AUG-2015, the clinical cut-off for this dataset. Another subject with SD progressed at 36 weeks. In a retrospective analysis, subjects with TFI of less than 3 months (90 days) from their last dose of anti-cancer treatment to the first dose of pembrolizumab (n=15) showed limited activity with 3 SDs and no responders. In the subgroup with TFI ≥3 months (n=11), there were 3 PRs and 3 SD including one with SD for 36 weeks (see Figure 3).

The study will enroll 2 separate cohorts of ROC subjects based on the number of prior lines received for ROC. All subjects are required to have a PFI/TFI of ≥3 months based on the last regimen received as based on the preliminary data from study KN028, those with short PFI/TFI of <3 months had very limited activity compared to those with PFI/TFI of ≥3 months. Whether this is due to higher immune suppression is unclear. In Cohort A, approximately 250 subjects with PFI or TFI of 3 to 12 months based on their last treatment, regardless of their PD-L1 expression status. The clinical activities in the overall population (All Comer) will be evaluated. The study will also evaluate the correlation of clinical activity and PD-L1 expression with a goal to identify a subgroup with better clinical benefit. In order to achieve this primary objective, the study population is separated into 2 parts, with first data from the 100 subjects being used as the "training set" for determining the cutpoint; the remaining subjects are used as the "confirmation set" for confirming the clinical activity in the biomarker selected population. Cohort B will enroll approximately 75 subjects with multiple lines of prior treatments to evaluate clinical activity and biomarker correlation.

### 4.2.2 Rationale for Dose Selection/Regimen/Modification

The planned dose of pembrolizumab for this trial is 200 mg Q3W. Based on the totality of data generated in the KEYTRUDA™ development program, 200 mg Q3W is the appropriate

dose of pembrolizumab across all indications and regardless of tumor type. As outlined below, this dose is justified by:

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

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and NSCLC, covering different disease settings (treatment-naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 B2, KN001 D, KN002, KN010 and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 B3, KN001 F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

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

### 4.2.3 Rationale for Endpoints

#### 4.2.3.1 Efficacy Endpoints

The study is designed as a Phase 2 single-arm study to explore clinical activities in subjects with platinum-resistant and partially platinum-sensitive ROC with ORR selected as the primary endpoint. The primary analysis of ORR will be based on the disease assessment by central imaging vendor per RECIST 1.1 to avoid bias. Progression-free survival and OS are

not appropriate as the primary endpoint for a single-arm trial. However, PFS, OS, DOR, DCR are included as secondary endpoints. It is worth noting that based on the available data, pembrolizumab has shown durable responses in several indications with long-term data such as melanoma and NSCLC. In addition, subjects with SD can stay in SD for an extended period as shown with the preliminary data of pembrolizumab in ovarian cancer (see Figure 3). Collectively, the study will show anti-tumor response rate as well as durability of response, disease control rate, PFS rate at certain time points. These can give a picture of overall anti-tumor activities of pembrolizumab in the selected ovarian cancer population and various subpopulations.

#### 4.2.3.2 Immune-related RECIST (irRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may, thus, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab.

Based on an analysis of patients with melanoma enrolled in KN001, 7% of evaluable patients experienced delayed or early tumor pseudoprogression. Of note, patients who had progressive disease by RECIST 1.1, but not by irRECIST, had longer OS than patients with progressive disease by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of patients. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enable treatment beyond initial radiographic progression.

Immune-related RECIST (i.e., irRECIST) is RECIST 1.1 adapted to account for the unique tumor response seen with immuno-therapeutics as described by Nishino et al.[39]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, Merck has implemented an adaptation related to new lesions, non-target and tumor burden assessment in order to confirm radiographic progression. irRECIST will be used by investigators to confirm disease progression and make treatment decisions. irRECIST will also be used for analyzing imaging based endpoint per assessment by central imaging vendor.

#### 4.2.3.3 Safety Endpoints

The safety objective is to characterize the safety and tolerability of pembrolizumab in subjects with advanced ovarian cancer. The following safety parameters will be analyzed: adverse events (AEs) and serious adverse events (SAEs) graded per National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0 criteria with time to onset/recovery, causality and outcome; changes in laboratory values, vital signs since baseline, treatment discontinuations and reason for discontinuation, and death and cause of death. Concomitant medications will be collected with time and reasons of use. These are routine safety parameters collected and analyzed in Phase 2/3 oncology trials. Furthermore,

specific immune-related adverse events (irAEs) will be collected as described in Section 5.2.1.2.

#### 4.2.3.4 Planned Biomarker Research

Even though PD-1 checkpoint inhibitors like pembrolizumab have shown unprecedented anti-cancer activities across a wide range of cancers, a good portion of patients are not responding to the treatments. Recent efforts have been sought to evaluate how the immune system functions and is regulated inside the tumor microenvironment.

**Tumor PD-L1 Expression**

High expression of PD-L1 was frequently found in tumor tissue samples of different cancer types including ovarian cancer and was often found correlated with poor prognosis or survival [40]. High PD-L1 expression has been associated with increased response to pembrolizumab treatment in advanced melanoma and NSCLC patients [32; 33] and has been used to enrich patient population with high response to pembrolizumab [41]. Therefore, the relationship between PD-L1 expression in ovarian tumor tissue and clinical activities by pembrolizumab will be evaluated. PD-L1 expression in tumor cells and inflammatory cells within pre-treatment tumor tissue samples will be characterized by IHC.

**Tumor-infiltrating Lymphocytes**

Tumor-infiltrating lymphocytes are frequently found inside tumor tissues indicating the presence of an immune response. In a pooled analysis across various cancer types for the presence of different TILs in tumor tissues, Presence of CD3+ TILs or CD8+ TILs was found to have a positive effect on survival in patients with various solid tumors including ovarian cancer. However, FoxP3+ TILs were not correlated with survival [42]. In a recent analysis of tumor tissue samples from melanoma patients treated with pembrolizumab, Tumeh et al found that responding patients have a much higher density of CD8+, PD-1+ and PD-L1+ cells at invasive margin as well as inside tumors compared to those who progress, suggesting that responding to PD-1 blockade requires pre-existing CD8+ T-cells that are negatively regulated by PD-1/PD-L1 mediated adaptive immune resistance [43]. Therefore CD8+, FoxP3 TILs will be evaluated using IHC for their ability to predict response to pembrolizumab.

**Immune-related Gene Expression Profile**

Gene expression profile (GEP) may be analyzed using archival tumor tissue samples from the enrolled ovarian cancer subjects using the NanoString platform. Association between GEP and response to pembrolizumab have been established using data from clinical studies KN012 (head and neck, bladder, gastric cancers) and KN028 (ovarian, esophageal, and other cancers). These signatures, which include genes from immune-regulatory pathways, may be tested for their association with response to pembrolizumab. The relationship between GEP and the probability of response may be used to identify subgroup that may have high clinical benefit.

**Circulating Protein Biomarkers**

In addition to expression on the tumor tissue, PD-L1 can be shed from tumor and released into the blood. Enzyme-linked immunoassay can measure PD-L1 in serum and correlate this expression with response to pembrolizumab therapy, as well as levels of PD-L1 IHC or protein in the tumor. Blood would be less invasive compartment compared to tumor from which to measure PD-L1 protein biomarker. In addition to this specific protein biomarker, both tissue and blood derivatives can be subjected to proteomic profiling studies using a variety of platforms that could include but are not limited to immunoassay and Liquid chromatography/Mass Spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab therapy.

**Genetic Analyses of Tumor Tissue Samples and Blood**

The application of next generation sequencing of DNA isolated from tumor or blood, defines certain tumor types at the genetic level as being 'hypermutated' or detects the presence of specific T-cell clones within the tumor microenvironment or in the peripheral blood. There is a potential that the hypermutated state and/or increased T-cell clonality may correlate with response to pembrolizumab therapy, and/or that the converse, 'hypomutated' state or lack of dominant T-cell clones may correlate with non-response.

This analysis may evaluate whether genetic mutation variation within this ovarian tumor population correlates with response to pembrolizumab. If genetic variation predicts efficacy or AEs, the data might inform optimal use of therapies in this population.

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

#### 4.2.3.5 Future Biomedical Research

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

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

material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

### 4.3 Benefit/Risk

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

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigator's Brochure and Informed Consent documents.

## 5.0 METHODOLOGY

### 5.1 Entry Criteria

#### 5.1.1 Diagnosis/Condition for Entry into the Trial

Female subjects with advanced ovarian cancer of at least 18 years of age will be enrolled in this trial.

#### 5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be ≥18 years of age on day of signing informed consent.
3. Have histologically confirmed epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer.
4. Have received a front line platinum-based regimen (administered via either IV or IP route) per local standard of care or treatment guideline following the primary or interval debulking surgery with documented disease recurrence.

   *Note:* Maintenance treatment following the front line treatment is permitted and counted together as part of the front line treatment.
5. Have fulfilled the following additional requirements regarding prior treatments for ROC depending on the cohort subject is to be enrolled. Each subject must have documented evidence of clinical response or disease stabilization to the last regimen received.

   ***Cohort A:*** Have received 0 to 2 additional prior lines for treating ROC (or 1 to 3 total prior lines counting the front line) and must have a PFI of ≥3 to 12 months if the last regimen received is a platinum-based, or a TFI of ≥3 to 12 months if the last regimen received is a non-platinum-based.

***Cohort B:*** Have received 3 to 5 additional prior lines for treating ROC (or 4 to 6 total prior lines counting the front line) and must have a PFI of ≥3 months if the last regimen received is a platinum-based, or a TFI of ≥3 months if the last regimen received is a non-platinum-based.

*Note:* PFI is defined as the time elapsed between the last dose of platinum and the documented evidence of disease progression per RECIST 1.1. Treatment-free interval is defined as the time elapsed between the last dose of the regimen received and the documented evidence of disease progression per RECIST 1.1.

6. Have measurable disease at baseline based on RECIST 1.1 as determined by the central imaging vendor.
   *Note:* Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
8. Have a life expectancy of ≥16 weeks.
9. Have provided a tumor tissue sample either collected from prior cytoreductive surgery or fresh newly obtained tumor tissue at screening. Formalin-fixed paraffin-embedded block specimens are preferred to slides. Additional samples may be requested if tumor tissue provided is not adequate for quality and/or quantity as assessed by the central laboratory.

   *Note 1:* Tumor tissue samples from recent biopsy are preferred as it represents the current disease status and is much more informative for understanding the correlation between clinical activity and tumor microenvironment.

   If available, paired tumor tissue samples from prior cytoreductive surgery and recent biopsy are strongly encouraged in order to understand the changes in tumor microenvironment during the course of the treatments.

   *Note 2:* For archival tumor tissue samples, block specimens are preferred than slides. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut. Refer to Section 4.2.3.4 in protocol for an explanation.
10. Have demonstrated adequate organ function as defined in Table 1. All screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

| System | Laboratory Value |
|---|---|
| **Hematological** | |
| Absolute neutrophil count (ANC) | ≥1,500 /mcL |
| Platelets | ≥100,000 / mcL |
| Hemoglobin | ≥9 g/dL or ≥5.6 mmol/L without transfusion or erythropoietin (EPO) dependency |
| **Renal** | |
| Creatinine **OR**<br>Measured or calculated[a] creatinine clearance (CrCl)<br><br>[Glomerular filtration rate (GFR) can also be used in place of creatinine or CrCl] | ≤1.5x upper limit of normal (ULN) **OR**<br>≥30 mL/min for subject with creatinine levels >1.5x institutional ULN |
| **Hepatic** | |
| Total bilirubin | ≤1.5x ULN, **OR**<br>Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5x ULN |
| Aspartate aminotransferase [AST (SGOT)] and alanine aminotransferase [ALT (SGPT)] | ≤2.5x ULN |
| Albumin | ≥3.0 g/dL |
| Lactate Dehydrogenase (LDH) | <2.5x ULN |
| **Coagulation** | |
| International Normalized Ratio (INR) or Prothrombin Time (PT) | ≤1.5x ULN<br>If a subject is receiving anticoagulant therapy, PT or INR can be >1.5x ULN as long as they are within therapeutic range of intended use of anticoagulants |
| Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT) | ≤1.5x ULN<br>If a subject is receiving anticoagulant therapy, aPTT or PTT can be >1.5x ULN as long they are within therapeutic range of intended use of anticoagulants |
| [a]Creatinine clearance should be calculated per institutional standard. | |

11. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

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

### 5.1.3 Subject Exclusion Criteria

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

1. Is currently participating in or has participated in a clinical study and received an investigational agent or used an investigational device within 4 weeks prior to the first dose of study treatment.

   *Note:* Subjects who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent or device.

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

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

4. Has had prior anti-cancer mAb, chemotherapy, targeted small molecule therapy, or radiation therapy within 4 weeks prior to the planned first dose of the study.

5. Has not recovered from AE to ≤Grade 1 or prior treatment level due to a previously administered agent.

   *Note:* Subjects with ≤Grade 2 neuropathy or alopecia of any grade are an exception to this criterion and may qualify for the study.

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

6. Has EOC with mucinous histology subtype.

7. Has a known additional malignancy that progressed or required active treatment within the last 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

8. Has known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they have stable brain metastases.

9. Has known history of, or any evidence of active, non-infectious pneumonitis.

10. Has an active infection requiring systemic therapy.

11. Has symptoms of bowel obstruction in the past 3 months.

12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation

for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
14. Is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
15. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137) or has participated in prior pembrolizumab trials.
16. Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
17. Has known active hepatitis B (e.g., Hepatitis B surface antigen reactive) or hepatitis C (e.g., hepatitis C virus RNA [qualitative] is detected).
18. Has received a live vaccine within 30 days of the planned first dose of the study.

    *Note:* Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

## 5.2 Trial Treatment(s)

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

Table 2 Trial Treatment

| Drug | Dose | Dose Frequency | Route of Administration | Regimen/ Treatment Period | Use |
|---|---|---|---|---|---|
| pembrolizumab | 200 mg | Q3W | IV infusion | Day 1 of each 3-week cycle | Experimental |

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

### 5.2.1 Dose Selection/Modification

#### 5.2.1.1 Dose Selection (Preparation)

Dose selection rationale has been provided in Section 4.2.2. Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

#### 5.2.1.2 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

.

