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| **Official Protocol Title:** | A phase IIb, clinical trial to study the safety and efficacy of Pembrolizumab (MK-3475) in combination with TS-1 +Cisplatin or TS-1+Oxaliplatin as a First Line Chemotherapy in participants with Advanced or Recurrent Gastric Cancer (KEYNOTE-659) |
| **NCT number:** | NCT03382600 |
| **Document Date:** | 27-Nov-2017 |

# Title Page

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**Protocol Title:** A phase IIb, clinical trial to study the safety and efficacy of Pembrolizumab (MK-3475) in combination with TS-1+Cisplatin or TS-1+Oxaliplatin as a First Line Chemotherapy in participants with Advanced or Recurrent Gastric Cancer (KEYNOTE-659)

**Protocol Number: 659-00**

**Compound Number: MK-3475**

**Sponsor Name and Legal Registered Address:**

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

**Regulatory Agency Identifying Number(s):**

**IND NUMBER:** 123,482

**EudraCT NUMBER:** Not Applicable

**Approval Date: 27-Nov-2017**

**Sponsor Signatory**

Typed Name: Date
Title:

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

**Investigator Signatory**

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Date
Title:

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## 1. Synopsis

**Protocol Title:**

**A phase IIb, clinical trial to study the safety and efficacy of Pembrolizumab (MK-3475) in combination with TS-1+Cisplatin or TS-1+Oxaliplatin as a First Line Chemotherapy in participants with Advanced or Recurrent Gastric Cancer (KEYNOTE-659).**

**Short Title:**

Phase IIb study of Pembrolizumab in combination with TS-1+Cisplatin or TS-1+Oxaliplatin in GC.

**Objectives/Hypotheses and Endpoints:**

In subjects with PD-L1 positive, advanced gastric or GEJ adenocarcinoma, the following objectives will be applied to Cohort 1 and Cohort 2 separately.

| Objective/Hypothesis | Endpoint |
|---|---|
| Primary | |
| • To evaluate ORR per RECIST 1.1 as assessed by blinded independent central review (BICR). | • ORR is defined as the proportion of participants who have a confirmed complete response (CR) or partial response (PR). |
| Secondary | |
| • To evaluate the Duration of Response (DOR) per RECIST 1.1 and per iRECIST as assessed by BICR. | • DOR defined as the time from the earliest date of qualifying response until earliest date of disease progression or death from any cause, whichever comes first. |
| • To evaluate ORR per iRECIST by BICR. | • ORR is defined as the proportion of participants who have a confirmed complete response (CR) or partial response (PR). |
| • To evaluate Disease Control Rate (DCR) per RECIST 1.1 and per iRECIST as assessed by BICR. | • DCR is defined as the proportion of participants who have a stable disease (SD) or better prior to any evidence of progression. |
| • To evaluate PFS per RECIST 1.1 and per iRECIST as assessed by BICR. | • PFS is defined as the time from date of enrollment to the first documented progressive disease (PD). Death due to any cause, whichever occurs first. |

| | |
|---|---|
| • To evaluate Time To Response (TTR) per RECIST 1.1 and per iRECIST as assessed by BICR.<br>• To assess OS.<br>• To evaluate safety. | • TTR is defined as a time from the date of enrollment day (a starting day) to the first date of confirmed CR or PR<br>• OS is defined as the period from the date of enrollment to the date of death due to any cause.<br>• Number of participants experiencing AEs and number of participants discontinuing study drug due to AEs. |

**Overall Design:**

| | |
|---|---|
| Study Phase | Phase IIb |
| Clinical Indication | First-line treatment for gastric cancer in programmed death-ligand 1 (PD-L1) positive (CPS ≥1%) |
| Population | Human epidermal growth factor receptor 2 (HER2/neu) negative subjects with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. |
| Study Type | Interventional |
| Type of Design | Single-arm multiple cohort |
| Type of Control | No treatment control |
| Study Blinding | Unblinded Open-label |
| Estimated Duration of Study | The Sponsor estimates that the study will require approximately 30 months from the time the first participant signs the informed consent until the last participant's last study-related phone call or visit. |

**Number of Participants:**

Approximately 90 participants will be enrolled.

**Treatment Groups and Duration:**

| | |
|---|---|
| Treatment Groups | Cohort 1: Pembrolizumab 200 mg fixed dose administered every 3 weeks (Q3W) + oxaliplatin 130 mg/m$^2$ IV infusion Q3W + TS-1 continuous oral administration twice daily (BID) for 14 days followed by a recovery period of 7 days<br>Cohort 2: Pembrolizumab 200 mg fixed dose administered Q3W + cisplatin 60 mg/m$^2$ IV infusion Q3W + TS-1 continuous oral administration BID for 14 days followed by a recovery period of 7 days |

| | |
|---|---|
| Duration of Participation | Each participant will participate in the study from the time the participant signs the informed consent form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, each eligible participant will be assigned to Cohort 1. After the target sample size of Cohort 1 is reached, allocation to Cohort 2 will be started. The study treatment will continue until disease progression is radiographically documented, when clinically appropriate, confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST) for participants treated with pembrolizumab, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab (approximately 2 years).<br><br>After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 9.3.<br><br>Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1, and confirmed by the site per iRECIST (for participants treated with pembrolizumab), initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study. |

## 2. Schedule of Activities (SoA)

| Trial Period: | Screening Phase | | Treatment Cycles[a] | | | | | | | | | | End of Treatment | Post-Treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle | Tumor Tissue collection/submission | Screening | 1 | | | 2 | | | 3 | 4 | 5 | Cycle 6 and beyond | Last Dose | Safety Follow-up | Follow Up Visits[b] | Survival Follow-up[c] |
| | | | Day 1 | Day 8 | Day 15 | Day 1 | Day 8 | Day 15 | Day 1 | Day 1 | Day 1 | Day 1 | At time of treatment discon | 30 days post last dose | Every 6 weeks | Every 12 weeks post last dose |
| Scheduling Window (Days)[d]: | -28 to -1 | -21 to -1 | | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 7 | ± 7 | ± 14 |
| **Administrative Procedures** | | | | | | | | | | | | | | | | |
| Informed Consent[e] | X | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | | X | | | | | | | | | | | | | | |
| Subject Identification Card | | X | | | | | | | | | | | | | | |
| Demographics and Medical History | | X | | | | | | | | | | | | | | |
| Prior and Concomitant Medication Review[f] | | | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Clinical Procedures/Assessments | | | | | | | | | | | | | | | | |
| Review Adverse Events[g] | | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| 12-Lead ECG | | X | | | | | | | | | | | | | | |
| Full Physical Examination | | X | | | | | | | | | | | X | | | |
| Directed Physical Examination | | | X | X | X | X | X | X | X | X | X | X | | | | |
| Vital Signs and Weight[h] | | X | X | | | X | | | X | X | X | X | X | | | |
| ECOG Performance Status[i] | | X | X | | | X | | | X | X | X | X | X | | | |
| Post-study Anticancer Therapy Status | | | | | | | | | | | | | | | X | X |
| Survival Status | | | | | | | | | | | | | | | | X |
| **Trial Treatment Administration** | | | | | | | | | | | | | | | | |
| Pembrolizumab[j] (Cohorts 1 and 2) | | | X | | | X | | | X | X | X | X | | | | |
| Oxaliplatin[k] (Cohort 1) | | | X | | | X | | | X | X | X | X | | | | |
| Cisplatin[l] (Cohort 2) | | | X | | | X | | | X | X | X | X | | | | |
| TS-1[m](Cohorts 1 and 2) | | | X | | | X | | | X | X | X | X | | | | |
| **Laboratory Procedures/Assessments: Analysis performed by LOCAL Laboratory** | | | | | | | | | | | | | | | | |
| Pregnancy Test – Serum or Urine[n] | | X | | | | X | | | X | X | X | X | | X | | |
| PT/INR and aPTT[o] | | X | | | | | | | | | | | | | | |
| CBC with Differential[i] | | X | | X | X | X | X | X | X | X | X | X | X | X | | |
| Chemistry Panel[i] | | X | | X | X | X | X | X | X | X | X | X | X | X | | |
| Urinalysis[i] | | X | | | | | | | | | | | | | | |