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

**General instructions:**

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.

| irAEs | Toxicity grade or conditions (NCI CTCAE v4.0) | Action taken to pembrolizumab | irAE management with corticosteroid and/or other therapies | Monitor and follow-up |
|---|---|---|---|---|
| Pneumonitis | Grade 2 | Withhold | • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper | • Monitor participants for signs and symptoms of pneumonitis<br>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment<br>• Add prophylactic antibiotics for opportunistic infections |
| | Grade 3 or 4, or recurrent grade 2 | Permanently discontinue | | |
| Diarrhea / colitis | Grade 2 or 3 | Withhold | • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper | • Monitor participants for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus).<br>• Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.<br>• Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. |
| | Grade 4 | Permanently discontinue | | |
| AST / ALT elevation or Increased | Grade 2 | Withhold | • Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper | • Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable |

| irAEs | Toxicity grade or conditions (NCI CTCAE v4.0) | Action taken to pembrolizumab | irAE management with corticosteroid and/or other therapies | Monitor and follow-up |
|---|---|---|---|---|
| Bilirubin | Grade 3 or 4 | Permanently discontinue | • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper | |
| Type 1 diabetes mellitus (T1DM) or Hyperglycemia | Newly onset T1DM or<br>Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure | Withhold | • Initiate insulin replacement therapy for participants with T1DM<br>• Administer anti-hyperglycemic in participants with hyperglycemia | • Monitor participants for hyperglycemia or other signs and symptoms of diabetes. |
| Hypophysitis | Grade 2 | Withhold | • Administer corticosteroids and initiate hormonal replacements as clinically indicated. | • Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) |
| | Grade 3 or 4 | Withhold or permanently discontinue[1] | | |
| Hyperthyroidism | Grade 2 | Continue | • Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate | • Monitor for signs and symptoms of thyroid disorders. |
| | Grade 3 or 4 | Withhold or<br>Permanently discontinue[1] | | |
| Hypothyroidism | Grade 2-4 | Continue | • Initiate thyroid replacement hormones (e.g. 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 1-2 mg/kg or equivalent) followed by taper. | • Monitor changes of renal function |
| | Grade 3 or 4 | Permanently discontinue | | |

| irAEs | Toxicity grade or conditions (NCI CTCAE v4.0) | Action taken to pembrolizumab | irAE management with corticosteroid and/or other therapies | Monitor and follow-up |
|---|---|---|---|---|
| Myocarditis | Grade 1 or 2 | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 3 or 4 | Permanently discontinue | | |
| All Other irAEs | Intolerable/ persistent Grade 2 | Withhold | • Based on type and severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 3 | Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis | | |
| | Grade 4 or recurrent Grade 3 | Permanently discontinue | | |

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

**NOTE:**

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

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

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

| NCI CTCAE Grade | Treatment | Premedication at Subsequent Dosing |
|---|---|---|
| **Grade 1**<br>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**<br>Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDs<br>Acetaminophen<br>Narcotics<br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>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.<br>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:<br>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).<br>Acetaminophen 500-1000 mg po (or equivalent dose of analgesic). |

| | | |
|---|---|---|
| **Grades 3 or 4**<br>Grade 3:<br>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)<br>Grade 4:<br>Life-threatening; pressor or ventilator support indicated | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>Epinephrine**<br>IV fluids<br>Antihistamines<br>NSAIDs<br>Acetaminophen<br>Narcotics<br>Oxygen<br>Pressors<br>Corticosteroids<br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>**In cases of anaphylaxis, epinephrine should be used immediately.<br>**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.<br>For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov | | |

**Other allowed dose interruption for pembrolizumab**

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

### 5.2.2 Timing of Dose Administration

Pembrolizumab should be administered on Day 1 of each 3-week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). On Cycle 1 Day 1, trial treatment should begin on the day of allocation or as close as possible to the date on which the subject is allocated/assigned. After Cycle 1 Day 1, trial treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons.

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

### 5.2.3 Trial Blinding/Masking

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

## 5.3 Randomization or Treatment Allocation

Centralized interactive voice response system/integrated web response system (IVRS/IWRS) will be utilized. The IVRS/IWRS will be used for assignment of both the screening number and the randomization/treatment number of all subjects in this trial. Subjects will be assigned to all study therapy in an unblinded fashion.

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

## 5.4 Stratification

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

## 5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

### 5.5.1 Acceptable Concomitant medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 7.2.

### 5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol

- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor (except during screening).
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, intranasal influenza, rabies, Bacillus Calmette–Guérin, and typhoid vaccine.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology or from symptomatic brain metastasis(es) (also during whole brain radiation therapy). The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
  - Note: Inhaled steroids are allowed for management of asthma.
  - Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contract dye) is permitted.

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

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

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

## 5.6 Rescue Medications & Supportive Care

### 5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Table 3. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance.

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

## 5.7 Diet/Activity/Other Considerations

### 5.7.1 Diet

Subjects should maintain a normal diet unless modification is 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.

Female subjects will be considered to be 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 2 of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)

- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†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 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, they 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. 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.

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

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

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

### 5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, 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 Use in Nursing Women

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 breastfeeding are not eligible for enrollment.

## 5.8 Subject Withdrawal/Discontinuation Criteria

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

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject is lost to follow-up.

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

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

  *Note*: For unconfirmed radiographic disease progression, please see Section 7.1.2.6.2.

- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw subject
- The subject has a confirmed positive serum pregnancy test

- Noncompliance with trial treatment or procedure requirements
- Completed 35 treatments (approximately 2 years) with pembrolizumab

  *Note:* 35 treatments (approximately 2 years) are calculated from the first dose. Subjects who stop pembrolizumab after receiving 35 treatments may be eligible for retreatment if they progress after stopping study treatment if they meet the requirements detailed in Section 7.1.5.2.1. Subjects may be retreated in the Second Course Phase with up to 17 (approximately 1 year) of additional trial treatments.
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Trial Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for AE monitoring (SAEs will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anti-cancer therapy, whichever is earlier, as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression, each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

### 5.8.1 Discontinuation of Study Therapy after Complete Response

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to 17 additional treatments (approximately 1 year) with pembrolizumab via the Second Course Phase at the discretion of the investigator if:

- No cancer treatment was administered since the last dose of pembrolizumab
- The subject meets the safety parameters listed in the Inclusion/Exclusion criteria
- The trial is ongoing

Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.2.1. Response or progression in this Second Course Phase will not count towards the ORR as the primary endpoint in this trial.

## 5.9 Subject Replacement Strategy

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

## 5.10 Beginning and End of the Trial

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

Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study.

## 5.11 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems, or the number of discontinuations for administrative reasons is too high.

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this and other studies indicates a potential health hazard
4. Planned to modify or discontinue the development of the study drug
5. In the event of Sponsor decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

# 6.0 TRIAL FLOW CHART

## 6.1 Initial Treatment Phase

| Trial Period: | Screening Phase | Treatment Cycles | | | | | | | | End of Treatment | Post-treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle/Title: | Screening (Visit 1) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 and Beyond | Discon | Safety Follow-up | Follow Up Visits[a] | Survival Follow-Up[b] |
| | | | | | | | | | | At time of Discon | 30 Days after Last Dose | Every 9 or 12 Weeks Post-discon | Every 12 Weeks or as directed by Sponsor |
| **Scheduling Window (Days)[c]** | -28 to -1 | | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 7 | ± 7 | ± 7 |
| **Administrative Procedures** | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | |
| Informed Consent for Future Biomedical Research (optional) | X | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | | |
| Subject Identification Card | X | | | | | | | | | | | | |
| Demographics and Medical History | X | | | | | | | | | | | | |
| Prior and Concomitant Medication Review | X | X | X | X | X | X | X | X | X | X | X | | |
| Post-study Anti-cancer Therapy Status | | | | | | | | | | | X | X | X |
| Survival Status[b] | | ← | | | | | | | | | | → | X |
| **Clinical Procedures/Assessments** | | | | | | | | | | | | | |
| Review Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X[r] | |
| Full Physical Examination | X | | | | | | | | | X | | | |
| Directed Physical Examination | | X | X | X | X | X | X | X | X | | | | |
| Height, Weight, and Vital Signs (T,P,RR,BP)[d] | X | X | X | X | X | X | X | X | X | X | | | |
| 12-Lead Electrocardiogram | X | | | | | | | | | | | | |
| ECOG Performance Status | X[f] | X | X | X | X | X | X | X | X | X | | | |
| Pembrolizumab Administration | | X[c] | X | X | X | X | X | X | X | | | | |
| **LOCAL Laboratory Assessments** | | | | | | | | | | | | | |
| Pregnancy Test[e] | X[f] | | X | X | X | X | X | X | X | X | X | | |

| Trial Period: | Screening Phase | Treatment Cycles | | | | | | | | End of Treatment | Post-treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle/Title: | Screening (Visit 1) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 and Beyond | Discon | Safety Follow-up | Follow Up Visits[a] | Survival Follow-Up[b] |
| | | | | | | | | | | At time of Discon | 30 Days after Last Dose | Every 9 or 12 Weeks Post-discon | Every 12 Weeks or as directed by Sponsor |
| PT/INR and aPTT | X[f] | | | | | | | | | | | | |
| CBC with Differential[g] | X[f] | | X | X | X | X | X | | X[g] | X | X | | |
| Chemistry Panel[g] | X[f] | | X | X | X | X | X | | X[g] | X | X | | |
| Urinalysis[h] | X[f] | | X | | X | | X | | X[h] | X | X | | |
| T3, FT4, and TSH[h] | X[f] | | X | | X | | X | | X[h] | X | X | | |
| **CENTRAL Laboratory Assessments** | | | | | | | | | | | | | |
| Pembrolizumab Pharmacokinetics[i, j] | | X[i] | X | | X | | X | | X[i,j] | | | | |
| Pembrolizumab Anti-Drug Antibodies (ADA)[i] | | X | X | | X | | X | | X[i] | | | | |
| Blood for Genetics[k] | | X | | | | | | | | | | | |
| Correlative Blood Samples (serum and plasma)[l] | | X | | | | | | | | | | | |
| Correlative Blood Samples (RNA and DNA)[l] | | X | X | X | | | | | | X | | | |
| Blood for CA125[m] | X | | | | X | | | X[m] | | X | | X[s] | |
| **Tumor Tissue Collection** | | | | | | | | | | | | | |
| Newly obtained or Archival Tumor Tissue[n] | X | | | | | | | | | | | | |
| **Efficacy Measurements** | | | | | | | | | | | | | |
| Tumor Imaging | X[o] | X[p] ⟷ | | | | | | | | X[q] | | X | |

a. Subjects who discontinue study therapy due to unacceptable toxicity without documented disease progression (PD) should continue disease monitoring per study schedule, i.e. Q9W before Week 54 or Q12W after Week 54. See Section 7.1.2.6.2 for more details
b. After documented local site assessed disease progression, or the start of new anti-cancer treatment, contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
c. Cycle 1 treatment must be given within 3 days of allocation. The window for each visit is ± 3 days unless otherwise noted.
d. Height will be measured at Visit 1 only.

| Trial Period: | Screening Phase | Treatment Cycles | | | | | | | | End of Treatment | Post-treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle/Title: | Screening (Visit 1) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 and Beyond | Discon | Safety Follow-up | Follow Up Visits[a] | Survival Follow-Up[b] |
| | | | | | | | | | | At time of Discon | 30 Days after Last Dose | Every 9 or 12 Weeks Post-discon | Every 12 Weeks or as directed by Sponsor |

e. For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours prior to each cycle of trial treatment, and 30 days post-treatment. Additionally, if urine test is positive or is not evaluable, a serum test is required. Subjects must be excluded/discontinued in the event of a positive test result. Monthly pregnancy testing should be conducted as per local regulations where applicable.
f. ECOG Performance Status and Laboratory tests for screening and determining eligibility are to be performed within 10 days prior to the first dose of trial treatment.
g. CBC with diff and Chemistry to be performed every cycle through Cycle 6 and then every other cycle thereafter.
h. UA and thyroid function tests will be performed every other cycle.
i. Both PK and Anti-pembrolizumab Samples: pre-dose (trough) PK and anti-pembrolizumab antibody samples will be collected at within 24 hours before infusion at Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter.
j. PK Samples: additional post-dose (peak) PK samples will be drawn within 30 minutes after end of pembrolizumab infusion at Cycles 1 and 8. An additional single PK sample should be drawn at; 24 hours (± 4 hours) [Day 2], between 72 and 168 hours[Day 4-8] and 336 hours (±48 hours) [Day 15] after Cycle 1 dosing.
k. Sample should be drawn for planned genetic analysis of DNA and drug response unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection of the sample for these purposes. Leftover extracted DNA will be stored for future biomedical research if the subject signs the ICF for FBR.
l. 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.
m. Blood for tumor biomarker CA-125 at screening and at the time of each tumor imaging assessment
n. Newly obtained tissue is preferred. If a newly obtained tumor tissue sample cannot be obtained, an archived tumor tissue sample can be submitted. Samples that are formalin-fixed paraffin-embedded must be provided to the designated central laboratory in order to be eligible. Adequacy and quality or the archived tissue samples must be confirmed by the central laboratory before enrollment
o. Screening tumor imaging will be performed within 28 days prior to the date of allocation. Confirmation of baseline measurable disease per RECIST 1.1 by the central imaging vendor is required prior to subject allocation.
p. The first on-study imaging time point will be performed at 9 weeks (63 days ± 7 days) calculated from the date of allocation during the first 54 weeks, and every 12 weeks (84 days ± 7 days) thereafter, or earlier if clinically indicated.
q. In subjects who discontinue study therapy without confirmed PD by the site per irRECIST, tumor imaging should be performed at the time of treatment discontinuation (± 4 weeks). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.

| Trial Period: | Screening Phase | Treatment Cycles | | | | | | | | End of Treatment | Post-treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle/Title: | Screening (Visit 1) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 and Beyond | Discon | Safety Follow-up | Follow Up Visits[a] | Survival Follow-Up[b] |
| | | | | | | | | | | At time of Discon | 30 Days after Last Dose | Every 9 or 12 Weeks Post-discon | Every 12 Weeks or as directed by Sponsor |

r. SAEs will be followed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anti-cancer therapy, whichever is earlier.
s. CA-125 to be collected locally after the 3rd post treatment follow up visit.

## 6.2 Second Course Phase (Retreatment)

| Trial Period: | Treatment Cycles | | | | | | | | End of Treatment | Post-treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle/Title: | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 and Beyond | Discon | Safety Follow-up | Follow Up Visits[a] | Survival Follow-Up[b] |
| | | | | | | | | | At time of Discon | 30 Days after Last Dose | Every 9 or 12 Weeks Post-discon | Every 12 Weeks |
| **Scheduling Window (Days)[c]** | | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 7 | ± 7 | ± 7 |
| **Administrative Procedures** | | | | | | | | | | | | |
| Eligibility Criteria | X | | | | | | | | | | | |
| Concomitant Medication Review | X | X | X | X | X | X | X | X | X | X | | |
| **Clinical Procedures/Assessments** | | | | | | | | | | | | |
| Review Adverse Events | X | X | X | X | X | X | X | X | X | X | X[j] | |
| Full Physical Examination | X | | | | | | | | X | | | |
| Directed Physical Examination | | X | X | X | X | X | X | X | | | | |
| Weight, and Vital Signs (T,P,RR,BP) | X | X | X | X | X | X | X | X | X | | | |
| ECOG Performance Status | X | X | X | X | X | X | X | X | X | | | |
| Post-study anti-cancer Therapy Status | | | | | | | | | | X | X | X |
| Survival Status | ← | | | | | | | | | | → | X |
| **Trial Treatment Administration** | | | | | | | | | | | | |
| Pembrolizumab | X | X | X | X | X | X | X | X | | | | |
| **LOCAL Laboratory Assessments** | | | | | | | | | | | | |
| Pregnancy Test[d] | X | X | X | X | X | X | X | X | X | X | | |
| PT/INR and aPTT | X[e] | | | | | | | | | | | |
| CBC with Differential[f] | X[e] | X | X | X | X | X | | X | X | X | | |
| Chemistry Panel[f] | X[e] | X | X | X | X | X | | X | X | X | | |
| Urinalysis[f] | X[e] | | X | | X | | X | | X | X | | |
| T3, FT4, and TSH [f] | X[e] | | X | | X | | X | | X | X | | |
| **CENTRAL laboratory Assessments** | | | | | | | | | | | | |
| Blood for CA125[g] | X | | | X | | | X | | X | | X[k] | |
| **Efficacy Measurements** | | | | | | | | | | | | |
| Tumor Imaging | X[h] | ← X[h] → | | | | | | | X[i] | | X | |

a. Subjects who discontinue study therapy due to unacceptable toxicity without documented disease progression (PD) should continue disease monitoring per study schedule, i.e. Q9W before Week 54 or Q12W after Week 54. See Section 7.1.2.6.5 for more details.
b. After the start of new anti-cancer treatment or PD the subject should be contacted (example; by telephone) Q12W to assess for survival status.

| Trial Period: | Treatment Cycles | | | | | | | | End of Treatment | Post-treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle/Title: | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 and Beyond | Discon | Safety Follow-up | Follow Up Visits[a] | Survival Follow-Up[b] |
| | | | | | | | | | At time of Discon | 30 Days after Last Dose | Every 9 or 12 Weeks Post-discon | Every 12 Weeks |

c. In general, the window for each visit is ± 3 days unless otherwise noted.
d. For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours prior to each cycle of trial treatment and 30 days post-treatment.
e. Laboratory tests for determining eligibility are to be performed within 10 days prior to the first retreatment dose of pembrolizumab
f. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. CBC and Chemistry, to be performed every cycle through Cycle 6 and then every other cycle thereafter. UA and Thyroid function tests to be performed every other cycle.
g. Blood for tumor biomarker CA-125 at screening and at the time of each tumor imaging assessment.
h. Tumor imaging should be performed within 28 days prior to restarting treatment with pembrolizumab and continue to be performed every 9 weeks (63 ± 7 days) after the first dose of retreatment for the first 54 weeks and then every 12 weeks thereafter, or more frequently if clinically indicated.
i. Tumor imaging should be performed at the time of treatment discontinuation (i.e., date of discontinuation ± 4 week window). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation isn't mandatory.
j. SAEs will be followed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anti-cancer therapy, whichever is earlier.
k. CA-125 to be collected locally after the third post treatment follow up visit.

# 7.0 TRIAL PROCEDURES

## 7.1 Trial Procedures

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

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

### 7.1.1 Administrative Procedures

#### 7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

##### 7.1.1.1.1 General Informed Consent

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

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

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

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

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

##### 7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before

performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

#### 7.1.1.2 Inclusion/Exclusion Criteria

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

#### 7.1.1.3 Subject Identification Card

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

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

#### 7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Any autoimmune disorders, regardless of onset, should be recorded. Disease and treatment history for ovarian cancer will be recorded separately (see Section 7.1.1.4.1) and not listed under medical history eCRF form.

##### 7.1.1.4.1 Ovarian Cancer Disease Details

The investigator or qualified designee will obtain the following information regarding the subject's ovarian cancer including date of and stage at initial diagnosis, prior surgery and radiation therapy, prior systemic anti-cancer therapy with indications (e.g. neo-adjuvant, adjuvant, maintenance treatment, or for relapsed disease), start/stop dates and reason for stopping a systemic anti-cancer regimen, time of disease progression/ recurrence following each systemic regimen and criteria used for evaluation of disease progression (e.g. RECIST 1.1 or GCIG). Sites should obtain a dated imaging and/or CA125 report documenting progressive disease on the most recent treatment.

##### 7.1.1.4.2 Menopausal Details

The investigator or qualified designee will obtain details regarding the subject's menopausal status.

#### 7.1.1.5 Prior and Concomitant Medications Review

##### 7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medications taken by the subject

within 28 days before first dose of trial medication. Prior treatment details for ovarian cancer will be recorded separately from prior medications (see Section 7.1.1.4.1 for details).

#### 7.1.1.5.2 Concomitant Medications

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

### 7.1.1.6 Subsequent Anti-Cancer therapy Status

All new anti-cancer therapy initiated after the study start must be recorded in the subsequent anti-cancer therapy eCRF page. If a subject initiates another anti-cancer therapy while receiving pembrolizumab, pembrolizumab must be discontinued and subject will move into Survival Follow-up Phase; if a subject initiates a new anti-cancer therapy within 30 days after the last dose of the trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy.

### 7.1.1.7 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

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

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

### 7.1.1.8 Assignment of Treatment/Randomization Number

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

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

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

### 7.1.1.9 Trial Compliance (Medication/Diet/Activity/Other)

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

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

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

### 7.1.2 Clinical Procedures/Assessments

#### 7.1.2.1 Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE version 4.0 (see Appendix 12.5). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab, all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly a potentially immunologic etiology (irAEs); see Section 5.6. regarding the identification, evaluation and management of potential irAEs.

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

After preliminary screening based on subjects' medical and cancer history, candidate subjects will have the following assessments for evaluating baseline safety and ovarian cancer disease status. Safety tests include physical examination, vital signs, clinical laboratory tests (clinical chemistry, hematology), urinalysis, electrocardiogram (ECG) and ECOG performance status. Baseline safety assessments must be performed within 10 days of the planned study entry on Day 1 (i.e., first dose).

#### 7.1.2.2 Physical Exam

##### 7.1.2.2.1 Full Physical Exam

The investigator or clinical designee will perform a complete (full) physical exam during the screening period and at discontinuation of treatment as specified in the Trial Flow Chart. Clinically significant abnormal findings at screening should be recorded as medical history. New clinically significant abnormal findings at discontinuation of treatment should be recorded as AEs.

##### 7.1.2.2.2 Directed Physical Exam

Other than the Screening and treatment discontinuation visit, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to dosing on Day 1 of each treatment cycle (see Trial Flow Chart). New clinically significant abnormal findings should be recorded as AEs.

#### 7.1.2.3 Vital Signs

The investigator or qualified designee will assess vital signs (including temperature, pulse, respiratory rate, and blood pressure) and weight at screening, prior to dosing on Day 1 of

each treatment cycle, and at treatment discontinuation as specified in the Trial Flow Chart. Height will be measured at screening only.

#### 7.1.2.4 12-Lead Electrocardiogram

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

#### 7.1.2.5 Eastern Cooperative oncology Group Performance Status

The investigator or qualified designee will assess ECOG status (see Appendix 12.4) at screening, prior to dosing on Day 1 of each treatment cycle, at treatment discontinuation, and at progressive disease (PD) follow-up visit as specified in the Trial Flow Chart.

#### 7.1.2.6 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual. For this study, imaging of chest abdomen, and pelvis are required at Screening and at each scheduled disease assessment visit after enrollment. Computed tomography (CT) is the modality strongly preferred for chest. For abdomen and pelvis CT or magnetic resonance imaging (MRI) are both acceptable. However, the same imaging modality and technique, such as use of contrast should be used consistently for an anatomic region in a subject throughout the trial.

All scheduled images for all study subjects from the sites will be submitted to the central imaging vendor. In addition, additional imaging (including other modalities) that are obtained at an unscheduled time point to determine if the subject has progressed, as well as imaging obtained for other reasons but captures radiologic progression, should be submitted to the central vendor as well.

##### 7.1.2.6.1 Screening Tumor Imaging

At Screening, imaging scans must be performed within 28 days prior to date of allocation. The site study team must review screening images to confirm the subject has measurable disease per RECIST 1.1. The screening images must be submitted to the central imaging vendor for confirmation of measurable disease per RECIST 1.1 for eligibility prior to allocation.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and are performed within 28 days prior to the date of allocation and can be assessed by the central imaging vendor.

Subjects with previously treated brain metastases may participate provided they have stable brain metastases, ie. without evidence of progression by imaging (confirmed by MRI if MRI was used at prior imaging, or confirmed by CT imaging if CT used at prior imaging for at least 4 weeks prior to the first dose of trial treatment; also, any neurologic symptoms must have returned to baseline), have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 28 days prior to trial initiation as per local

site assessment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

#### 7.1.2.6.2 Disease Assessments During Treatment Period

After study start, study scheduled imaging assessments will be performed at 9 weeks (63 days ± 7 days) from the date of allocation up to 54 weeks. Subsequent imaging should be performed Q12W (84 days ± 7 days) or more frequently, if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or any dose interruptions that may occur. Imaging assessments should continue until disease progression per RECIST 1.1 or to confirm disease progression per irRECIST to avoid pseudoprogression (see Section 7.1.2.6.7 for details), the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

Per RECIST 1.1, PR and CR should be confirmed by a repeat tumor imaging assessment no less than 4 weeks from the date the response was first documented. Therefore, the scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (9 or 12 weeks later), whichever is clinically indicated. Subjects will then return to regular scheduled imaging Q9W (or Q12W), starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per irRECIST (section 7.1.2.6.7), disease progression should be confirmed by the site at least 4 weeks after site-assessed first radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment at the discretion of the site investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 7.1.2.6.7. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Subjects who have confirmed disease progression as assessed by the site will discontinue the treatment. Exception is detailed in Section 7.1.2.6.7.

#### 7.1.2.6.3 Bone Scans

Subjects with known history or new symptoms that are suggestive of osseous metastasis (e.g., new bone pain and/or new persistently elevated alkaline phosphatase) should obtain a bone scan at baseline. At follow-up, subjects with new symptoms or those suggestive of worsening osseous metastasis should obtain a bone scan. Additionally, plain X-ray evaluation should be obtained for symptomatic skeletal sites with negative bone scan evaluations. New osseous uptake, upon confirmation with CT or per institutional standard, will be assessed for progression per RECIST 1.1. Lytic/mixed lesions with soft tissue component may be included in the evaluation of disease burden if they meet measurability criteria, while blastic lesions are considered non-measurable, in accordance with RECIST 1.1. Note: if a bone scan is obtained that is positive for metastatic disease and the patient ultimately achieves a CR per RECIST 1.1; a follow-up bone scan should be obtained.

#### 7.1.2.6.4 End of Treatment and Follow-up Tumor Imaging

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (Q9W (63 days ± 7 days) from the date of allocation up to 54 weeks with subsequent imaging performed Q12W (84 days ± 7 days).) to monitor disease status until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.

#### 7.1.2.6.5 Second Course (Retreatment) Tumor Imaging

A scan must be performed within 28 days prior to restarting treatment with pembrolizumab. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. Imaging should be submitted to the central imaging vendor for retrospective verification.

The first on study imaging assessment should be performed at 9 weeks (63 days ±7 days) after the restart of treatment up to 54 weeks. Subsequent tumor imaging should be performed Q12W (84 days ±7 days) or more frequently if clinically indicated.

Per RECIST 1.1, PR or CR should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated. Subjects will then return to regular scheduled imaging every 9 (or 12) weeks (63 or 84 days ±7 days), starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is <4 weeks later and may wait until the next scheduled imaging time point.

Per irRECIST (Section 7.1.2.6.7) , if tumor imaging shows initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Subjects who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is <4 weeks later and may wait until the next scheduled imaging time point if clinically stable.

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

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging Q9W (63 days ± 7 days) from the date of allocation up to 54 weeks; with subsequent imaging performed Q12W (84 days ± 7 days until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.

#### 7.1.2.6.6 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be applied by the sites and the central imaging vendor as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). Although

RECIST 1.1 references to maximum of 5 target lesions in total and 2 per organ, Merck allows maximum of 10 target lesions in total and 5 per organ.

#### 7.1.2.6.7 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.

When feasible, subjects should not be discontinued from study treatment until progression is confirmed by the local site investigator/radiology assessment. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. The following may present as tumor flare:

- 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, the investigator needs to decide whether to continue a subject on study treatment until repeat imaging is obtained (using irRECIST for subject management. See Table 5), which should be based on assessing subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. If the subject is clinically stable and can continue on study treatment, repeat scan should be performed ≥4 weeks later in order to confirm PD. Clinical stable status is defined as the following:

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

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

In determining whether or not the tumor burden has increased or decreased per irRECIST, the 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 qualitatively stable or improved
- New lesion resulting in initial PD is qualitatively stable or 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 investigator and the subject continues to be clinically stable, study treatment tumor imaging assessment may continue per study schedule.

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

- Target lesion sum of diameters remain ≥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 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 Section 6.0 (Trial Flowchart) and be submitted to the central imaging vendor.

Additional details about irRECIST are referenced in Merck TIP Sheet for RECIST 1 1 and irRECIST.

Table 5 irRECIST Imaging and Treatment after First Radiologic Evidence of PD

| | Clinically Stable | | Clinically Unstable | |
|---|---|---|---|---|
| | Imaging | Treatment | Imaging | Treatment |
| First radiologic evidence of PD by RECIST 1.1 | Repeat imaging at ≥4 weeks at site to confirm PD | May continue study treatment at the Investigator's discretion while awaiting confirmatory scan by site | Repeat imaging at ≥4 weeks to confirm PD per physician discretion only | Discontinue treatment |
| Repeat scan confirms PD by irRECIST at the local site | No additional imaging required | Discontinue treatment (exception is possible upon consultation with Sponsor). | No additional imaging required | N/A |
| Repeat scan shows SD, PR or CR by irRECIST at the local site* | Continue regularly scheduled imaging assessments | Continue study treatment at the local site Investigator's discretion | Continue regularly scheduled imaging assessments | May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule outlined in the protocol. |
| * SD,PR and CR for irRECIST are identical to RECIST 1.1 | | | | |

### 7.1.3 Laboratory Procedures/Assessments

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

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

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 6.

Table 6 Laboratory Tests

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| Hematocrit | Albumin | Blood | Pregnancy test (serum or urine)[a] |
| Hemoglobin | Alkaline phosphatase | Glucose | aPTT[d] |
| Platelet count | Alanine aminotransferase (ALT) | Protein | PT (INR)[d] |
| WBC (total and differential) | Aspartate aminotransferase (AST) | Specific gravity | Total triiodothyronine (T3)[e] |
| Red Blood Cell Count | Bicarbonate[b] | Microscopic exam, if abnormal results are noted | Free thyroxine (FT4) |
| Absolute Neutrophil Count | Calcium | | Thyroid stimulating hormone (TSH) |
| Absolute Lymphocyte Count | Chloride | | FSH, estradiol[f] |
| | Creatinine | | Blood for correlative studies |
| | Glucose | | Blood for genetics |
| | Lactate Dehydrogenase | | |
| | Phosphorus | | |
| | Potassium | | |
| | Sodium | | |
| | Total Bilirubin | | |
| | Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal | | |
| | Total protein | | |
| | Blood Urea Nitrogen | | |
| | Carbon dioxide ($CO_2$ or bicarbonate)[b] | | |
| | Uric acid | | |
| | Urea[c] | | |
| | Amylase | | |

[a] Perform on women of childbearing potential only, 72 hours prior to Day 1 of each cycle and 30 days post treatment.
[b] If considered standard of care in your region. If these tests are not done as part of standard of care in your region then these tests do not need to be performed.
[c] Blood Urea Nitrogen is preferred; if not available urea may be tested.
[d] Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
[e] Total T3 is preferred; if not available free T3 may be tested.
[f] Blood for menopausal status is only required for some subjects as described in Section 7.1.3.2

Laboratory safety tests will be performed within 10 days prior to the first dose of trial treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found

to be acceptable prior to each dose of trial treatment. Blood draws for thyroid function tests should be done prior to dosing at the scheduled time point; however, results can be reviewed after dosing if not available prior to the subject's scheduled dose after the first cycle.

#### 7.1.3.2 Blood for Menopausal Status

Blood for evaluation of postmenopausal status (FSH and estradiol) will be evaluated if clear documentation of postmenopausal status in not obtained.

The menopausal status (pre- or post-menopausal) for all subjects younger than age 60 must be determined at screening according to the definitions below. The date of the subject's last menstrual period (LMP), bilateral ovariectomy/oophorectomy status (if applicable) and, when indicated, serum FSH and estradiol levels, must be assessed and recorded in the eCRFs.

Pre-menopausal

- ≤12 months since LMP

**OR**

- Biochemical evidence of pre-menopausal status according to serum FSH and estradiol levels and local institutional guidelines

Post-menopausal

- Subject has undergone prior bilateral ovariectomy/oophorectomy

**OR**

- >12 months since LMP and no hysterectomy, hormone replacement, estrogen receptor antagonist, chemotherapy or ovarian suppression at any time since LMP

**OR**

- Biochemical evidence of post-menopausal status according to serum FSH and estradiol levels and local institutional guidelines.