| Trial Period: | Screening Phase | | Treatment Cycles[a] | | | | | | | | | | End of Treatment | Post-Treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle | Tumor Tissue collection/submission | Screening | 1 | | | 2 | | | 3 | 4 | 5 | Cycle 6 and beyond | Last Dose | Safety Follow-up | Follow Up Visits[b] | Survival Follow-up[c] |
| | | | Day 1 | Day 8 | Day 15 | Day 1 | Day 8 | Day 15 | Day 1 | Day 1 | Day 1 | Day 1 | At time of treatment discon | 30 days post last dose | Every 6 weeks | Every 12 weeks post last dose |
| Scheduling Window (Days)[d]: | -28 to -1 | -21 to -1 | | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 7 | ± 7 | ± 14 |
| T3 (or Free T3), FT4 and TSH[i] | | X | | | | X | | | | X | | X | | X | | |
| Serum carcinoembryonic antigen (CEA)[p] | | X | | | | | | | X | | X | X[p] | | | | |
| Serum CA19-9[p] | | X | | | | | | | X | | X | X[p] | | | | |
| **Efficacy Measurements** | | | | | | | | | | | | | | | | |
| Tumor Imaging[q] | | X | → | → | → | → | → | → | → | → | → | → | → | → | X | |
| **Tumor Tissue Collection** | | | | | | | | | | | | | | | | |
| Archival or Newly Obtained Tissue Collection[r] | X | | | | | | | | | | | | | | | |

a. Unless otherwise specified, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (± 7 days) until (1) disease progression as assessed by investigator or qualified designee, (2) death, or (3) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression by investigator or qualified designee, the subject should be contacted by telephone every 12 weeks to assess for survival status. Note: Every effort should be made to ensure telephone contact at least 90 days post discontinuation to capture SAEs/ECIs The Sponsor may request survival status be assessed at additional time points during the course of the study. All subjects who are not known to have died prior to the request for these additional survival status time points will be contacted at that time.
d. Unless otherwise specified, the window for each visit is ± 3 days. Cycle 1 treatment must be given within 8 days after enrollment.
e. Written consent must be obtained prior to performing any protocol specified procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 21 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
f. Concomitant medications – Enter new medications started during the treatment until the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 9.3.
g. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever occurs first. Afterwards, report only SAEs and ECIs that are related to trial treatment.
h. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured in screening phase only.
i. ECOG PS for screening is to be performed within 3 days of enrollment. Laboratory tests for screening are to be performed within 7 days of enrollment. See Section 7.1.3 for details regarding laboratory tests. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. CBC with Differential and Chemistry panel are to be performed prior to the administration of all the cycles. Thyroid function tests should be collected every 6 weeks (every 2 cycles, e.g., Cycles 8, 10, 12, etc). Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
j. Pembrolizumab should be administered on Day 1 of each 3 week cycle after all procedures/assessments have been completed. Pembrolizumab 200 mg should be

| Trial Period: | Screening Phase | | Treatment Cycles[a] | | | | | | | | | | End of Treatment | Post-Treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle | Tumor Tissue collection/submission | Screening | 1 | | | 2 | | | 3 | 4 | 5 | Cycle 6 and beyond | Last Dose | Safety Follow-up | Follow Up Visits[b] | Survival Follow-up[c] |
| | | | Day 1 | Day 8 | Day 15 | Day 1 | Day 8 | Day 15 | Day 1 | Day 1 | Day 1 | Day 1 | At time of treatment discon | 30 days post last dose | Every 6 weeks | Every 12 weeks post last dose |
| Scheduling Window (Days)[d]: | -28 to -1 | -21 to -1 | | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 3 | ± 7 | ± 7 | ± 14 |

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 order of administration of pembrolizumab, oxaliplatin/cisplatin and TS-1, pembrolizumab infusion is administered first followed by the oxaliplatin/cisplatin infusion and then TS-1.

k. Oxaliplatin 130 mg/m$^2$ will be administered as a 120 minute IV infusion Q3W on Day 1 of each treatment cycle.
l. Cisplatin 60 mg/m$^2$ will be administered as a 120 minute IV infusion Q3W on Day 1 of each treatment cycle.
m. TS-1 40 to 60 mg/body/dose will be orally administered bid at Days 1 to 14 Q3W.
n. For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to each cycle of trial treatment and 30 days post treatment. A urine test can be considered if serum is not appropriate. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
o. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. And to be performed within 7 days of enrollment.
p. Serum CEA and CA 19-9 should be collected at screening (baseline), Cycle 3 and every 6 weeks (conducted at corresponding study visit; Cycle 5, Cycle 7, etc.) until study treatment discontinuation. When overall response is graded as CR, the examination will be performed 4 weeks after the CR assessment (accepted if performed up to 7 days after a reference day).
q. Baseline tumor imaging will be performed within 21 days prior to enrollment. Scans performed as part of routine clinical management are acceptable for use as the baseline scan if they are of diagnostic quality and performed within the allotted screening window for each cohort. The exact same image acquisition and processing parameters are recommended throughout the study. The first on-study imaging time point will be performed 6 weeks (± 7 days) after the subject has been enrolled, or earlier if clinically indicated and will continue to be performed every 6 weeks (± 7 days). When overall response is graded as CR or PR based on RECIST 1.1, the examination interval is changed and imaging that will confirm the best overall response (in case of CR, tumor maker levels will also be measured) will be performed 4 weeks after the last assessment (accepted if performed up to 7 days after a reference day). When assessment consecutively results in CR or PR, confirming the best overall response, examinations will be performed thereafter at an interval of 6 weeks from the day of enrollment. First examination after confirming the best over response as CR or PR will not be required. Imaging should be repeated until PD. Imaging timing should follow calendar days. On-study scans (scheduled and unscheduled) should be submitted to the BICR.
r. Tumor tissue from newly obtained core or excisional biopsy (FNA not adequate) and archival tissue sample (where available) should be tested for PD-L1 (evaluation of eligibility). Only PD-L1 positive subjects will be eligible for this trial. Tumor submission can occur up to 28 days prior to enrollment. Consent must be obtained prior to tumor tissue submission/collection. Detailed instructions for tissue collection, process and shipment are provided in the Procedures Manual.

# 3. Introduction

## 3.1 Study Rationale

Trials evaluating pembrolizumab (MK-3475) in gastric cancer have demonstrated clinical activity in subjects with recurrent and/or metastatic disease. Refer to Section 3.2.4, Ongoing Clinical Trials, for results from the studies of pembrolizumab in subjects with gastric cancer (KN012 and KN059).

The gastric cancer proof-of-concept from KN012 data was obtained in subjects with a PD-L1 positive expression only; no data is currently available regarding the performance of pembrolizumab in subjects without a detectable PD-L1 expression.