Blood collection at screening for biochemical evidence of menopausal status (FSH and estradiol) will be needed if patient:

1. Is ≤60 years old, and
2. Has not had a bilateral oophorectomy, and
3. Has not had a menstrual period for at least 12 months, and
4. Had a hysterectomy or was on hormone replacement, estrogen receptor antagonist, chemotherapy or ovarian suppression at any time since LMP.

#### 7.1.3.3 Blood for Tumor Biomarker CA-125

Blood for tumor biomarker CA-125 will be obtained at the time of each tumor imaging assessment; this blood sample will not be used for determining eligibility for study participation. After the 3rd post treatment follow up visit, this sample will be collected locally.

#### 7.1.3.4 Pharmacokinetics/Pharmacodynamic Evaluations

To evaluate the immunogenicity and exposure of pembrolizumab in this indication, sample collections for analysis of anti-pembrolizumab antibodies (ADA) and PK are currently planned as shown in the Trial Flowchart (Section 6.1). Blood samples for PK and ADA collected may be stored only at this time. Further sample analysis may be performed if required. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

##### 7.1.3.4.1 Blood Collection for Serum Pembrolizumab Pharmacokinetics

Sample collection, storage and shipment instructions for serum samples will be provided in the Procedures manual. Pharmacokinetic samples should be drawn according to the PK collection schedule for subjects who receive pembrolizumab.

##### 7.1.3.4.2 Blood Collection for Anti Drug Pembrolizumab Antibodies

Sample collection, storage and shipment instructions for serum samples will be provided in the Procedures manual. Anti-pembrolizumab antibody samples should be drawn according to the ADA collection schedule for subjects who receive pembrolizumab (Section 6.1). Simultaneous PK sampling is required for interpretation of ADA analysis.

#### 7.1.3.5 Tumor Tissue Collection

During Screening, a fresh newly-obtained tumor tissue sample or an archived tumor tissue sample either collected from prior cytoreductive surgery must be obtained and submitted to the designated central laboratory for PD-L1 status and other biomarker assessments as specified in Section 3.3 and Section 4.2.3.4. The samples must be of adequate amount and quality. Formalin-fixed paraffin-embedded tumor blocks are much preferred. If after agreement with the Sponsor, unstained slides are submitted, the slides should be freshly cut and submitted to the testing laboratory within 14 days from site slide sectioning date otherwise a new specimen will be requested.

For subjects with tumor tissue samples available for different time points in the past, submission of a sample from each time point is strongly encouraged as this will provide us with good understanding of markers that may or may not change during the course of disease and treatment. If after agreement with the Sponsor, unstained slides are submitted, the slides should be freshly cut and submitted to the testing laboratory within 14 days from site slide sectioning date otherwise a new specimen will be requested.

If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR (see Section 4.2.3.5 for rationale). Details regarding time points for collection of tumor tissue are outlined in the Study Flow Chart (Section 6.1).

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

#### 7.1.3.6 Correlative Blood Collections- Samples for Correlative and Biomarker Analyses

Details regarding time points for blood collection to support analysis of exploratory biomarkers presented in Section 4.2.3.4 are outlined in the Study Flow Chart (Section 6.1).

Samples for planned, exploratory genetic analysis of DNA should be drawn unless there is a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection.

Blood for correlative biomarker studies should be collected prior to treatment at each specified cycle and at treatment discontinuation.

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

#### 7.1.3.7 Planned Genetic Analysis Sample Collection

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

#### 7.1.3.8 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research.
- Leftover tumor tissue

### 7.1.4 Other Procedures

#### 7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 35 trial treatments (approximately 2 years) of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1. After discontinuing treatment following assessment of CR or of the 35 trial treatments, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.2) and then proceed to the Follow-up Period of the study (described in Section 7.1.5.3.3).

##### 7.1.4.1.1 Withdrawal From Future Biomedical Research

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

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

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

#### 7.1.4.2 Blinding/Unblinding

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

#### 7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Laboratory equipment – as required for satisfaction of entry criteria and trial assessments and routine safety evaluation of subjects
- Imaging equipment – as required for study objectives
- Drug administration equipment – as required for storage, preparation and administration(infusion) of pembrolizumab

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

### 7.1.5 Visit Requirements

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

#### 7.1.5.1 Screening

Written consent for the main study must be obtained prior to performing any protocol specific procedure including the mandatory newly obtained (fresh) tumor biopsy that is required for eligibility. Potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in Section 6.0 (Trial Flow Chart). Results of a test performed prior to the subject signing consent as part of

routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

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

- Laboratory tests and evaluation of ECOG status are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- Initial tumor imaging must be performed within 28 days of the first dose of study.

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

#### 7.1.5.2 Treatment Cycles

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

##### 7.1.5.2.1 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to 17 additional trial treatments (approximately 1 year) if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

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

    **OR**

    - Had SD, PR or CR and stopped pembrolizumab treatment after 35 trial treatments ( approximately 2 years) for reasons other than disease progression or intolerability

**AND**

- Experienced an investigator-determined confirmed radiographic disease progression or clinical progression after stopping their initial treatment with pembrolizumab.

Subjects being considered for second course retreatment after experiencing clinical progression may only be enrolled in second course after consulation with the Sponsor.

- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- Female subject of childbearing potential (Section 5.7.1) should be willing to use an adequate method of contraception as outlined in Section 5.7.1- Contraception, for the retreatment period of the study through 120 days after the last dose of study medication.

  Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Pembrolizumab will be administered for up to an additional 17 trial treatments (approximately 1 year).

Visit requirements are outlined in Section 6.0 (Trial Flow Chart).

#### 7.1.5.3 Post-Treatment

##### 7.1.5.3.1 Discontinuation Visit

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

##### 7.1.5.3.2 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0 to 1 or until the beginning of a new anti-cancer therapy, whichever occurs first. Serious adverse events that occur within 90 days of the end of treatment or before initiation of a new

anti-cancer treatment should also be followed and recorded regardless of causality. Beyond 90 days, only SAE and ECIs that are considered related to trial treatment should be reported.

Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.2.1) may have up to 2 safety follow-up visits, 1 after the Treatment Period and 1 after the Second Course Phase.

#### 7.1.5.3.3 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-up Phase and should be assessed per study schedule to monitor disease status. The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of trial (or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1). Information regarding post-trial anti-cancer treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 5.2.3 will move from the Follow-up Phase to the Second Course Phase when they experience disease progression. Details are provided in the Trial Flow Chart (Section 6) for retreatment with pembrolizumab.

#### 7.1.5.3.4 Survival Follow-up

Subjects who experience confirmed disease progression or start a new anti-cancer therapy, will move into the Survival Follow-up Phase and should be contacted by telephone approximately Q12W to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

### 7.1.5.4 Survival Status

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

## 7.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

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

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

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose of 1000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic

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

### 7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

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

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

### 7.2.3 Immediate Reporting of Adverse Events to the Sponsor

#### 7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 7 for additional details regarding each of the above criteria.

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

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

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time following consent through the end of the 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:

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

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

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

#### 7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outline in this section will not be reported to the Sponsor as outlined 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 an 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. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

Table 7 Evaluating Adverse Events

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

| | | |
|---|---|---|
| **V4.0 CTCAE Grading** | **Grade 1** | **Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.** |
| | **Grade 2** | **Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.** |
| | **Grade 3** | **Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.** |
| | **Grade 4** | **Life threatening consequences; urgent intervention indicated.** |
| | **Grade 5** | **Death related to AE** |
| **Seriousness** | A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that: | |
| | †**Results in death**; or | |
| | †**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or | |
| | †**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or | |
| | †**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or | |
| | †**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or | |
| | **Is a** new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or** | |
| | **Is an overdose** (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours. | |
| | **Other important medical events** that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †). | |
| **Duration** | Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units | |
| **Action taken** | Did the adverse event cause the Sponsor's product to be discontinued? | |
| **Relationship to Sponsor's Product** | Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.<br>**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?<br>If yes, did the AE resolve or improve?<br>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.<br>(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?<br>If yes, did the AE recur or worsen?<br>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.<br>(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).<br>NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL. |
| | **Consistency with Trial Treatment Profile** | Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology? |
| The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements. | | |
| **Record one of the following** | **Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).** | |
| **Yes, there is a reasonable possibility of Sponsor's product relationship.** | There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause. | |
| **No, there is not a reasonable possibility of Sponsor's product relationship** | Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.) | |

### 7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

## 7.3 TRIAL GOVERNANCE AND OVERSIGHT

### 7.3.1 Scientific Advisory Committee

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

# 8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in the supplemental Statistical Analysis Plan SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post-hoc exploratory analyses will be clearly identified in the CSR. The sSAP will also document the detailed biomarker analysis strategy including determination of the PD-$L1_H$ cut-off selection .

## 8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2 through 8.12.

| | |
|---|---|
| **Study Design Overview** | A Phase 2, open-label, single-arm, two-cohort, multi-center trial of pembrolizumab monotherapy in subjects with advanced ovarian cancer who have demonstrated recurrent disease following the front line treatment and received up to 5 lines of treatments for ROC. |
| **Treatment Assignment** | Cohort A will enroll subjects with ROC who have received 0 to 2 prior lines for treating ROC (i.e., 1 to 3 total prior lines counting the front line) and with a platinum-free interval or treatment-free interval of 3 to 12 months based on the last regimen received.<br><br>Cohort B will enroll subject with ROC who have received 3 to 5 prior lines for treating ROC (i.e., 4 to 6 total prior lines counting the front line) and with a platinum-free interval or treatment-free interval ≥3 months based on the last regimen received.<br><br>In both cohorts, subjects will be treated with pembrolizumab monotherapy 200 mg Q3W as trial treatment by non-randomized assignment in an unblinded fashion. |
| **Analysis Populations** | Efficacy: Full Analysis Set (FAS)<br>Safety: All Subjects as Treated (ASaT) |
| **Primary Endpoint(s)** | ORR by RECIST 1.1 per BICR review |

| | |
|---|---|
| **Key Secondary Endpoints** | • DOR, DCR, PFS, per RECIST 1.1 as assessed by BICR<br>• ORR, DOR, DCR, PFS per RECIST 1.1 as assessed by investigator<br>• OS<br>• Proportions of PFS at 6, 12 and 18 months and proportions of survival at 6, 12, 18, and 24 months |
| **Statistical Methods for Key Efficacy Analyses** | The primary objectives will be evaluated by the point estimate and 95% confidence interval for the ORR in the Cohort A-All Comer Population and Cohort A PD-$L1_H$ subgroup, respectively, using an exact binomial distribution. ORR will be evaluated similarly in the Cohort B-All Comer group and Cohort B PD-$L1_H$ subgroup, respectively. |
| **Statistical Methods for Key Safety Analyses** | Summary statistics, and 95% CI for the incidence rate of Grade 2 or higher adverse events with an immune etiology and the incidence rate of Grade 4/5 AEs. |
| **Interim Analyses** | An interim analysis is planned at 4 months after the first 100 subjects have been enrolled in Cohort A, which will be used as the training set. IA will evaluate clinical activity and the correlation of PD-L1 in tumor tissue samples in the training set to facilitate the PD-L1 expression cut-off selection. |
| **Multiplicity** | No multiplicity adjustment has been planned. |
| **Sample Size and Power** | Cohort A-All Comer group include the first 180 enrolled subjects fulfilling the eligibility of Cohort A. A minimum of 75 subjects will be enrolled for the subgroup with a PFI/TFI of 3 to <6 months and the subgroup with a PFI/TFI of 6 to 12 months. The first 100 enrolled Cohort A subjects will be used as the training set for determining a PD-L1 expression cut point. The additional 150 enrolled Cohort A subjects will be in the confirmation set, therefore, the study will enroll approximately 250 Cohort A subjects regardless of the PD-L1 status. The exact number of subjects enrolled in the confirmation set will depend on the prevalence of the PD-$L1_H$ as determined by the biomarker analysis. Approximately 75 subjects will be enrolled in Cohort B. |

## 8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the clinical biostatistics department of the Sponsor. This trial is being conducted as an open-label non-randomized single-arm clinical trial (i.e., subjects, investigators, and Sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned). The study team at the Sponsor consisting of clinical, statistical, statistical programming, and data management personnel will be blinded to subject-level PD-L1 biomarker results. An unblinded Sponsor biomarker statistician will have access to the subject-level PD-L1 results for the purpose of data review and biomarker correlation analysis. The unblinded Sponsor biomarker statistician will have no other responsibilities associated with the study.

## 8.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.0.

## 8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

### 8.4.1 Efficacy Endpoints

The primary efficacy endpoint is ORR, defined as the proportion of subjects in the analysis population who have CR or PR at any time during the study using RECIST 1.1 criteria assessed by the blinded central imaging vendor review.

Secondary efficacy endpoints include:

- RECIST 1.1 ORR by investigator review.
- Duration of response, defined as the time from first response to disease progression in subjects who achieve a PR or better, based on assessments by the central imaging vendor per RECIST 1.1.
- Progression-free survival, defined as the time from first dose of study medication to the first documented disease progression per RECIST 1.1 based on assessments by the central imaging vendor or death due to any cause, whichever occurs first.
- Overall survival, defined as the time from first dose of study medication to death due to any cause.
- Proportions of PFS at 6, 12 and 18 months and proportions of survival at 6, 12, 18 and 24 months.
- Disease Control Rate, defined as the percentage of subjects who have achieved confirmed CR or PR or have demonstrated SD for at least 24 weeks prior to any evidence of progression, based on assessments by the central imaging vendor per RECIST 1.1.

Overall response rate, DOR, PFS per irRECIST 1.1 by the central imaging vendor, and restricted mean survival time estimate of PFS over time are the exploratory efficacy endpoints.

### 8.4.2 Safety Endpoints

Safety measurements are as described in Section 7.2.

The primary safety endpoints are AEs graded using CTCAE v4.0 criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including SAEs and ECIs. Other safety endpoints include laboratory safety assessments, ECOG performance status, vital signs, reasons for treatment discontinuation, dose interruptions or reductions, and physical examinations.

## 8.5 Analysis Populations

### 8.5.1 Efficacy Analysis Populations

**Cohort A**

The Full Analysis Set (FAS) population for All Comers, which consists of 180 first enrolled subjects in Cohort A who receive at least 1 dose of study treatment and with measurable disease at baseline, will serve as the primary population for the analyses of efficacy data for

Cohort A All Comers. The FAS population for PD-L1$_H$ subgroup in Cohort A, which includes the subjects in the confirmation set above the PD-L1 cut-off, will be used for the analyses of efficacy data for PD-L1$_H$ subjects in Cohort A. Supportive analyses of efficacy will be conducted in the All Subjects as Treated (ASaT) population, defined as all enrolled subjects in all comers or PD-L1$_H$ in the confirmation set respectively who receive at least 1 dose of study medication (not applicable if there is no difference with the FAS population).

**Cohort B**

The FAS population consists of all subjects in Cohort B who receive at least 1 dose of study treatment and with measurable disease at baseline. The FAS population for PD-L1$_H$ subgroup in Cohort B, which includes the subjects in Cohort B above the PD-L1 cut-off, will be used for the analyses of efficacy data for PD-L1$_H$ subjects in Cohort B.

### 8.5.2 Safety Analysis Populations

The ASaT population will be used for the analysis of safety data. At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 8.6 (Statistical Methods).