## 3.2 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 programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator's Brochure.

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

### 3.2.1 Pharmaceutical and Therapeutic Background

#### 3.2.1.1 Pembrolizumab

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies [Dong, H., et al 2002] [Sharpe, A. H. and Freeman, G. J. 2002] [Brown, J. A., et al 2003] [Francisco, L. M., et al 2010] [Thompson, R. H., et al 2007]. In particular, the presence of cluster of differentiation CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells correlates with improved prognosis and long term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD L1 and/or PD-L2) [Talmadge, J. E., et al 2007] [Usubütün, A., et al 1998].

The structure of murine PD-1 has been resolved [Al-Shibli, K. I., et al 2008]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable-type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Talmadge, J. E., et al 2007] [Deschoolmeester, V., et al 2010] [Diez, M., et al 1998] [Galon, J., et al 2006]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [Hiraoka, N. 2010] [Nobili, C., et al 2008]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B cells, Tregs and natural killer cells [Hodi, F. S. and Dranoff, G. 2010] [Kloor, M. 2009]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [Hillen, F., et al 2008]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non hematopoietic tissues as well as in various tumors [Lee, H. E., et al 2008] [Leffers, N., et al 2009] [Nishimura, H., et al 2000] [Hiraoka, N. 2010]. Both ligands are type I transmembrane receptors containing both IgV and IgC like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [Hiraoka, N. 2010]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor specific T-cell expansion in participants with melanoma [Liotta, F., et al 2011].

In gastric cancer PD-L1 and PD-L2 overexpression have recently been associated with EBV-positive tumors [Cancer Genome Atlas Research Network 2014]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and can be an attractive target for therapeutic intervention.

#### 3.2.1.2 TS-1

S-1 is a combination product containing FT, a prodrug of Fluorouracil (5-FU), and 2 modulators, CDHP and Oxo, in a molar ratio of 1:0.4:1. CDHP increases 5-FU concentration by reversible inhibition of dihydropyrimidine dehydrogenase (DPD), an enzyme that degrades 5-FU, while Oxo, densely distributed in gastrointestinal tissues, prevents gastrointestinal toxicity of 5-FU by inhibiting its local activation.

S-1 is an oral anticancer treatment, which has been developed by combining the three components to enhance therapeutic efficacy in comparison with conventional 5-FU products and also to reverse the resulting increase in adverse drug reactions.

S-1 has been marketed in Japan since 1999. As of January 2017, S-1 is approved in the countries of the world for the treatment of gastric cancer, head and neck cancer, colorectal cancer, non-small cell lung cancer, breast cancer, pancreatic cancer and/or biliary tract cancer. It is approved under the trade name of TS-1, S-1, TS-ONE or Teysuno in over 45 countries, including the European countries [mainly the European Union (EU)/ European Economic Area (EEA)] and Asian countries (mainly Japan). To date, cumulative post-marketing exposure to S-1 is estimated to be 1,771,593 patients in Japan since first approval in 1999, approximately 126,964 patients in other Asian Countries, and 3,966 patients from EEA, Israel, and Russia since marketing on 14 March 2012.

#### 3.2.1.3 Oxaliplatin

Oxaliplatin is a platinum complex-based antitumor agent and the mechanism of the drug is considered to be the inhibition of DNA synthesis and the inhibition of protein synthesis from cross-link formation with DNA base, like other platinum complex-based antitumor agents.

In Japan, Oxaliplatin was approved for "Unresectable advanced/recurrent gastric cancer" at dosage of 130 mg/m$^2$, every 3 weeks in combination with other anticancer agents in March 2015. In November 2015, when the indication for "postoperative adjuvant chemotherapy in gastric cancer" was added, Oxaliplatin was approved for "gastric cancer" at the same dosage and dose.

#### 3.2.1.4 Cisplatin

Cisplatin binds to the N7-position of guanine and adenine, which is a constituent base of DNA. Since Cisplatin binds to DNA at two chloride sites, it forms cross-link formation within the DNA chain and inhibits DNA synthesis and subsequent division of cancer cells. Even monotherapy is effective for gastric cancer, Cisplatin is known to show a synergistic effect when combined with 5-FU, CPT-11, etc. Cisplatin has renal toxic and requires adequate replacement fluid.

### 3.2.2 Pre-clinical and Clinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [Ropponen, K. M., et al 1997] [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008] [Pölcher, M., et al 2010] [Okazaki, T., et al 2001] [Greenwald, R. J., et al 2005]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

Clinical trials have demonstrated efficacy in subjects with advanced melanoma, non-small cell lung cancer, head and neck cancer, bladder cancer, Hodgkin's lymphoma, triple-negative breast cancer, and gastric adenocarcinoma.

### 3.2.3 Ongoing Clinical Studies

Ongoing clinical trials are being conducted in advanced melanoma, non-small cell lung cancer, a number of advanced solid tumor indications and hematologic malignancies. For study details please refer to the IB.

### 3.2.4 Ongoing Clinical Trials in Gastric Cancer

Preliminary interim data is available from a cohort of gastric and GEJ adenocarcinoma subjects studied in the KEYNOTE 012 trial [Muro, K., et al 2014]. The KEYNOTE 012 trial is a multi-cohort, Phase IB study of subjects with recurrent or metastatic gastric or GEJ adenocarcinoma who expressed PD-L1 (≥1% by immunohistochemistry). This cohort enrolled 39 subjects (19 from Asia and 20 outside of Asia). The primary endpoint was overall response rate (ORR). Although 69% of subjects received 2 or more prior chemotherapy lines, pembrolizumab monotherapy demonstrated an ORR of 20.5% by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per central radiology assessment (95% CI: 9.3%, 36.5%; 7 PRs, 1 CR), and was similar in subjects from Asia and outside of Asia. Responses were observed across all lines of treatment. Forty-four percent of the subjects with measurable disease displayed some degree of tumor shrinkage from baseline. As of the data cutoff date of 26-Apr-2016, the median duration of response was 9.5 months. The 6-month progression-free survival (PFS) and OS was 24% and 67%, respectively, in this heavily pretreated group. Based on these data, there appears to be a correlation between response and degree of PD-L1 positivity.

Single agent pembrolizumab at a dose and frequency of 10 mg/kg every 2 weeks was generally well tolerated, with the type, severity, and frequency of AEs in the gastric cancer subjects of KEYNOTE 012.

The overall safety results of pembrolizumab in subjects treated with single agent pembrolizumab at a dose and frequency of 10 mg/kg every 2 weeks with gastric cancer reported in this trial were consistent with the previously established pembrolizumab safety profile based on data in melanoma, NSCLC, and head and neck cancer (see the IB for information about AEs in other indications). There were 3 deaths reported in the gastric cancer cohort, with none of these death serious adverse events (SAEs) attributed to study treatment.

The KEYNOTE 028 study treated 23 patients with PD-L1 positive esophageal cancer; 17 with squamous cell cancer and 5 with adenocarcinoma [Semrad, T. J. 2015]. Seven out of 23 patients (30%) had PR and of the 5 patients with adenocarcinoma, 2 patients had PR and 2 patients had stable disease.

KEYNOTE 059 is a non-randomized, multi-site, open-label trial of pembrolizumab in subjects with gastric or GEJ adenocarcinoma. Enrollment in this trial was completed and 316 subjects were enrolled across 3 cohorts to examine the safety and efficacy of pembrolizumab. Cohort 1 subjects who had progressed on at least 2 prior systemic treatments for advanced disease (third line [3L]+subjects) that received pembrolizumab as

monotherapy; (Cohort 2) subjects who had not previously received systemic therapy for advanced disease (1L subjects) received pembrolizumab in combination with cisplatin and 5-FU. Sites in Japan also administered pembrolizumab in combination with cisplatin and capecitabine; and (Cohort 3) PD-L1-positive subjects who had not previously received systemic therapy for advanced disease (1L subjects) who received pembrolizumab as monotherapy. The primary objectives of the trial were to determine the safety, tolerability, and ORR of pembrolizumab (200 mg fixed dose every 3 weeks) given as first and third-line monotherapy to subjects with gastric or GEJ adenocarcinoma whose tumors expressed PD-L1, and to determine the safety and tolerability of pembrolizumab administered in combination with cisplatin and 5-FU as first-line therapy in subjects with gastric or GEJ adenocarcinoma. The trial is currently ongoing and following subjects for OS.

KEYNOTE 061 is a randomized, multi-center, open-label trial of pembrolizumab versus paclitaxel in subjects with advanced gastric or GEJ adenocarcinoma who had progressed after failure of any combination chemotherapy containing a platinum and a fluoropyrimidine agent. Enrollment in this trial was completed and 592 subjects were randomized. The enrollment included all subjects without regard for PD-L1 expression status. The overall study enrollment was driven by the number of subjects with PD-L1 positive expression on their tumor (n=360). That is, enrollment was stopped when approximately 360 subjects with PD-L1 positive expression on their tumor had been randomized. Additionally, there was a cap on enrollment (30% of the total) for subjects residing in the Asia Pacific region for this study. The primary efficacy endpoints were PFS and OS. The primary PFS analysis was based on RECIST v1.1 by blinded central radiologists' review. RECIST v1.1 was also used by the local site for treatment decisions. The trial is currently ongoing and following subjects for OS.

KEYNOTE 062 is a randomized, active-controlled, multi-site, partially blinded, trial of pembrolizumab, or pembrolizumab + cisplatin + 5-FU versus placebo + cisplatin + 5-FU, as first-line treatment in PD-L1 positive, human epidermal growth factor receptor 2 negative subjects with advanced gastric or GEJ adenocarcinoma. The trial is currently enrolling with a target of approximately 750 subjects to be randomized to compare the efficacy and safety of pembrolizumab or pembrolizumab + cisplatin +5-FU versus placebo + cisplatin + 5-FU as a first-line treatment. Subjects will be randomized in a 1:1:1 ratio among the 3 treatment arms, stratified by geographic region, disease status, and fluoropyrimidine treatment. There will be 1 interim PFS/OS analysis, 1 planned interim safety analysis, and safety monitoring every 6 months.

### 3.2.5 Information on Other Study-Related Therapy

A variety of chemotherapies are used for subjects with advanced, first line gastric and GEJ adenocarcinoma. Early studies demonstrated small survival benefits after treatment with cisplatin alone or chemotherapy combinations.

A number of ongoing Phase 3 trials are evaluating the addition of targeted monoclonal antibodies or small molecules to standard chemotherapy regimens. First positive result was shown from ToGA study comparing cisplatin/fluoropyrimidine plus trastuzumab, a monoclonal antibody against the human epidermal growth factor receptor 2 (HER2), with the same chemotherapy alone in subjects with HER2-positive gastric or gastroesophageal adenocarcinoma.. The study demonstrated significantly improved OS associated with the

trastuzumab-containing regimen over chemotherapy alone (median 13.8 and 11.1 months, respectively, p = .0048). The outcome of ToGA study supported the approval of Trastuzumab for HER2-positive gastric cancer subjects [Bang, Y. J., et al 2010].

#### 3.2.5.1 Current Standard Therapies

With regard to chemotherapy for advanced and metastatic gastric cancer, since MacDonald, et al. reported FAM therapy, a triple therapy with 5-FU + doxorubicin + mitomycin C [median survival time (MST), 5.5 months] [Macdonald, J. S., et al 1980] in 1980, multidrug combination therapy mainly with 5-FU has been most commonly used. ECF [epirubicin + cisplatin + 5-FU] therapy, and EOX [epirubicin + oxaliplatin + capecitabine] therapy of which noninferiority to ECF therapy was demonstrated in the results of REAL2 trial [Cunningham, D., et al 2008], mainly in Europe; DCF (docetaxel + cisplatin + 5-FU) therapy of which superiority to CF (cisplatin + 5-FU) therapy was shown in V325 trial [Van Cutsem, E., et al 2006] in the US. At present platinum/fluoropyrimidine doublet regimens are the most broadly used for first-line chemotherapy regimen for advanced gastric cancer.

In Japan, combination therapy with fluorinated pyrimidine anticancer agents and platinum-containing drugs has been recommended as standard treatment. JCOG9912 Study [5-FU vs. irinotecan + cisplatin vs. S-1] [Boku, N., et al 2009] conducted in Japan revealed noninferiority of S-1 monotherapy to continuous IV 5-FU infusion, which was the standard treatment at that time, in terms of OS, and SPIRITS Study (S-1 vs. S-1 + cisplatin) [Koizumi, W., et al 2008] demonstrated that S-1 + cisplatin therapy significantly prolonged OS compared with S-1 monotherapy. ToGA study [Bang, Y. J., et al 2010] involving HER2-positive gastric cancer patients showed that trastuzumab, a molecular-targeted agent, added to capecitabine (or 5-FU) + cisplatin therapy significantly prolonged OS. On the basis of these results, the Japanese gastric cancer treatment guidelines 4th edition (revised in May 2014) [Japanese Gastric Cancer Association 2017] recommend S-1 + cisplatin therapy and S-1 monotherapy for HER2-negative patients who are capable of orally taking drugs, and capecitabine (or 5-FU) + cisplatin + trastuzumab therapy for patients with HER2-positive, advanced or recurrent gastric cancer.

#### 3.2.5.2 Comparison between Cisplatin and Oxaliplatin

When cisplatin and oxaliplatin are compared, hydration for the prevention of renal toxicity before administration is required for cisplatin; thus, whether or not cisplatin can be replaced with oxaliplatin not requiring hydration has been studied. Because REAL-2 trial (ECF vs. ECX vs. EOF vs. EOX) [Cunningham, D., et al 2008] revealed the noninferiority of the oxaliplatin group to the cisplatin group in terms of OS, the efficacy of cisplatin and oxaliplatin is considered to be equivalent. In Japan, G-SOX study (S-1 + cisplatin vs. S-1 + oxaliplatin) [Yamada, Y., et al 2015] was conducted to demonstrate the noninferiority of S-1 + oxaliplatin therapy to S-1 + cisplatin therapy. While the noninferiority of S-1 + oxaliplatin therapy to S-1 + cisplatin therapy in terms of PFS was shown, the OS result was slightly above the upper limit (1.15) of the noninferiority margin (OS, 13.1 months vs. 14.1 months; hazard ratio, 0.969 [95% confidence interval, 0.812 to 1.157]). Nonetheless, an ex-post facto analysis using a method to combine 1 subject excluded at the time of the primary analysis revealed that the upper limit of the hazard ratio was below 1.15 (hazard ratio, 0.958 [95% confidence interval, 0.803 to 1.142]). In 2009, the Japanese Gastric Cancer Association

submitted a request for the expansion of the indication for oxaliplatin for unresectable advanced or recurrent gastric cancer. On the basis of results of REAL-2 trial and G-SOX study, the clinical usefulness of combination therapy with other anticancer agents and oxaliplatin for unresectable advanced or recurrent gastric cancer was determined to be a medically and pharmacologically known fact; thus, it was included in health insurance treatment in September 2014. In addition, SOPP study (S-1 + cisplatin vs. S-1 + oxaliplatin) [Ryu, M. H., et al 2016] conducted in South Korea showed the noninferiority of S-1 + oxaliplatin therapy to S-1 + cisplatin therapy in terms of PFS. Consequently, S-1 + oxaliplatin Q3W regimen is likely to be used as a standard first-line chemotherapy regimen for patients with metastatic gastric cancer.