## 8.6 Statistical Methods

### 8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

Data from the training set (first 100 subjects in Cohort A) will be evaluated for biomarker analysis and cut point determination. The analysis of confirmation set (150 subjects in Cohort A) will focus on verifying the response rate above the cut point is consistent with predictions made based on the training set data used to set the cut point via the interim analysis. Results for the cut point will be considered confirmed in a direction that supports the proposition of enrichment provided the observed response rate in the confirmation set for subjects above the selected cut point is greater than or equal to the 20th percentile of its posterior predictive distribution as determined using the training set at the time the cut point is set. In other words, consistency of effect is defined as not belonging to the lower 20% of the training set's predictions for enrichment associated with use of the cut point.

Efficacy will be evaluated in the All Comer group and the PD-L1$_H$ subgroup for Cohort A and B respectively. For the primary efficacy endpoint, the ORR based on RECIST 1.1 by the blinded central imaging vendor review, the point estimate, and 95% CI (as determined by the upper and lower 97.5% one-sided confidence bounds) will be provided using an exact binomial distribution. Subjects without response data will be counted as non-responders. Secondary efficacy evaluations of ORR based on RECIST 1.1 by investigator review, and

ORR based on modified RECIST 1.1 by blinded central imaging vendor review will also be conducted using the same methodology as for the primary efficacy analysis.

Duration of response by blinded central imaging vendor review and investigator review will be summarized using KM method in all responders.

For PFS and OS, KM curves, median estimates, and survival at 6, 12 and 18 months based on the KM curves (95% CI is based on Greenwood's formula) will be provided as appropriate. Subjects without efficacy evaluation data or without survival data will be censored at Day 1. The DCR will be summarized at the end of the trial. The restricted Mean Survival Time estimate of PFS and OS will also be calculated and plotted over time.

An outline of the key efficacy analysis strategy is presented in Table 8.

Table 8 Analysis Strategy for Key Efficacy Endpoints

| Endpoint | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|
| • ORR by BICR per RECIST1.1<br>• ORR by investigator assessment per RECIST1.1 | Exact test of binomial parameter; 95% CI† | FAS‡/ASaT | Subjects with missing data are considered non-responders |
| • DOR by BICR per RECIST1.1<br>• DOR by investigator assessment per RECIST1.1 | Summary statistics using KM method | All responders | Non-responders are excluded in analysis |
| • PFS by BICR and investigator assessment per RECIST 1.1OS<br>• Proportion of subjects with PFS at 6, 12 and 18 months; Proportion of survival at 6, 12, 18, and 24 months | Summary statistics using KM method | FAS‡/ASaT | Censored at last assessment |
| • DCR by BICR and investigator assessment per RECIST 1.1 | Exact test of binomial parameter; 95% CI† | FAS‡/ASaT | Subjects with missing data are considered non-responders |

†95% CI is determined by the upper and lower 97.5% one-sided confidence bounds.
‡Primary population for efficacy analyses

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

The association between biomarker values and ORR will be investigated via logistic regression using one-sided tests on the regression coefficient. Cut-off evaluation and selection will involve a review of how the positive predictive value (PPV, response rate in those above a cut-off) and negative predictive value (NPV, response rate in those below the

cut-off) vary with putative cut-offs. A cut-off that maintains high NPV (e.g., above 90%) while achieving meaningful enrichment of response and largely capturing patients showing durable clinical benefit is ideal. The profiles of PPV, NPV, and the percentage of patients above a given cut-off along with intervals quantifying the uncertainty in those profiles will be estimated as a function of potential cut-offs. Receiver operating characteristic curve analysis will also be used to understand the sensitivity and specificity profile and examine cut-offs that might be suggested based on the ROC curve and their appropriateness with regard to PPV and NPV. If the operating characteristics associated with a single biomarker cutpoint are not sufficiently optimized, up to 2 biomarker cutpoints may be carried forward for efficacy endpoint analyses (i.e., a biomarker positive cutpoint and a biomarker high positive cutpoint), as has been implemented in other tumor types within the pembrolizumab program (e.g., bladder cancer) [44]. Details of the biomarker analysis strategy will be documented in the sSAP.

### 8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. Summary statistics (e.g., counts, percentage, mean, standard deviation) will be provided for the safety endpoints as appropriate. The 95% CI for the incidence rate of Grade 2 or higher AEs with an immune etiology (irAEs) and the incidence rate of Grade 4/5 AEs will be provided as appropriate. The All Comer group and the PD-L1$_H$ subgroup will be summarized separately for Cohort A and Cohort B.

### 8.6.3 Demographic and Baseline Characteristics

Baseline characteristics will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, enrolled, primary reasons for screening failure, and discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables. The All Comer group and the PD-L1$_H$ subgroup will be summarized separately for Cohort A and Cohort B.

## 8.7 Interim Analyses

An interim analysis will be performed after 100 subjects in Cohort A have been enrolled and followed up for at least 4 months to determine a PD-L1 expression cutpoint based on PD-L1 biomarker and tumor response data. The results of this analysis will be presented to the study team without unblinding anyone to individual results. The efficacy data from the interim analysis may facilitate further interactions with regulatory agencies.

## 8.8 Multiplicity

The primary objectives for ORR per RECIST 1.1 in All Comer Population and PD-L1$_H$ subgroup for Cohort A and Cohort B will be assessed by point estimate and 95% CI. There are no formal hypotheses and no adjustments for multiplicity are planned. Evaluation of objectives should be interpreted with caution due to the potential for an increase in the false positive rate.

## 8.9 Sample Size and Power Calculations

Based on the preliminary data of pembrolizumab in ovarian cancer patients as described in Section 4.1.2, we expect an ORR of approximately 25% for the All Comer population. These responding subjects expect to have durable responses. In addition we expect additional subjects will have durable SD. We expect in a PD-L1 enriched population, ORR may reach to above 35% with durable response in majority of the subjects.

Table 9 shows the two-sided 95% CI of ORR for different observed response rates based on different sample size in the All Comer group for Cohort A or Cohort B.

Table 9 Two-sided 95% Confidence Interval of ORR in All Comer

| Sample Size | Observed ORR | 95% CI of ORR (%) |
|---|---|---|
| 75 | 17% | (9.3, 27.4) |
| | 25% | (15.7, 36.3) |
| | 30% | (20.0, 41.7) |
| | 35% | (24.3, 46.9) |
| 100 | 17% | (10.2, 25.8) |
| | 25% | (16.9, 34.7) |
| | 30% | (21.2, 40.0) |
| | 35% | (25.7, 45.2) |
| 180 | 17% | (12.0, 23.5) |
| | 25% | (18.9, 32.0) |
| | 30% | (23.4, 37.3) |
| | 35% | (28.1, 42.4) |
| 250 | 17% | (12.7, 22.5) |
| | 25% | (20.0, 31.1) |
| | 30% | (24.4, 36.1) |
| | 35% | (29.3, 41.5) |

For the PD-L1$_H$ subgroup, if the prevalence of PD-L1$_H$ is about 40%, there will be approximately 60 PD-L1$_H$ subjects if there are 150 all comer subjects in the confirmation set, and approximately 30 PD-L1$_H$ subjects if there are 75 all comer subjects in Cohort B. Table 10 shows the two-sided 95% CI of ORR with 30 and 60 subjects for different response rates.

Table 10 Two-sided 95% Confidence Interval for ORR in PD-L1$_H$

| Sample Size | Observed ORR | 95% CI of ORR (%) |
|---|---|---|
| 30 | 25% | (12.2, 45.9) |
| | 30% | (14.7, 49.4) |
| | 35% | (17.3, 52.8) |
| | 40% | (22.7, 59.4) |
| 60 | 25% | (14.7, 37.9) |
| | 30% | (18.9, 43.2) |
| | 35% | (23.1, 48.4) |
| | 40% | (27.6, 53.5) |

The sample size for the training set (n=100), was selected to achieve adequate precision on the PPV and NPV profiles as a function of putative cut-offs.

### 8.10 Subgroup Analyses and Effect of Baseline Factors

The estimate of the treatment effect for the primary endpoint will be estimated and/or plotted within each category of the following classification variables:

- Age category (<65 and ≥65 years)
- Race (Asian , non-Asian)
- Platinum sensitivity (platinum-resistant recurrent, partial platinum-sensitive recurrent)
- ECOG Performance Status (0,1)
- Histology (high-grade serous, endometroid, clear cell, and other)

### 8.11 Compliance (Medication Adherence)

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

### 8.12 Extent of Exposure

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

## 9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

### 9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of

investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 11.

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

Table 11 Product Descriptions

| Product Name & Potency | Dosage Form | Source/Additional Information |
|---|---|---|
| Pembrolizumab 50 mg/vial | Lyophilized powder for injection | Provided centrally by the Sponsor |
| Pembrolizumab 25mg/mL | Solution for infusion | Provided centrally by the Sponsor |

## 9.2 Packaging and Labeling Information

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

All supplies will be provided open label. Pembrolizumab will be provided as non-kitted single vials.

## 9.3 Clinical Supplies Disclosure

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

## 9.4 Storage and Handling Requirements

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

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

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

## 9.5 Discard/Destruction/Returns and Reconciliation

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

discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

### 9.6 Standard Policies

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

## 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. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

## 10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

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

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

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

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

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

## 10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

## 10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted

standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

## 10.6 Data Management

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

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

## 10.7 Publications

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

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

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

paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

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

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

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# 12.0 APPENDICES

## 12.1 Merck Code of Conduct for Clinical Trials

**Merck***
**Code of Conduct for Clinical Trials**

**I. Introduction**

**A. Purpose**

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

**B. Scope**

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

**II. Scientific Issues**

**A. Trial Conduct**

**1. Trial Design**

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

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

**2. Site Selection**

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

**3. Site Monitoring/Scientific Integrity**

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

**B. Publication and Authorship**

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

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

**III. Subject Protection**

**A. IRB/ERC review**

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

**B. Safety**

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

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

**C. Confidentiality**

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

**D. Genomic Research**

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

**IV. Financial Considerations**

**A. Payments to Investigators**

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

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

**B. Clinical Research Funding**

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

**C. Funding for Travel and Other Requests**

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

**V. Investigator Commitment**

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

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

## 12.2 Collection and Management of Specimens for Future Biomedical Research

### 1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

### 2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.8 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

### 3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

**4. Confidential Subject Information for Future Biomedical Research**

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

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

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

**5. Biorepository Specimen Usage**

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

**6. Withdrawal From Future Biomedical Research**

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated

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

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

**7. Retention of Specimens**

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

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

**8. Data Security**

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

**9. Reporting of Future Biomedical Research Data to Subjects**

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

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available

through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

**10. Future Biomedical Research Study Population**

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

**11. Risks Versus Benefits of Future Biomedical Research**

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

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

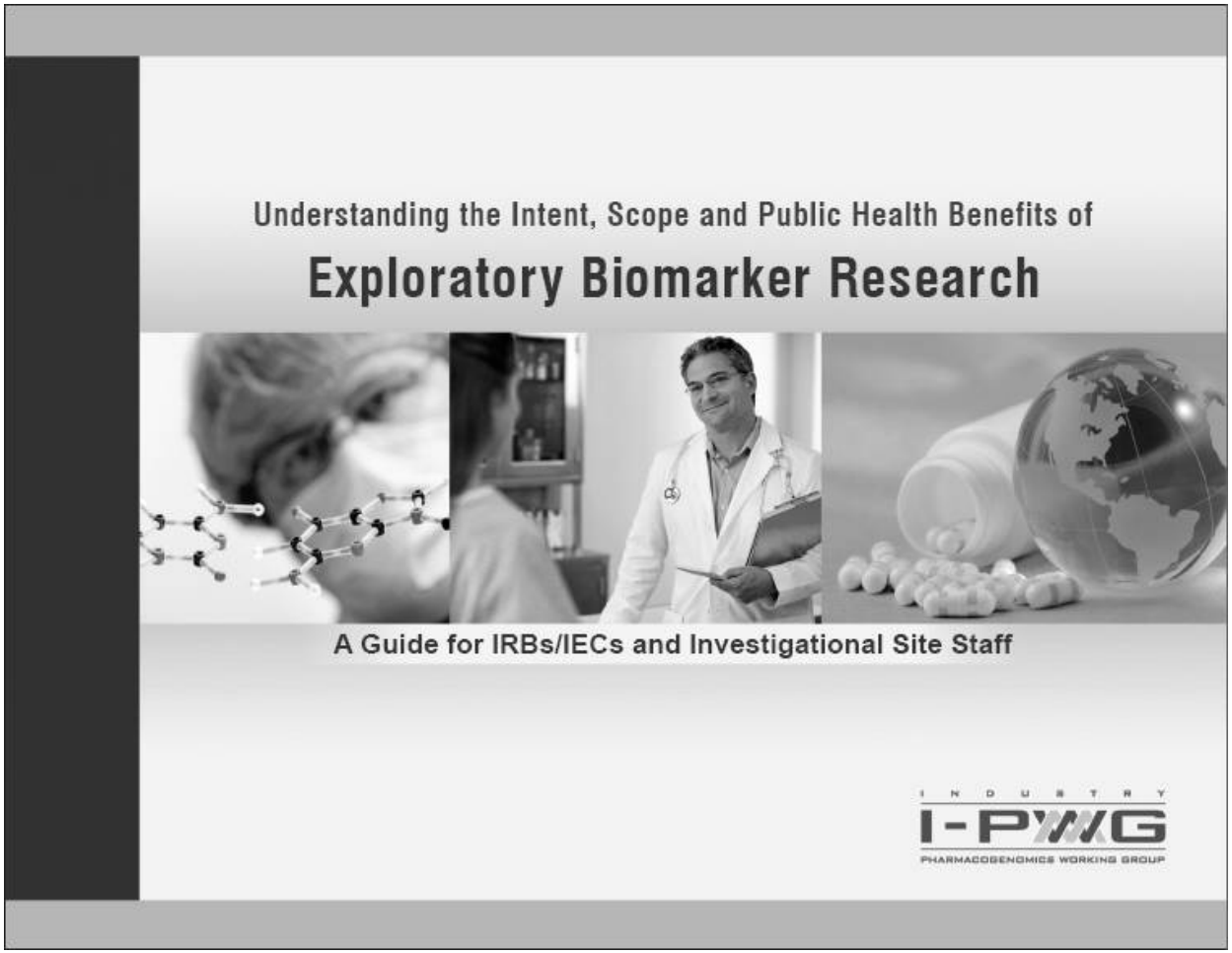
**12. Questions**

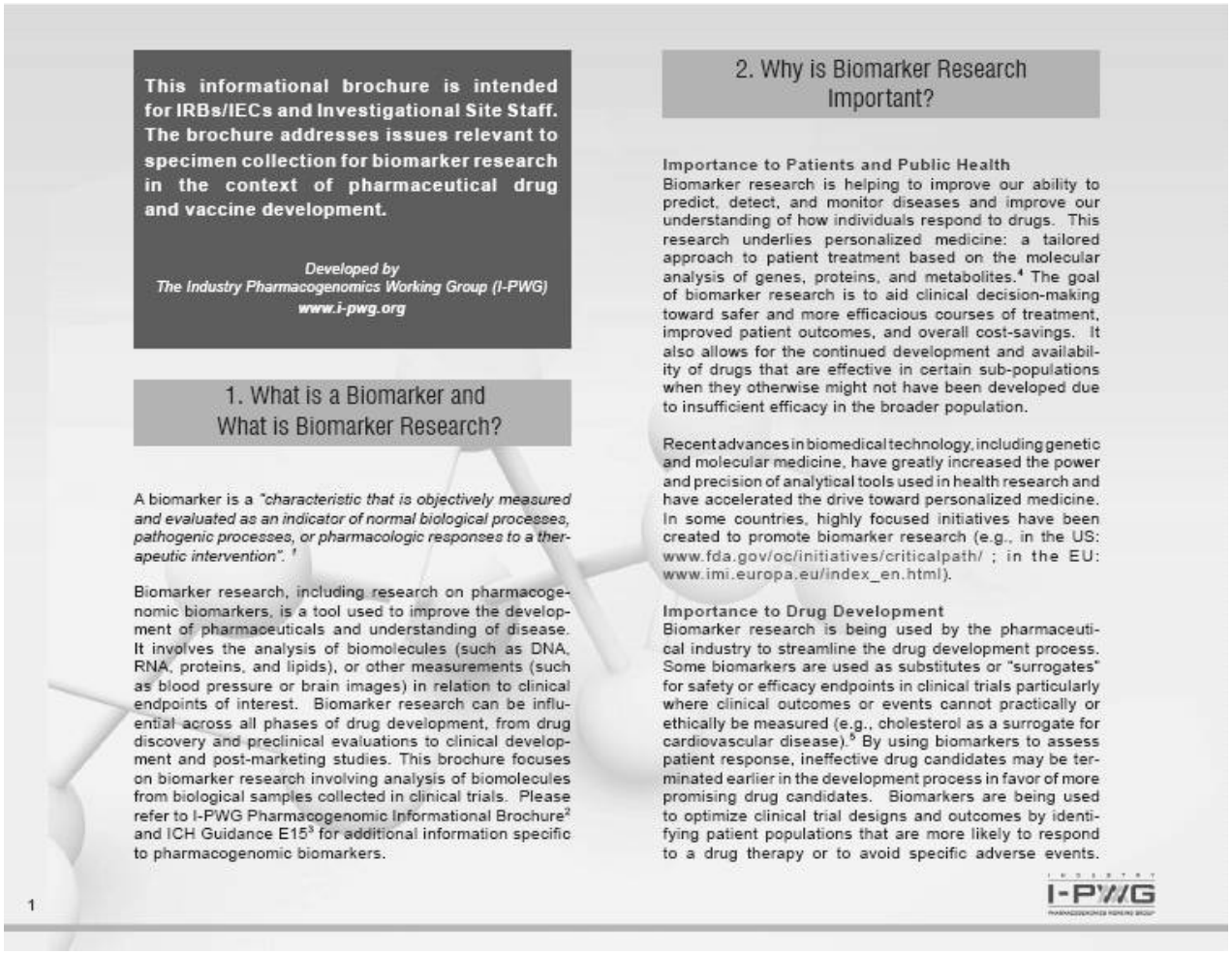
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

**13. References**

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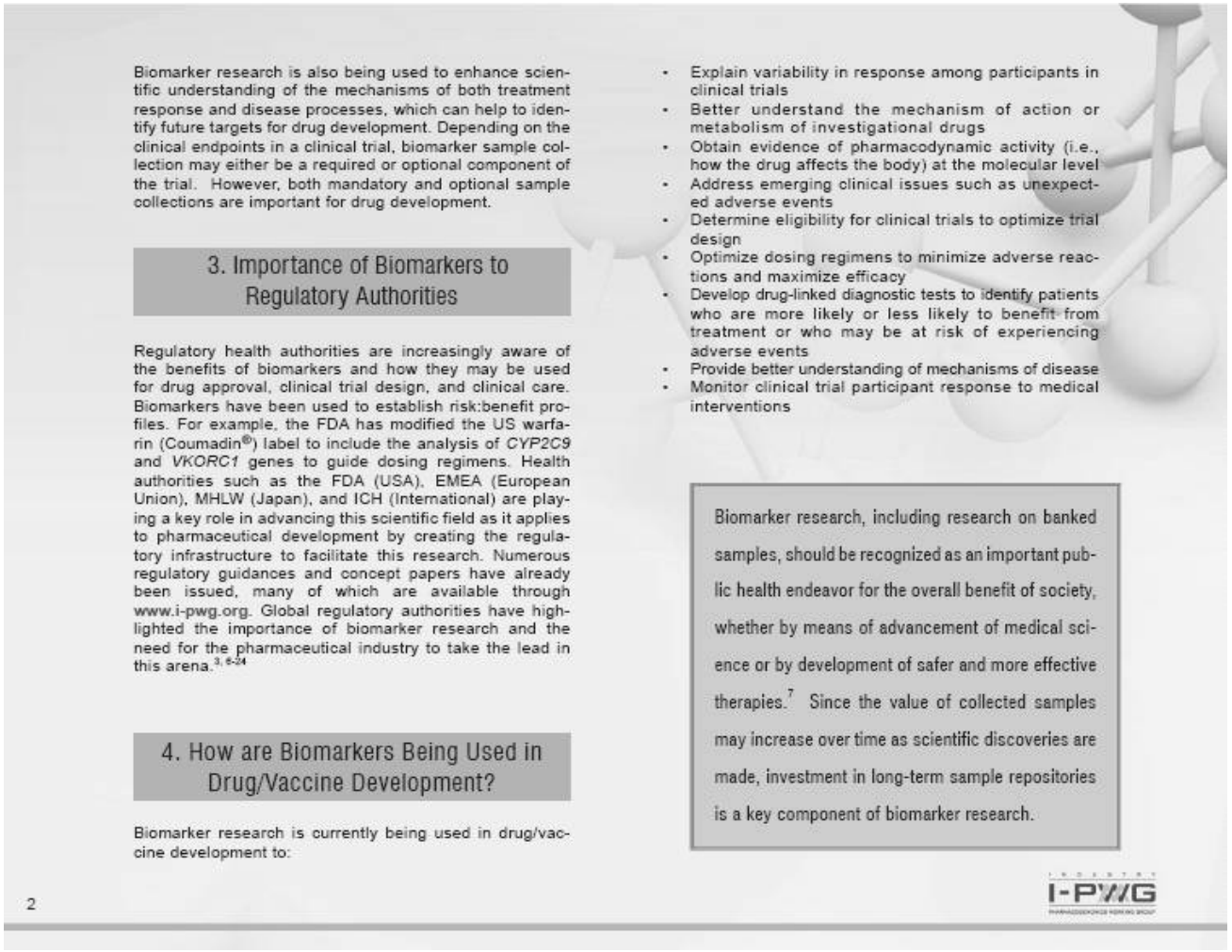

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either 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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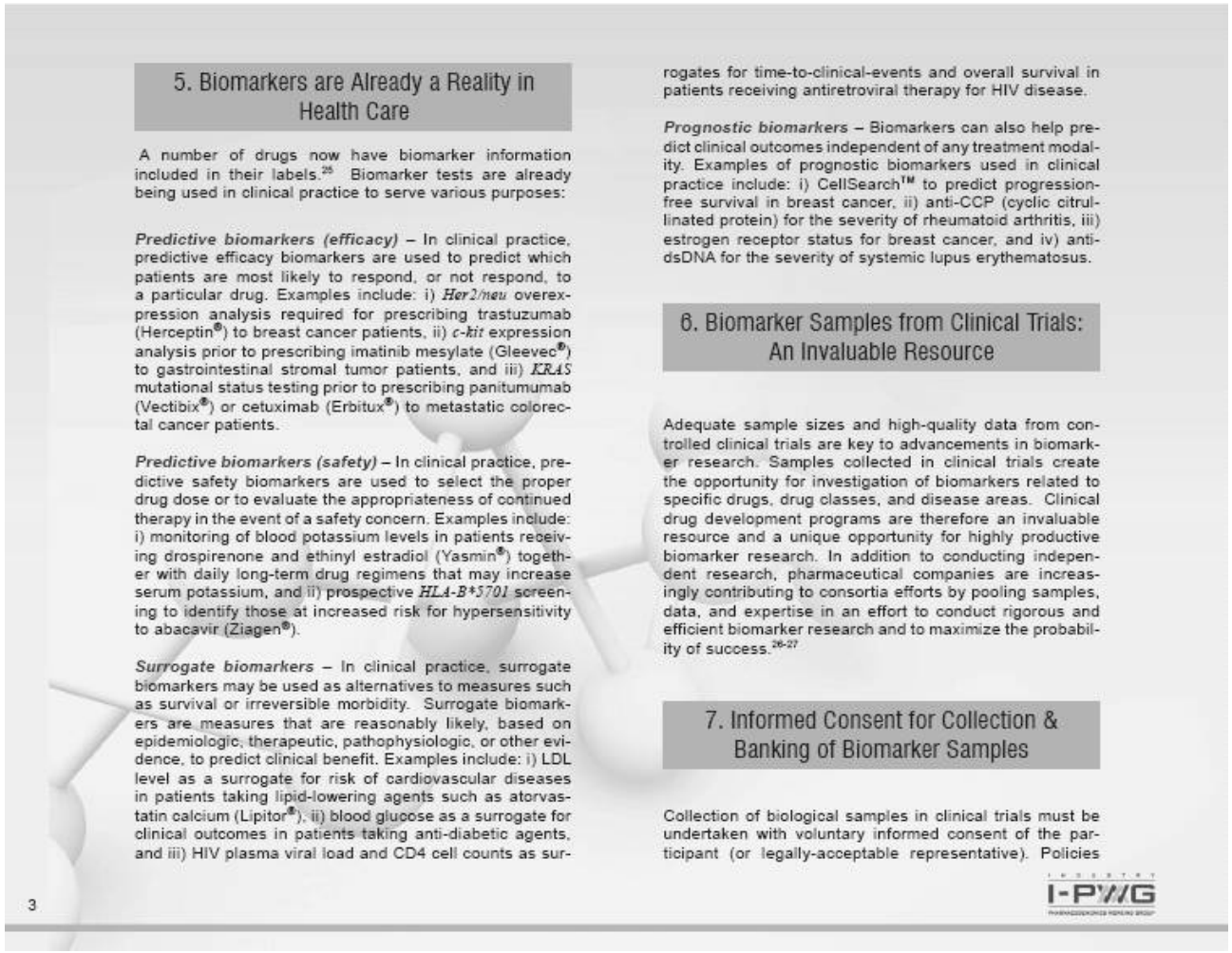

## 5. Biomarkers are Already a Reality in Health Care

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

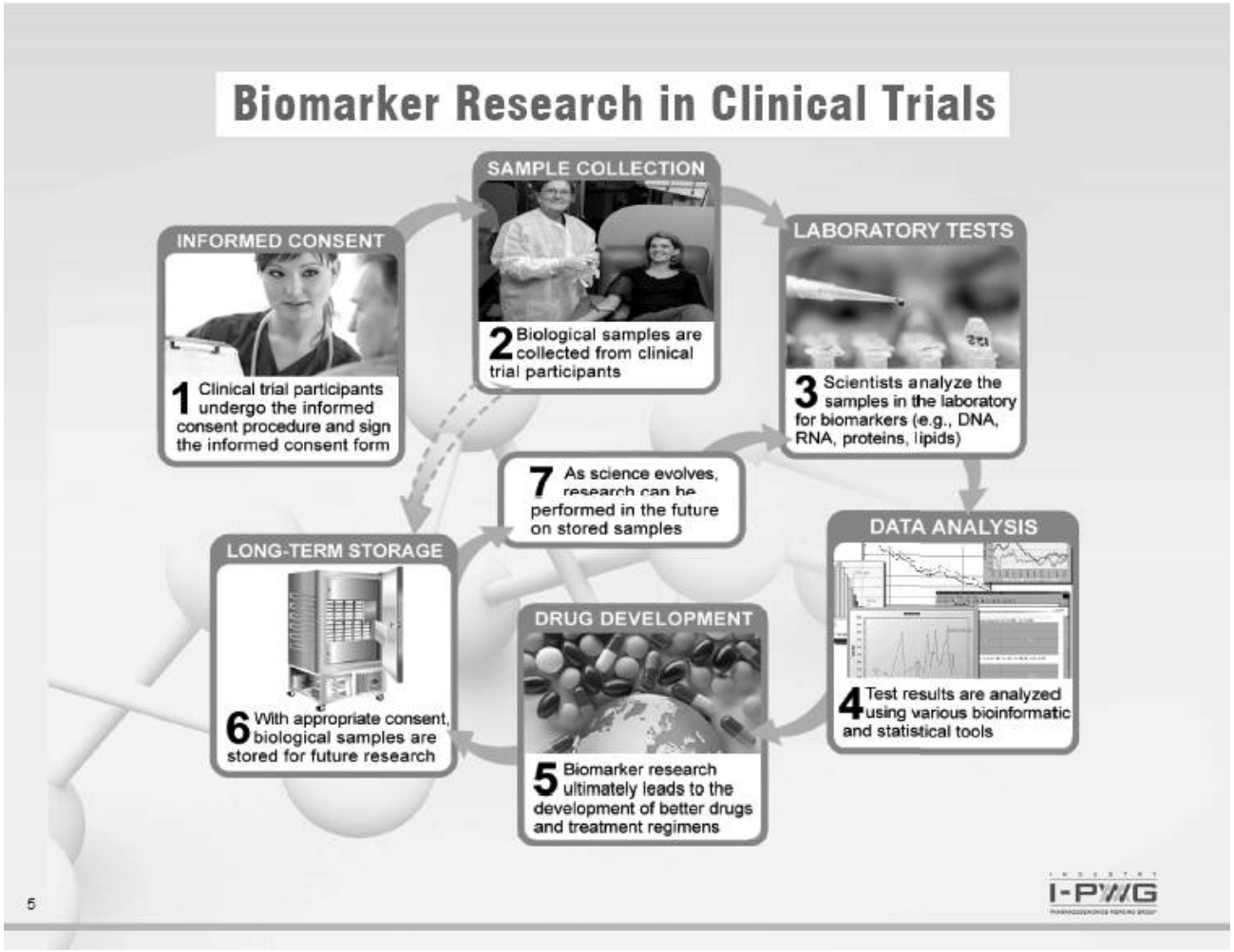
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants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


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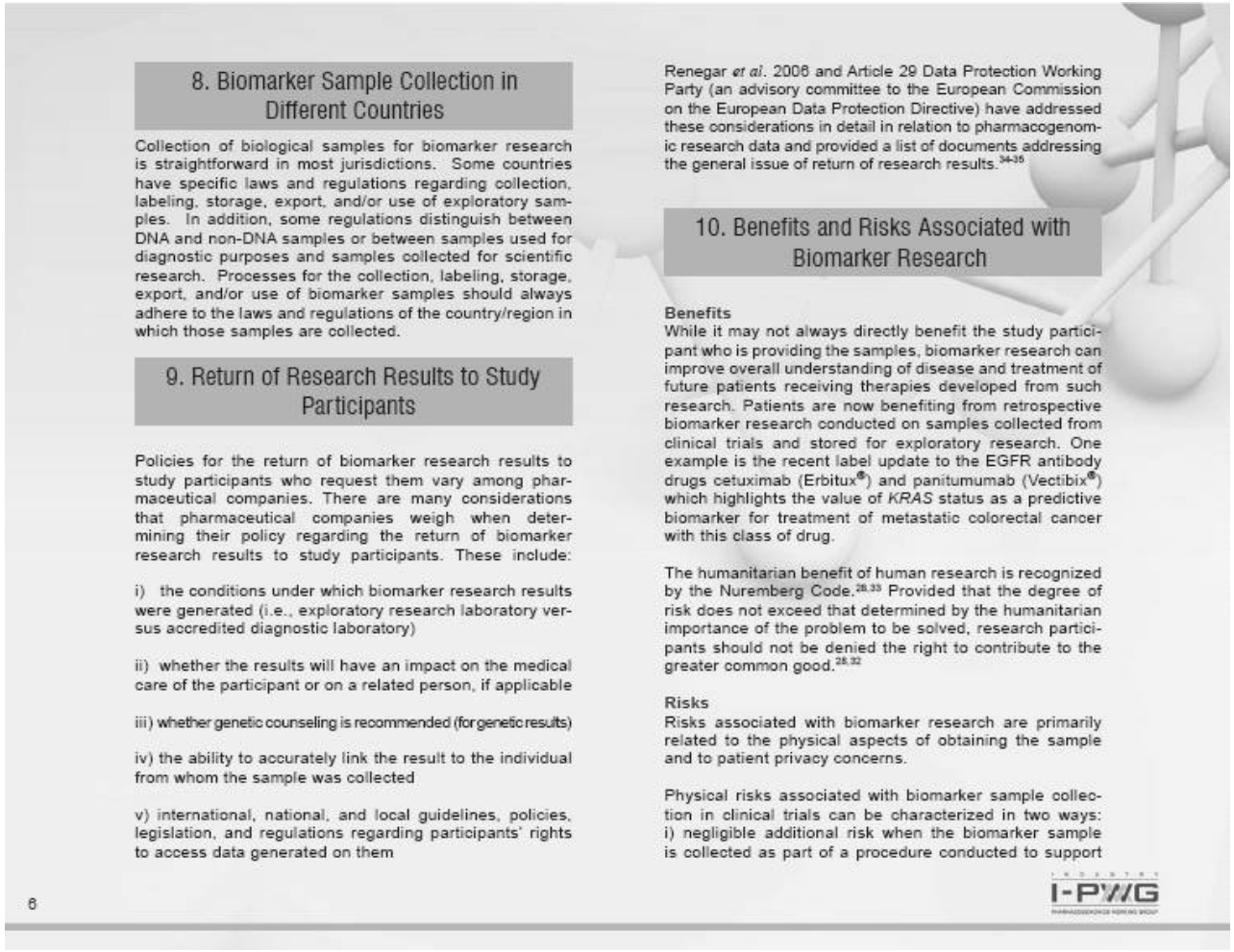