With regard to an evaluation of the initial dose of oxaliplatin, in three overseas comparative studies involving patients with unresectable advanced or recurrent gastric cancer used in a metaanalysis [Montagnani, F., et al 2011], oxaliplatin 130 mg/m$^2$ administered Q3W or 85 mg/m$^2$ administered every other week was used (drug potency, 43 mg/m$^2$/week for both regimens). The hazard ratios of OS compared with cisplatin were 0.65 to 0.91 in the each study and 0.88 (95% confidence interval, 0.78 to 0.99) for all the studies. Compared with these, the point estimate of the hazard ratio in G-SOX study was as high as 0.969, and it cannot be denied that oxaliplatin 100 mg/m$^2$ administered Q3W (drug potency, 33 mg/m$^2$/week) may not adequately exert the effects of this drug. Consequently, the initial oxaliplatin dose of 130 mg/m$^2$ is to be used in this study.

#### 3.2.5.3 S-1 + Cisplatin Regimen

With regard to comparison between S-1 + cisplatin Q3W and Q5W, SOS study (S-1 + cisplatin therapy, every 3 weeks vs. every 5 weeks) [Ryu, M. H., et al 2015] revealed equivalence between the two groups for OS (MST, 14.1 months vs. 13.9 months), whereas the superiority of the Q3W groups for PFS was showed (PFS, 5.5 months vs. 4.9 months; hazard ratio, 0.82 [95% confidence interval, 0.68 to 0.99]). In SPIRITS Study [Koizumi, W., et al 2008] conducted in Japan, MST was 13.0 months for the S-1 + cisplatin Q5W regimen. In consideration of obtaining almost reproducible results for the therapeutic results of S-1 + cisplatin therapy while the countries where the studies were implemented varied, the superiority of the Q3W group for PFS shown in SOS study, and the dosing interval of pembrolizumab, the S-1 + cisplatin Q3W regimen is to be utilized in this study.

#### 3.2.5.4 Combination of Pembrolizumab and Chemotherapy

With ToGA study, mentioned also in Section 3.2.5.1, combination therapy of trastuzumab with standard therapy including 5-FU in HER-2-positive patients has become a new standard therapy; similarly, combination of MK-3475 with standard therapy in PD-L1-positive patients can become a new therapeutic option for treating gastric cancer in Japan.

#### 3.2.5.5 Comparison with Study 062 (Keynote062)

A Phase III global study (Study 062) of pembrolizumab as first-line treatment in patients with advanced gastric or GEJ adenocarcinoma is underway with Japan included. In Study 062, three groups have been compared: pembrolizumab monotherapy, pembrolizumab + cisplatin + 5-fluorouracil/ cisplatin + capecitabine therapy, and placebo + cisplatin + 5-fluorouracil/ cisplatin + capecitabine. Capecitabine + cisplatin therapy is a standard

treatment in foreign countries, but the Japanese gastric cancer treatment guidelines 4th edition (revised in May 2014) state that it is not a recommended but optional regimen among treatments for HER2-negative patients. Consequently, it has been found to be useful for the treatment of gastric cancer in Japan to combine pembrolizumab with TS-1 + oxaliplatin therapy or TS-1 + cisplatin therapy, which are standard first-line treatment for Japanese patients with advanced gastric or GEJ adenocarcinoma, and to evaluate the efficacy and safety of pembrolizumab in combination with these therapies in this study.

### 3.3 Benefit/Risk Assessment

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

Beneficial effects of pembrolizumab have been seen in several trials to date. Publications of a significantly positive benefit/risk ratio have been reported for melanoma in a single arm study encompassing nearly 1,000 patients (KEYNOTE 001), which led to FDA approval in September 2014, and in a randomized comparison to chemotherapy (KEYNOTE 002 is further detailed in the IB). Additional potential benefits are addressed in Section 3.2.4, which details responses of the KEYNOTE 012 trial; a multi cohort Phase Ib study of which 1 cohort enrolled subjects with recurrent or metastatic gastric or GEJ adenocarcinoma that expressed PD-L1 (≥1% by immunohistochemistry). Although two-thirds of subjects received at least 2 prior therapies for advanced disease, pembrolizumab monotherapy achieved an ORR of 20.5% by RECIST v.1.1 central radiology assessment (95% confidence interval [9.3%, 36.5%]; 7 partial responses, 1 complete response). The median duration of response was 9.5 months (range 5.6 to 22.1 months).

In KEYNOTE 012, the most common AEs included abdominal pain (35.9%), decreased appetite (30.8%), fatigue (30.8%), nausea (28.2%), and vomiting (25.6%). Fatigue (10.3%) was the only Grade 3 to 5 AE that was reported in >10% of subjects. There were 12.8% of subjects who experienced drug-related Grade 3 to 4 AEs. There were no drug-related Grade 5 (fatal) AEs reported.

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

## 4. Objectives/Hypotheses and Endpoints

In subjects with PD-L1 positive, advanced gastric or GEJ adenocarcinoma, the following objectives will be applied to Cohort 1 and Cohort 2 separately.

| Objective/Hypothesis | Endpoint |
|---|---|
| **Primary** | |
| • To evaluate ORR per RECIST 1.1 as assessed by BICR. | • ORR is defined as the proportion of participants who have a confirmed complete response (CR) or partial response (PR). |
| **Secondary** | |
| • To evaluate the Duration of Response (DOR) per RECIST 1.1and per iRECIST as assessed by BICR.<br>• To evaluate ORR per iRECIST by BICR.<br>• To evaluate Disease Control Rate (DCR) per RECIST 1.1and per iRECIST as assessed by BICR.<br>• To evaluate PFS per RECIST 1.1 and per iRECIST as assessed by BICR.<br>• To evaluate Time To Response (TTR) per RECIST 1.1 and per iRECIST as assessed by BICR.<br>• To assess OS<br>• To evaluate safety | • DOR defined as the time from the earliest date of qualifying response until earliest date of disease progression or death from any cause, whichever comes first.<br>• ORR is defined as the proportion of participants who have a confirmed complete response (CR) or partial response (PR).<br>• DCR is defined as the proportion of participants who have a stable disease (SD) or better prior to any evidence of progression.<br>• PFS is defined as the time from date of enrollment to the first documented progressive disease (PD). Death due to any cause, whichever occurs first.<br>• TTR is defined as a time from the date of enrollment day (a starting day) to the first date of confirmed CR or PR<br>• OS is defined as the period from the date of enrollment to the date of death due to any cause.<br>• Number of participants experiencing AEs and number of participants discontinuing study drug due to AEs. |

# 5. Study Design

## 5.1 Overall Design

This is a nonrandomized, multi-site, open-label trial to estimate overall response rates (ORRs) of pembrolizumab + oxaliplatin + TS-1 and pembrolizumab + cisplatin + TS-1, as first-line treatment for gastric cancer in programmed death-ligand 1 (PD-L1) positive, human epidermal growth factor receptor 2 (HER2/neu) negative subjects with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma.