## 8. Biomarker Sample Collection in Different Countries

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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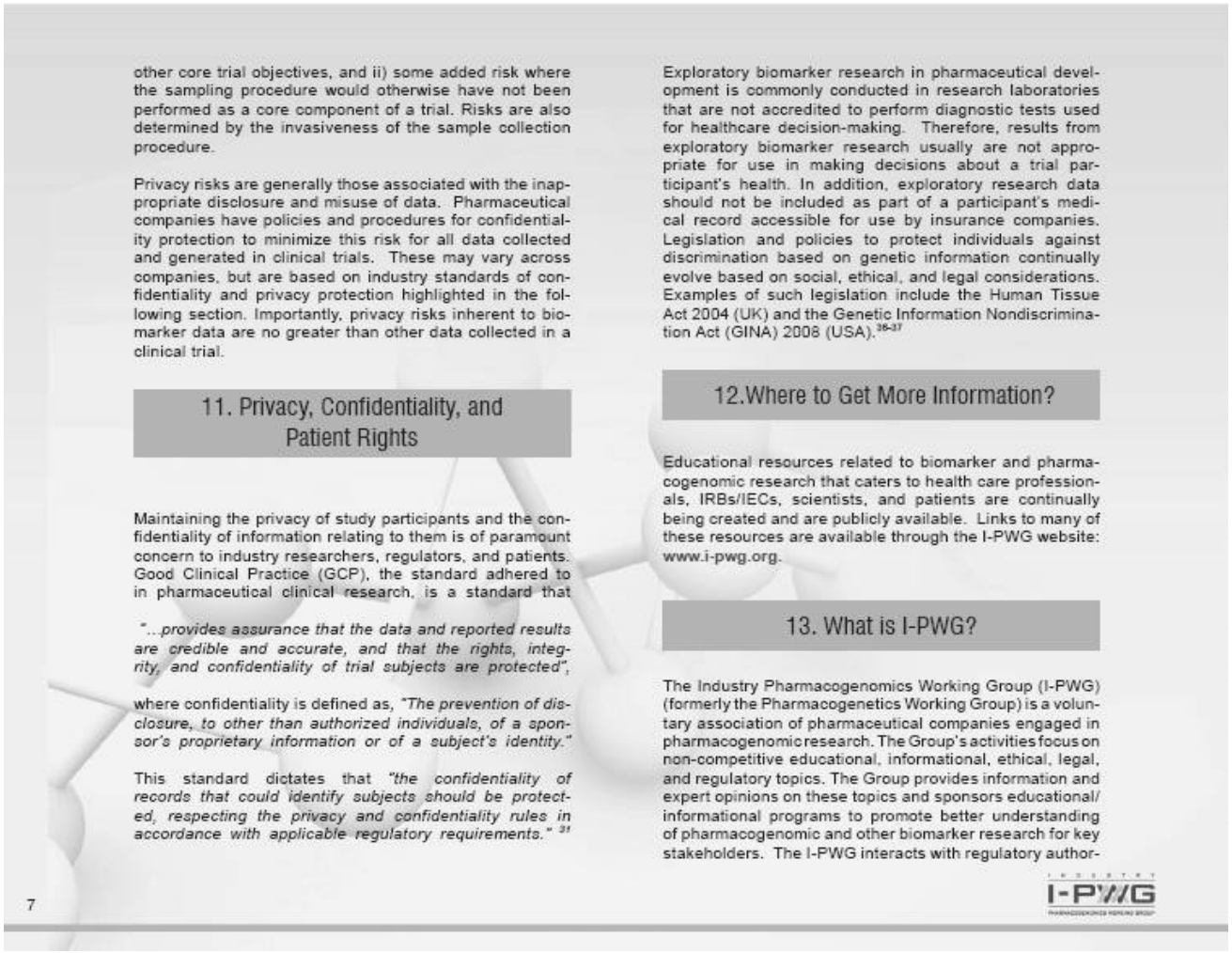

other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

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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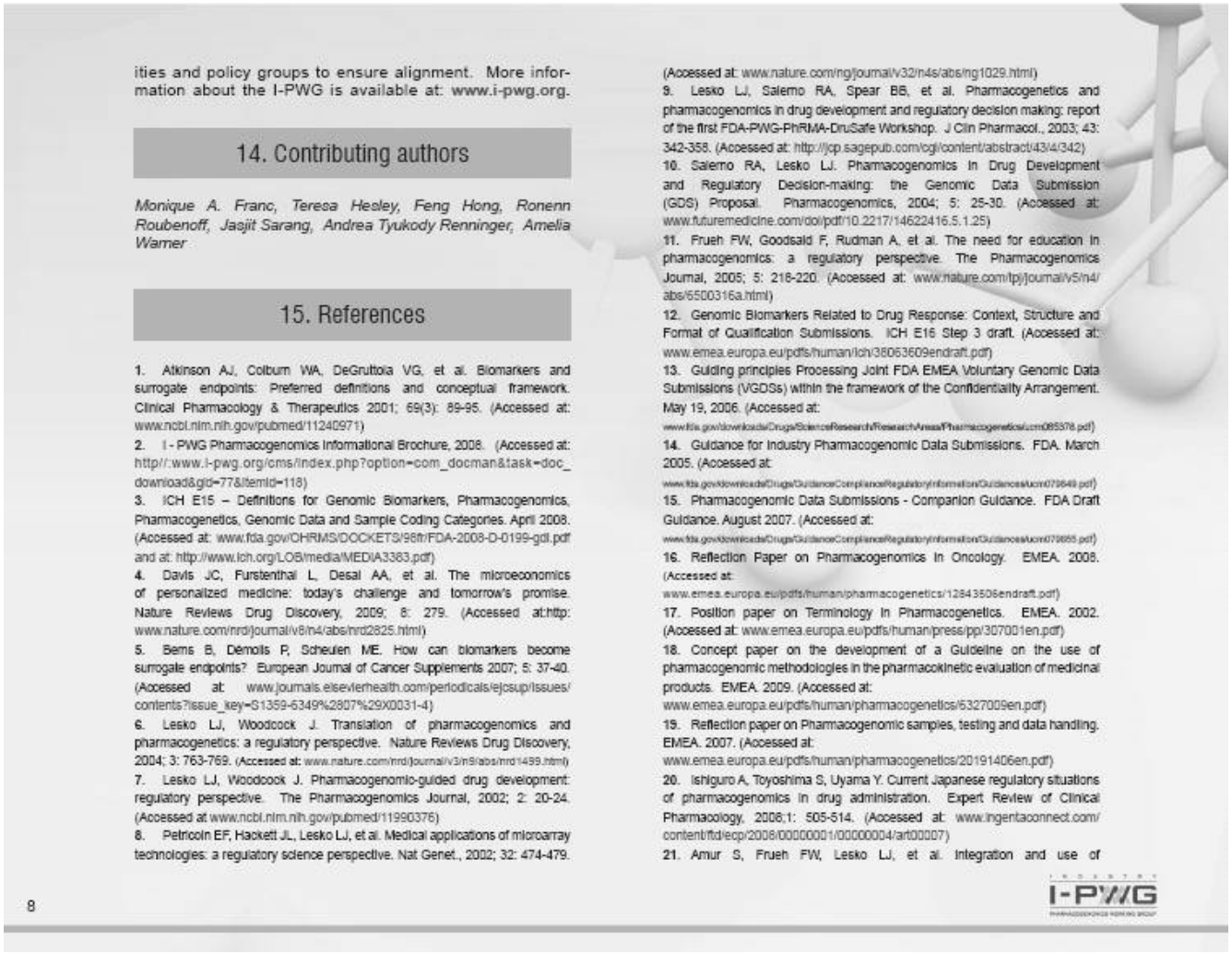

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

## 14. Contributing authors

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

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www.i-pwg.org

## 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 self-care. Totally confined to bed or chair. |
| 5 | Dead. |

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

## 12.5 Common Terminology Criteria for Adverse Events

The descriptions and grading scales found in the revised NCI CTCAE v4.0 will be utilized for AE reporting. (http://ctep.cancer.gov/reporting/ctc.html).

## 12.6 Abbreviations

| Abbreviation/Term | Definition |
|---|---|
| AE | adverse event |
| ADA | anti-drug antibodies |
| ASaT | All Subjects as Treated |
| BICR | Blinded Independent Central Review |
| CA 125 | cancer antigen 125 |
| CD | carboplatin plus pegylated liposomal doxorubicin |
| CI | confidence interval |
| CP | carboplatin plus paclitaxel |
| CR | complete response |
| CSR | clinical study report |
| CT | computed tomography |
| CTCAE | Common Toxicity Criteria for Adverse Events |
| CTLs | cytotoxic t lymphocytes cells |
| CTLA-4 | cytotoxic t-lymphocyte-associated antigen-4 |
| DCR | disease control rate |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECI | events of clinical interest |
| ECOG | Eastern Cooperative Oncology Group |
| EDC | electronic data capture |
| eCRFs | electronic case report forms |
| EOC | epithelial ovarian cancer |
| ERC | Ethics Review Committee |
| FAS | Full Analysis Set |
| FBR | future biomedical research |
| FDAAA | Food and Drug Administration Amendments Act |
| FDAMA | Food and Drug Administration Modernization Act |
| FSH | follicle-stimulating hormone |
| GCIG | Gynecologic Cancer InterGroup |
| GCP | Good Clinical Practice |
| GEP | gene-expression profile |
| HGSC | high-grade serous carcinoma |
| HIV | human immunodeficiency virus |
| HR | hazard ratio |
| ICH | International Conference for Harmonization |
| IgG4 | immunoglobulin g4 |
| IHC | immunohistochemistry |
| IP | intraperitoneal |
| irAEs | immune-related adverse events |
| irRECIST | Immune-related Response Evaluation Criteria in Solid Tumors |
| IRB | Institutional Review Board |
| IUD | intrauterine device |
| IV | intravenous |
| IVRS | interactive voice response system |
| IWRS | integrated web response system |
| KM | Kaplan-Meier |
| KN | KEYNOTE |
| LMP | last menstrual period |

| Abbreviation/Term | Definition |
|---|---|
| mAb | monoclonal antibody |
| MRI | magnetic resonance imaging |
| MSD | Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. |
| NCI | National Cancer Institute |
| NPV | negative predictive value |
| NSCLC | non-small cell lung cancer |
| ORR | overall response rate |
| OS | overall survival |
| OTC | over-the-counter |
| PBPK | physiologically-based pharmacokinetic |
| PD | progressive disease |
| PD-1 | programmed cell death protein 1 |
| PD-L1 | program cell death-ligand protein 1 |
| PD-L2 | program cell death-ligand protein 2 |
| PFI | platinum-free interval |
| PFS | progression-free survival |
| PK | pharmacokinetic |
| PLD | pegylated liposomal doxorubicin |
| PPV | positive predictive value |
| PR | partial response |
| Q2W | every 2 weeks |
| Q3W | every 3 weeks |
| Q9W | every 9 weeks |
| Q12W | every 12 weeks |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | ribonucleic acid |
| ROC | recurrent ovarian cancer |
| SAC | Scientific Advisory Committee |
| SAE | serious adverse events |
| SD | stable disease |
| sSAP | supplemental Statistical Analysis Plan |
| TFI | treatment-free interval |
| TILs | tumor-infiltrating lymphocytes |
| TTR | time to recurrence |
| ULN | upper limit of normal |

# 13.0 SIGNATURES

## 13.1 Sponsor's Representative

| | |
|---|---|
| TYPED NAME | |
| TITLE | |
| SIGNATURE | |
| DATE SIGNED | |

## 13.2 Investigator

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

| | |
|---|---|
| TYPED NAME | |
| TITLE | |
| SIGNATURE | |
| DATE SIGNED | |

# MK 3475-P100

## Supplemental Statistical Analysis Plan (sSAP)

# TABLE OF CONTENTS

TABLE OF CONTENTS....2
1. INTRODUCTION....3
2. SUMMARY OF CHANGES....3
3. ANALYTICAL AND METHODOLOGICAL DETAILS....4
3.1 Statistical Analysis Plan Summary....4
3.2 Responsibility for Analyses/In-House Blinding....5
3.3 Hypotheses/Estimation....5
3.4 Analysis Endpoints....5
3.4.1 Efficacy Endpoints....5
3.4.2 Safety Endpoints....6
3.5 Analysis Populations....6
3.5.1 Efficacy Analysis Populations....6
3.5.2 Safety Analysis Populations....7
3.6 Statistical Methods....7
3.6.1 Statistical Methods for Efficacy Analyses....7
3.6.2 Statistical Methods for Safety Analyses....10
3.6.3 Demographic and Baseline Characteristics....10
3.7 Interim Analysis....10
3.8 Multiplicity....10
3.9 Sample Size and Power Calculations....11
3.10 Subgroup Analyses and Effect of Baseline Factors....12
3.11 Extent of Exposure....12

## 1. INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

## 2. SUMMARY OF CHANGES

**PRIMARY REASON(S) FOR THIS AMENDMENT:**

| Section Number (s) | Section Title(s) | Description of Change (s) | Rationale |
|---|---|---|---|
| 3.1 | Statistical Analysis Plan Summary | Population of primary efficacy analysis changed to All Subjects as Treated (ASaT). | Per FDA requirement. |
| 3.1 | Statistical Analysis Plan Summary | Delete 95% CI for safety analysis. | For single arm study, 95% CI for AE incidence rate is not required. |
| 3.4.1 | Efficacy Endpoints | Reorganized. | To align with protocol section 3 Objectives. |
| 8.4.1 | Efficacy Endpoints | Updated definition of PFS | Editorial update |
| 3.6.1 | Statistical Methods for Efficacy Analysis | Censoring rules for DOR and PFS added. | To provide more details about censoring rule. |
| 3.6.1 | Statistical Methods for Efficacy Analysis | Added information regarding data cutpoint | To provide maximum flexibility to perform additional data analysis |
| 3.11 | Compliance | Section deleted. | Per new alignment. |

# 3. ANALYTICAL AND METHODOLOGICAL DETAILS

## 3.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 3.2-3.12.

| | |
|---|---|
| Study Design Overview | A Phase II, open-label, single arm, two-cohort, multi-center trial of pembrolizumab monotherapy in subjects with advanced ovarian cancer who have demonstrated recurrent disease following the front line treatment and received up to 5 lines of treatments for ROC. |
| Treatment Assignment | Cohort A will enroll subjects with ROC who have received 0-2 prior lines for treating ROC (i.e., 1-3 total prior lines counting the front line) and with a platinum-free interval or treatment-free interval of 3 to 12 months based on the last regimen received.<br><br>Cohort B will enroll subject with ROC who have received 3 to 5 prior lines for treating ROC (i.e., 4-6 total prior lines counting the front line) and with a platinum-free interval or treatment-free interval ≥3 months based on the last regimen received.<br><br>In both cohorts, subjects will be treated with pembrolizumab monotherapy 200 mg every 3 weeks (Q3W) as trial treatment by non-randomized assignment in an unblinded fashion. |
| Analysis Populations | Efficacy: All Subjects as Treated (ASaT)<br><br>Safety: All Subjects as Treated (ASaT) |
| Primary Endpoint(s) | ORR by RECIST 1.1 per BICR review |
| Key Secondary Endpoints | • DOR, DCR, PFS per RECIST 1.1 as assessed by BICR<br>• OS |
| Statistical Methods for Key Efficacy Analyses | The primary objectives will be evaluated by the point estimate and 95% confidence interval for the ORR in the Cohort A-All Comer Population and Cohort A PD-$L1_H$ subgroup, respectively, using an exact binomial distribution. ORR will be evaluated similarly in the Cohort B-All Comer group and Cohort B PD-$L1_H$ subgroup, respectively. |
| Statistical Methods for Key Safety Analyses | Summary statistics for the incidence rate of Grade 2 or higher adverse events with an immune etiology and the incidence rate of Grade 4/5 AEs. |
| Interim Analyses | An interim analysis is planned at 4 months after the first 100 subjects have been enrolled in Cohort A, which will be used as the training set. IA will evaluate clinical activity and the correlation of PD-L1 in tumor tissue samples in the training set to facilitate the PD-L1 expression cutoff selection. |
| Multiplicity | No multiplicity adjustment has been planned. |

| | |
|---|---|
| Sample Size and Power | Cohort A-All Comer group include all enrolled subjects of Cohort A. A minimum of 75 subjects will be enrolled for the subgroup with a PFI/TFI of 3-<6 months and a minimum of 75 subjects will be enrolled for the subgroup with a PFI/TFI of 6 to 12 months. The first 100 enrolled Cohort A subjects will be used as the training set for determining a PD-L1 expression cut point. The additional 150 enrolled Cohort A subjects will be in the confirmation set, therefore, the study will enroll approximately 250 Cohort A subjects regardless of the PD-L1 status. The exact number of subjects enrolled in the confirmation set will depend on the prevalence of the PD-$L1_H$ as determined by the biomarker analysis. Approximately 75 subjects will be enrolled in Cohort B. |

## 3.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the clinical biostatistics department of the SPONSOR. This trial is being conducted as an open-label non-randomized single-arm clinical trial, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned. The study team at the Sponsor consisting of clinical, statistical, statistical programming and data management personnel, will be blinded to subject-level PD-L1 biomarker results. An unblinded Sponsor biomarker statistician will have access to the subject-level PD-L1 results for the purpose of data review and biomarker correlation analysis. The unblinded SPONSOR biomarker statistician will have no other responsibilities associated with the study.

## 3.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.0 of the protocol.

## 3.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

### 3.4.1 Efficacy Endpoints

**Primary**

- **Objective response rate (ORR) - per RECIST 1.1 assessed by BICR**

Objective Response Rate (ORR), defined as the proportion of subjects in the analysis population who have confirmed complete response (CR) or partial response (PR) at any time during the study.

**Secondary**

- **Duration of Response (DOR) - per RECIST 1.1 assessed by BICR and by investigator**

Duration of response (DOR), defined as the time from first documented evidence of response to disease progression in subjects who achieve a confirmed PR or CR.

- **Progression-free Survival (PFS) - per RECIST 1.1 assessed by BICR and by investigator**

Progression-free survival (PFS), defined as the time from the first day of study treatment to the first documented disease progression or death due to any cause, whichever occurs first.

- **Overall survival (OS)**

Overall survival (OS), defined as the time from the first day of study treatment to death due to any cause.

- **Disease Control Rate (DCR) - per RECIST 1.1 assessed by BICR**

Disease Control Rate (DCR), defined as the percentage of subjects who have achieved confirmed CR or PR or have demonstrated SD for at least 24 weeks prior to any evidence of progression.

**Exploratory**

- **Progression-free survival (PFS) – irRECIST assessed by BICR**

Progression-free-survival (PFS) is defined as the time from first day of study treatment to the first confirmed disease progression or death due to any cause, whichever occurs first.

ORR and DOR per irRECIST by BICR are also the exploratory efficacy endpoints.

### 3.4.2 Safety Endpoints

Safety measurements are as described in Section 4.2.3.2 of the protocol.

The primary safety endpoints are AEs graded using CTCAE (Version 4.0 or above) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including serious adverse events (SAEs) and events of clinical interest (ECIs). Other safety endpoints include laboratory safety assessments, vital signs, reasons for treatment discontinuation, dose interruptions or reductions, and physical examinations.

## 3.5 Analysis Populations

### 3.5.1 Efficacy Analysis Populations

**Cohort A**

The all subjects as treated (ASaT) in Cohort A who receive at least one dose of study treatment, will serve as the primary population for the analyses of efficacy data for Cohort A *All Comers*. The all subjects as treated (ASaT) population for PD-L1$_H$ subgroup in Cohort A, which includes the subjects in the confirmation set above the PD-L1 cut-off, will be used for the analyses of efficacy data for PD-L1$_H$ subjects in Cohort A

**Cohort B**

The all subjects as treated (ASaT) population consists of all subjects in Cohort B who receive at least one dose of study treatment. The all subjects as treated (ASaT) population for PD-$L1_H$ subgroup in Cohort B, which includes the subjects in Cohort B above the PD-L1 cut-off, will be used for the analyses of efficacy data for PD-$L1_H$ subjects in Cohort B.

### 3.5.2 Safety Analysis Populations

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

## 3.6 Statistical Methods

### 3.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives.

Data from the training set (first 100 subjects in Cohort A) will be evaluated for biomarker analysis and cut point determination. Subjects who did not meet Treatment-free Interval/Platinum-free Interval inclusion criteria for Cohort A would be excluded from the cut point determination analysis.

Efficacy will be evaluated in the *All Comer* group and the PD-$L1_H$ subgroup for Cohort A and B respectively. For the primary efficacy endpoint, the ORR based on RECIST 1.1 by the BICR, the point estimate, and 95% confidence interval (as determined by the upper and lower 97.5% one-sided confidence bounds) will be provided using an exact binomial distribution. Secondary efficacy evaluations of ORR based on RECIST 1.1 by investigator review, DCR based on RECIST 1.1 by the BICR and ORR based on irRECIST by BICR will also be conducted using the same methodology as for the primary efficacy analysis. Subjects without response data will be counted as non-responders and disease not controlled.

Duration of response by BICR and investigator review will be summarized using Kaplan-Meier method in all responders.

For PFS and OS, Kaplan-Meier (KM) curves, median estimates, and survival at 6, 12 and 18 months based on the KM curves (95% CI is based on Greenwood's formula) will be provided as appropriate. Subjects without efficacy evaluation data or without survival data will be censored at Day 1. The restricted Mean Survival Time estimate of PFS and OS will also be calculated and plotted over time. Censoring rules for DOR and PFS are summarized in Table 1 and Table 2 respectively.

Table 1 Censoring Rules for Analyses of DOR

| Situation | Date of progression or censoring | Outcome |
|---|---|---|
| No progression nor death, no new anti-cancer therapy initiated | Last adequate assessment | Censor (non-event) |
| No progression nor death, new anti-cancer therapy initiated | Last adequate assessment before new anti-cancer therapy initiated | Censor (non-event) |
| Death or progression after ≥ 2 consecutive missed adequate disease assessments | Last adequate assessment prior to ≥ 2 missed adequate disease assessments | Censor (non-event) |
| Death or progression after ≤1 missed adequate disease assessments | Death or progression | End of response (Event) |
| A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response. | | |

Table 2 Censoring Rules for Analyses of PFS

| Situation | Date of progression or censoring |
|---|---|
| No PD and no death; new anticancer treatment is not initiated | Censored at last disease assessment |
| No PD and no death; new anticancer treatment is initiated | Censored at last disease assessment before new anticancer treatment |
| PD or death documented after ≤ 1 missed disease assessment | Progressed at date of documented PD or death |
| PD or death documented after ≥ 2 missed disease assessments | Progressed at date of documented PD or death |

An outline of the key efficacy analysis strategy is presented in Table 3.

Table 3 Analysis Strategy for Key Efficacy Endpoints

| Endpoint | Statistical Method | Analysis Population | Missing Data Approach |
|---|---|---|---|
| • ORR by BICR per RECIST1.1<br>• ORR by investigator assessment per RECIST1.1 | Exact test of binomial parameter; 95% CI† | ASaT | Subjects with missing data are considered non-responders |
| • DOR by BICR per RECIST1.1<br>• DOR by investigator assessment per RECIST1.1 | Summary statistics using<br>Kaplan-Meier method | All responders | Refer to Table 1 |
| • PFS by BICR and investigator assessment per RECIST 1.1 | Summary statistics using<br>Kaplan-Meier method | ASaT | Refer to Table 2 |
| • DCR by BICR and investigator assessment per RECIST 1.1 | Exact test of binomial parameter; 95% CI† | ASaT | Subjects with missing data are considered disease not controlled |
| • OS | Summary statistics using Kaplan-Meier method | ASaT | Censored at last known alive date |

†95% confidence interval is determined by the upper and lower 97.5% one-sided confidence bounds.

The strategy to address multiplicity issues with regard to multiple endpoints and interim analyses is described in Section 3.7, Interim Analyses and in Section 3.8, Multiplicity.

The evaluation of a general positive association between CPS and BOR will be investigated via standard logistic regression as well as generalized additive models. The potential for a cut-off greater than CPS 1% to define a PD-L1 positive population with good clinical utility will depend on the strength of evidence in the observed association, as well as a detailed evaluation of the relative improvement in clinical utility with higher cut-offs. This evaluation involves a review of the positive predictive value (PPV, response rate in those above a cut-off), sensitivity (proportion

above the cutoff among responders), negative predictive value (NPV, non-response rate in those below the cut-off), specificity (proportion below the cutoff among non-responders), and fraction of PD-L1 positive patients (prevalence) as functions of increasing cut-offs. A clinically useful PD-L1 positive cut-off should maintain high NPV (e.g. near or above 90%) while achieving a meaningful enrichment of response, and largely capturing patients showing durable clinical benefit is sought. A receiver operating characteristic curve, and graphical illustrations will be utilized to assess the performance of a binary classifier and to understand the sensitivity and specificity profile in the context of PPV and NPV. Analyses will also be performed on PFS and OS, as appropriate, examining associations using cox proportional hazards models and KM estimates with graphical illustrations. CPS ranges for any promising cut-offs will also have to be gauged in the context of practical implementation and interpretation by pathologists in clinical practice.

The associations between clinical response and other biomarkers, e.g., immune-related mRNA expression signatures and somatic mutational load, will be evaluated similarly.

### 3.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs. Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate.

### 3.6.3 Demographic and Baseline Characteristics

Baseline characteristics will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, enrolled, primary reasons for screening failure, and discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables. The *All Comer* group and the PD-L1$_H$ subgroup will be summarized separately for Cohort A and Cohort B.

## 3.7 Interim Analysis

An interim analysis will be performed after 100 subjects in Cohort A have been enrolled and followed up for at least 4 months to determine a PD-L1 expression cutpoint based on PD-L1 biomarker and tumor response data. The results of this analysis will be presented to the study team without unblinding anyone to biomarker results for any individuals. The efficacy data from the interim analysis may facilitate further interactions with regulatory agencies.

## 3.8 Multiplicity

The primary objectives for ORR per RECIST 1.1 in All Comer Population and PD-L1$_H$ subgroup for Cohort A and Cohort B will be assessed by point estimate and 95% confidence interval. There are no formal hypotheses and no adjustments for multiplicity are planned. Evaluation of objectives should be interpreted with caution due to the potential for an increase in the false positive rate.

## 3.9 Sample Size and Power Calculations

Based on the preliminary data of pembrolizumab in ovarian cancer patients as described in Section 4.1.2 of the protocol, we expect an ORR of approximately 25% for the *All Comer* population. These responding subjects expect to have durable responses. In addition we expect additional subjects will have durable stable disease. We expect in a PD-L1 enriched population, ORR may reach to above 35% with durable response in majority of the subjects.

Table 4 shows the two-sided 95% confidence interval of ORR for different observed response rates based on different sample size in the *All Comer* group for Cohort A or Cohort B.

Table 4 Two-sided 95% Confidence Interval of ORR in All Comer

| Sample Size | Observed ORR | 95% CI of ORR (%) |
|---|---|---|
| 75 | 17% | (9.3, 27.4) |
| | 25% | (15.7, 36.3) |
| | 30% | (20.0, 41.7) |
| | 35% | (24.3, 46.9) |
| 100 | 17% | (10.2, 25.8) |
| | 25% | (16.9, 34.7) |
| | 30% | (21.2, 40.0) |
| | 35% | (25.7, 45.2) |
| 180 | 17% | (12.0, 23.5) |
| | 25% | (18.9, 32.0) |
| | 30% | (23.4, 37.3) |
| | 35% | (28.1, 42.4) |
| 250 | 17% | (12.7, 22.5) |
| | 25% | (20.0, 31.1) |
| | 30% | (24.4, 36.1) |
| | 35% | (29.3, 41.5) |

For the PD-L1$_H$ subgroup, if the prevalence of PD-L1$_H$ is about 40%, there will be approximately 60 PD-L1$_H$ subjects if there are 150 all comer subjects in the confirmation set, and approximately 30 PD-L1$_H$ subjects if there are 75 all comer subjects in Cohort B. Table 5 shows the two-sided 95% CI of ORR with 30 and 60 subjects for different response rates.

The sample size for the training set (n=100), was selected to achieve adequate precision on the PPV and NPV profiles as a function of putative cut-offs.

Table 5 Two-sided 95% Confidence Interval for ORR in PD-L1$_H$

| Sample Size | Observed ORR | 95% CI of ORR (%) |
|---|---|---|
| 30 | 25% | (12.2, 45.9) |
| | 30% | (14.7, 49.4) |
| | 35% | (17.3, 52.8) |
| | 40% | (22.7, 59.4) |
| 60 | 25% | (14.7, 37.9) |
| | 30% | (18.9, 43.2) |
| | 35% | (23.1, 48.4) |
| | 40% | (27.6, 53.5) |

### 3.10 Subgroup Analyses and Effect of Baseline Factors

The estimate of the treatment effect for the primary endpoint will be estimated and/or plotted within each category of the following classification variables:

- Age category (<65 , ≥65 years)
- Race (Asian , non-Asian)
- Platinum sensitivity (platinum resistant recurrent, partial platinum sensitive recurrent)
- ECOG Performance Status (0,1)
- Histology (high-grade serous, mucinous, endometroid, clear cell, and other)

### 3.11 Extent of Exposure

The extent of exposure will be summarized as number of cycles in which the subject receives the study medication infusion.