First, 45 subjects will be assigned to Cohort 1, pembrolizumab + oxaliplatin + TS-1 combination therapy, and then, 45 subjects will be assigned to Cohort 2, pembrolizumab + cisplatin + TS-1 combination therapy.

In all the Cohorts, the study treatment will be started at Day 1 of each 3-week course.

Table 1 Treatments Dose and Schedule

| Cohort | Treatment Dose and Schedule |
|---|---|
| Cohort 1 | Pembrolizumab 200 mg Q3W + oxaliplatin 130 mg/$m^2$ Q3W IV infusion + TS-1 BID continuous oral administration for 14 days followed by a recovery period of 7 days |
| Cohort 2 | Pembrolizumab 200 mg Q3W + cisplatin 60 mg/$m^2$ Q3W IV infusion + TS-1 BID continuous oral administration for 14 days followed by a recovery period of 7 days |
| The body surface area [BSA ($m^2$)] should be calculated by the web registration system using the following DuBois formula:<br>$BSA\ (m^2) = ([body\ weight\ (kg)]^{0.425} \times [body\ height\ (cm)]^{0.725}) \times 0.007184$<br>The administration of oxaliplatin may be interrupted or reduced at the discretion of the investigator because the incidence of neuropathy has been reported to increase with increases in the dose.<br>The administration of cisplatin may be interrupted or reduced at the discretion of the investigator because the incidence of hearing impaired has been reported to increase with increases in the dose. | |

The study treatment should be started within 8 days after the day of enrollment.

Participation in this trial will be dependent upon supplying a tumor tissue specimen. **Newly obtained endoscopic biopsy or core biopsy of a metastatic site if obtained as part of normal clinical practice is preferred to archived samples.** Both formalin solution and formalin-fixed, paraffin embedded (FFPE) block specimens are acceptable. If submitting unstained slides, the slides should be freshly cut and received at the testing laboratory within 14 days from site slide section date, otherwise a new specimen will be requested. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a prospective manner. Only subjects whose tumors express PD-L1 (are PD-L1+) as determined by the central laboratory facility will be eligible for enrollment in this study. Subjects will also be required to be HER-2/neu negative.

Subjects will undergo the first imaging evaluation 6 weeks (± 7 days) after enrollment. Subsequently, subjects will be evaluated every 6 weeks (42 days ± 7 days), independent of any treatment delays, with radiographic imaging to assess response to treatment using

Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). When overall response is graded as CR or PR based on RECIST 1.1, the examination interval is changed and imaging that will confirm the best overall response (in case of CR, tumor maker levels will also be measured) will be performed 4 weeks after the last assessment (accepted if performed up to 7 days after a reference day). When assessment consecutively results in CR or PR, confirming the best overall response, examinations will be performed thereafter at an interval of 6 weeks from the day of enrollment. Subsequent scheduled examination after confirming the best over response as CR or PR will not be required. RECIST 1.1 responses as assessed by the BICR will be used as the primary efficacy endpoint; Overall Response Rate (ORR). The treatment will be continued until the first documented PD. RECIST 1.1 will be used by the local site for treatment decisions. Following verification of PD, treatment decision may be made by the adaptation of RECIST 1.1 [Ji, Y., et al 2010], as described in Section 9.2.1.5, termed immune-related RECIST (iRECIST) to accommodate for the tumor response patterns seen with pembrolizumab treatment (e.g., tumor flare).

Adverse events (AE) will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Treatment will continue until documented clinical PD, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, subject's request to discontinue, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, 35 administrations of pembrolizumab (approximately 2 years), or administrative reasons.

Subjects who have evidence of PD by imaging but are clinically stable may continue to be treated at the discretion of the investigator. In addition, subjects who attain an investigator-determined confirmed complete response (CR) may stop the trial treatment after receiving at least 8 administrations of pembrolizumab and at least two additional treatments of pembrolizumab between the confirmation of CR and the treatment discontinuation.

After the end of treatment, each subject will have a 30 day follow-up assessment for AE monitoring (serious adverse events and events of clinical interest (ECI) will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier). Subjects who discontinue treatment for reasons other than PD will have post-treatment follow-up for disease status until PD, withdrawing consent, or becoming lost to follow-up. All subjects will be followed for OS by telephone and other systems every 12 weeks (±7 days) or more frequently based on the necessity until death, withdrawal of consent or the end of the trial, whichever comes first.

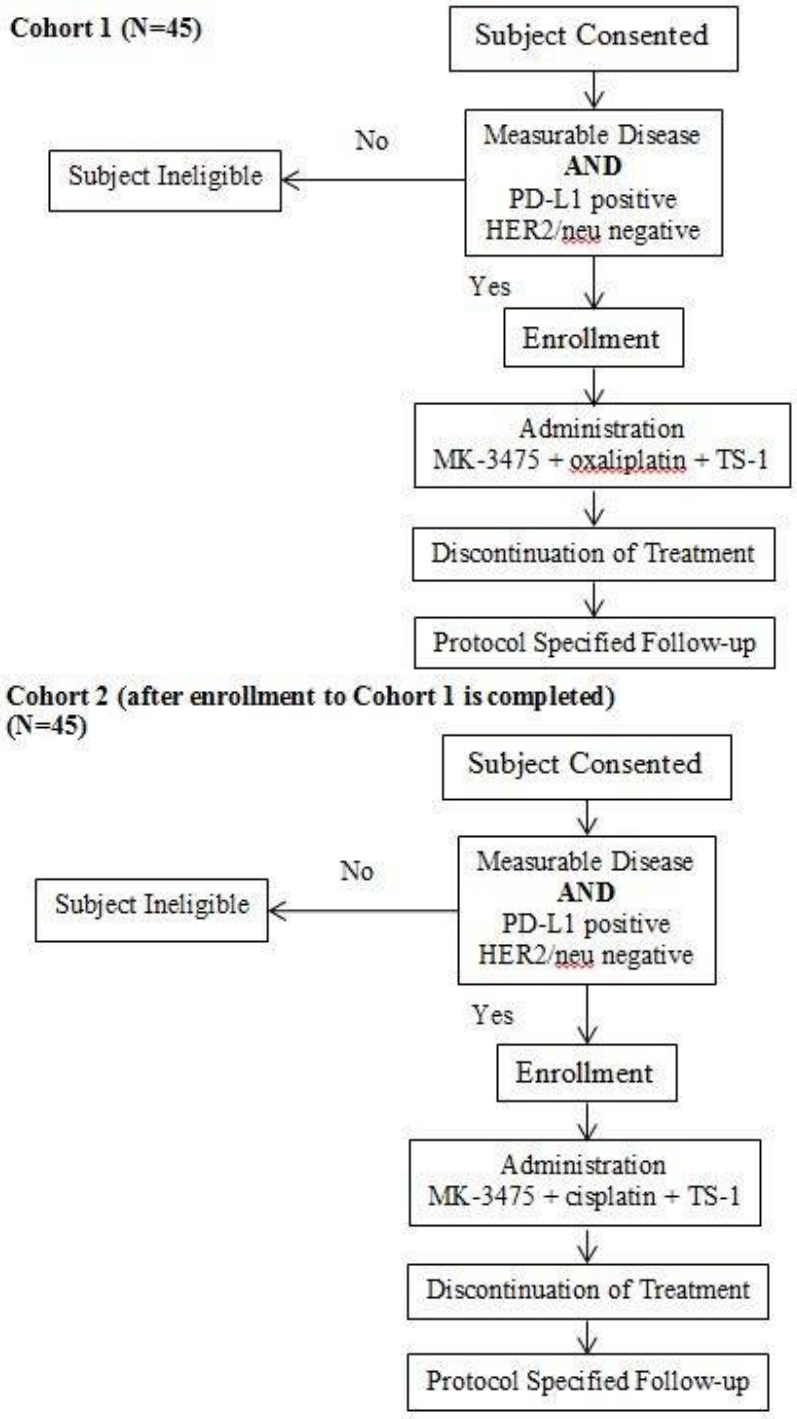
This study will be conducted in conformance with Good Clinical Practices.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the Study SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

No safety and/or efficacy interim analysis is planned. Statistical analyses will be carried out at the key evaluation time point for each cohort and the end of the study. More details are in Section 10.7.

### 5.1.1 Study Diagram

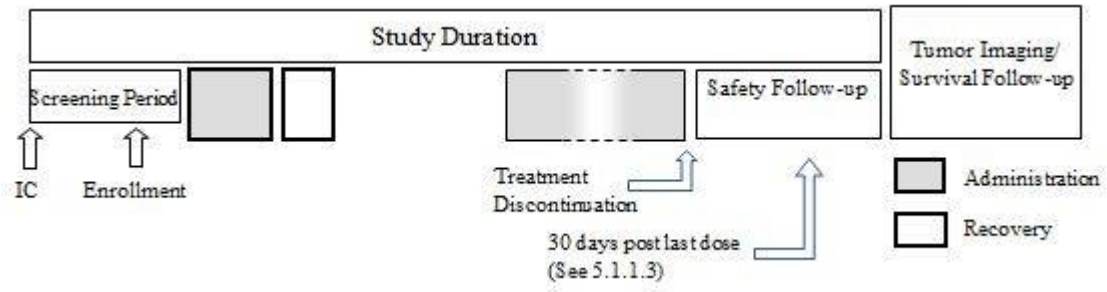
The study design is depicted in Figure 1.




HER2/neu negative is defined as: IHC (0, or 1+), or FISH negative (HER2:CEP17 ratio < 2). In place of FISH, available in situ hybridization (ISH) techniques, e.g., dual color in situ hybridization (DISH), can be employed according to trial site-specific guidelines.

Figure 1 Phase II Trial Design for Enrollment of PD-L1 Positive, HER2/neu Negative Subjects with Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma.

#### 5.1.1.1 Study Duration for each subject




Study periods for each subject are defined from below start date to end date.

Start date: the day the ICF is signed

End date: the day subjects complete the Safety Follow-up

#### 5.1.1.2 Definition of Study Period

Study periods for each subject are defined below.

Pre-Study duration: until the day the ICF is signed

Study duration: Begins the day the ICF is signed and lasts until the day prior to completion the Safety Follow-up

Administration period: Defined as the day IP is administered

Recovery period: Defined as the day IP is not administered

Safety Follow-up: Defined as the day after the end of study treatment until 30 days (non-serious adverse events)

90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier (serious adverse events and ECI)

Tumor Imaging/ Survival Follow-up: Defined as the day after the end of Safety Follow-up

### 5.2 Number of Participants

Approximately 90 participants will be allocated into the study.

### 5.3 Beginning and End of Study Definition

The overall study begins when the first participant signs the informed consent form (ICF). The overall study ends when the last participant completes the last study-related phone-call or visit, withdraws from the study or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

### 5.3.1 Clinical Criteria for Early Study Termination

The clinical study 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 study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study 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.

## 5.4 Scientific Rationale for Study Design

### 5.4.1 Rationale for Endpoints

#### 5.4.1.1 Efficacy Endpoints

This study will use ORR based on RECIST 1.1 criteria as assessed by BICR as the primary endpoint. Objective response rate (ORR) is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess ORR is typically considered acceptable by regulatory authorities. Images will be read by a BICR to minimize bias in the response assessments.

##### 5.4.1.1.1 RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures and by the local site when determining eligibility (Section 9.2.1.4). Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

##### 5.4.1.1.2 iRECIST

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab (Section 9.2.1.5). Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and patients treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudo-progression. Of note, participants who had progressive disease (PD) by RECIST 1.1 but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer overall survival than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

Modified RECIST 1.1 for immune-based therapeutics (iRECIST) assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the European Medicines Agency [Seymour, L., et al 2017]. The unidimensional measurement of target lesions, qualitative assessment of non-target lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a participant is clinically stable, additional imaging may be performed to confirm radiographic progression. iRECIST will be used by investigators to assess tumor response and progression and make treatment decisions, as well as for exploratory efficacy analyses where specified.

#### 5.4.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of adverse events (AEs)/serious adverse events (SAEs); and changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE, Version 4.0.

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

Trials evaluating pembrolizumab (MK-3475) in gastric cancer have demonstrated clinical activity in subjects with recurrent and/or metastatic disease. Refer to Section 3.2.4, Ongoing Clinical Trials. This trial is selected PD-L1 positive subjects like a KN062. There is no safety data of pembrolizumab in combination with oxaliplatin in the previous studies, the first 45 participants will be assigned to Cohort 1 to accumulate the data in combination with oxaliplatin prior to cisplatin.

## 5.5 Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults 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 every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (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 Cohort B2, KN001 Cohort D, KN002, KN010,

and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, 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 participant 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.

## 6. Study Population

Male/Female participants with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma of between 18 and 75 years of age will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

### 6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

**Type of Participant and Disease Characteristics**

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 to ≤ 75 years of age on day of signing informed consent.
3. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale at the timing of enrollment.
4. Have histologically or cytologically confirmed diagnosis of locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma.

5. Have a PD-L1 positive tumor as determined by IHC at a central laboratory.
   Note: PD-L1 positive is defined as a CPS of ≥1% by IHC 22C3 PharmDx assay
6. Have measurable disease as defined by RECIST 1.1 as determined by investigator assessment. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
   Note: The exact same image acquisition and processing parameters are recommended throughout the study.
7. Female subjects of childbearing potential must have a negative urine or serum pregnancy test at the timing of enrollment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
8. Female subjects of childbearing potential (Section 7.7.4.2) must be willing to use an adequate method of contraception as outlined in Section 7.7.4.2 – 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.
9. Male subjects of childbearing potential (Section 5.6.2) must agree to use an adequate method of contraception as outlined in Section 5.6.2- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.
   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
10. Demonstrate adequate organ function as defined in Table 2. All screening labs should be performed within 7 days of enrollment.

Table 2 Adequate Organ Function Laboratory Values

| System | Laboratory Value |
|---|---|
| Hematological | |
| Absolute neutrophil count (ANC) | ≥1500/μL |
| Platelets | ≥100 000/μL |
| Hemoglobin | ≥9.0 g/dL or ≥5.6 mmol/L[a] |
| Renal | |
| Measured or calculated[b] creatinine clearance | ≥60 mL/min |
| Hepatic | |
| Total bilirubin | ≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN |
| AST (SGOT) and ALT (SGPT) | ≤2.5 × ULN (≤5 × ULN for participants with liver metastases) |
| Albumin | ≥ 2.5 g/dL |
| Coagulation | |
| International normalized ratio (INR) OR prothrombin time (PT) | ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants |

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); ULN=upper limit of normal.
[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.
[b] Creatinine clearance (CrCl) should be calculated using the Cockcroft-Gault estimation formula as shown below.
Estimated creatinine clearance (mL/min)= (140 - age) x Body weight (kg) / [72 x Serum creatinine (mg/dL)]
For women, the obtained value is multiplied by a factor of 0.85..
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

## 6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

**Medical Conditions**

1. Has squamous cell or undifferentiated gastric cancer.
2. Participants with human epidermal growth factor receptor 2 (HER2)-positive status.
3. Has had previous therapy for locally advanced, unresectable or metastatic gastric/GEJ cancer. Subjects may have received prior neoadjuvant or adjuvant therapy as long as it was completed at least 6 months prior to enrollment.
4. A WOCBP who has a positive urine pregnancy test within 72 hours prior to allocation (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
5. Has received prior therapy with a platinum-based anti-cancer drug.

6. Has had major surgery, open biopsy or significant traumatic injury within 28 days prior to enrollment, or anticipation of the need for major surgery during the course of study treatment.
7. Has had radiotherapy within 14 days of enrollment. Subjects who received radiotherapy >14 days prior to enrollment must have completely recovered from any radiotherapy related AEs/toxicities.
8. Has a known additional malignancy that is progressing or has required active treatment within the past 5 years.
   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
9. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, ie, without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
10. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
11. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
12. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis
13. Has an active infection requiring systemic therapy.
14. Being on flucytosine at the time of enrollment.
15. Has grade ≥ 2 peripheral sensory neuropathy.
16. Has poorly controlled diarrhea (e.g., watery stool, uncontrollable bowel movement with drugs, grade ≥ 2 and number of defecations, ≥ 5/day).
17. Accumulation of pleural, ascitic, or pericardial fluid requiring drainage within 2 weeks prior to enrollment.
18. Has a history or current evidence of any condition (e.g. known deficiency of the enzyme dihydropyrimidine dehydrogenase [DPD]), 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.

19. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
20. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study treatment.
21. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137).
22. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
23. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
    Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
24. Is currently participating in and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to the first dose of trial treatment.
25. Has received a live vaccine within 30 days of planned start of study therapy.
    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.

### 6.3 Histological Classification in Target Patients

Target adenocarcinoma in the trial is provided below.

Common Type

- Papillary adenocarcinoma (pap)
- Tubular adenocarcinoma (tub)
  - Well-differentiated type (tub1)
  - Moderately-differentiated type (tub2)
- Poorly-differentiated adenocarcinoma (por)
  - Solid type (por1)
  - Non-solid type (por2)
- Signet-ring cell carcinoma (sig)
- Mucinous adenocarcinoma (muc)

## 6.4 Lifestyle Restrictions

### 6.4.1 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception.

Participants 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, participants of childbearing potential must adhere to the contraception requirement (Appendix 5) 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 study medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

### 6.4.2 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant'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 (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 7.7.4.3.

### 6.4.3 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, participants who are breastfeeding are not eligible for enrollment.

## 6.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the data entry guidelines.

## 6.6 Participant Replacement Strategy

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

# 7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies [study treatment(s) provided by the Sponsor] will be packaged to support enrollmentparticipants. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

## 7.1 Treatments Administered

The study treatments to be used in this study are outlined below in Table 3.

Table 3 Study Treatments

| **Study Treatment Name:** | Pembrolizumab (MK-3475) | Oxaliplatin* | Cisplatin** | TS-1*** |
|---|---|---|---|---|
| **Dosage Formulation:** | Solution for infusion | Solution for infusion | Solution for infusion | Capsule |
| **Unit Dose Strength(s):** | 100 mg/vial | | | 20 mg/capsule<br>25 mg/capsule |
| **Dosage Level(s):** | 200 mg Q3W Day 1 | 130 mg/m$^2$ Q3w Day 1 | 60 mg/m$^2$ Q3W Day 1 | 40 to 60 mg/body/dose BID Q3W Day 1-14 |
| **Route of Administration:** | IV infusion | IV infusion | IV infusion | Oral |
| **Sourcing:** | Provided centrally by the Sponsor | Locally by the study site | Locally by the study site | Provided centrally by the Sponsor |

***The administration of oxaliplatin may be interrupted or reduced at the discretion of the investigator because the incidence of neuropathy has been reported to increase with increases in the dose; however, treatment with TS-1 should be continued per protocol.**

****The administration of cisplatin may be interrupted or reduced at the discretion of the investigator because the incidence of hearing impaired has been reported to increase with increases in the dose; however, treatment with TS-1 should be continued per protocol.**

***** For the initial dose, TS-1 shall be administered orally twice daily after breakfast and after dinner according to the following dose depending on the BSA.**

| **Body Surface Area (m$^2$)** | **Dosage in each dose (Number of capsules)** | **Total daily dose (Number of capsules)** |
|---|---|---|
| **< 1.25** | **40 mg (2)** | **80 mg (4)** |
| **≥ 1.25 - < 1.5** | **50 mg (2)** | **100 mg (4)** |
| **≥ 1.5** | **60 mg (3)** | **120 mg (6)** |

All supplies indicated in will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 7.2.6 for details regarding administration of the study treatment.

The study treatment should be started within 8 days after the day of enrollment.

Pembrolizumab and TS-1 will be provided by the designee, depending on regulatory requirements.

For any commercially available product that is provided by the trial site, designee every attempt will be made to source these supplies from a single lot/batch number.

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.

## 7.2 Dose Modification (Escalation/Titration/Other)

### 7.2.1 Dose Selection (Preparation)

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

Preparation of oxaliplatin, cisplatin, and TS-1 should follow the local product label. The body surface area (BSA) in $m^2$ should be calculated by the web registration system using the DuBois formula. The dose of oxaliplatin and cisplatin shall not be recalculated by body weight fluctuation in principle, but for 10% or higher fluctuation of body weight, recalculation is possible at the discretion of the investigator. When recalculation, the BSA will be calculated using the DuBois formula.

### 7.2.2 Dose Modification

The Investigator may attribute each toxicity event to oxaliplatin, cisplatin, TS-1 or pembrolizumab alone and use a stepwise dose reduction according to Table 4 to Table 8. Dose modification should be performed with the following taken into consideration.

- Treatment for each new cycle may be delayed if the scheduled off-drug periods are not adequate to allow for recovery to the guideline for restarting each study treatment.
- Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity.
- If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated.
- Subjects can have a maximum of 2 dose modifications (if applicable) to the TS-1, a maximum of 3 dose modifications to the oxaliplatin and cisplatin, throughout the course of the study for toxicities. If a subject experiences several toxicities and there are conflicting recommendations, please follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).
- Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the Investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs may be considered to be reduced according to recommended dose modifications. If the toxicity is related to the combination of three agents, chemotherapy may be considered to be reduced, interrupted or discontinued, pembrolizumab should be interrupted or discontinued according to the recommended dose modifications.

- Both cohorts may have the oxaliplatin, cisplatin and TS-1 discontinued and continued on pembrolizumab alone.
- Both cohorts may have the pembrolizumab discontinued and continued on TS-1 + oxaliplatin or TS-1 + cisplatin. Also, both cohorts may have the oxaliplatin and cisplatin discontinued and continued on TS-1 alone. But both cohorts may not have the TS-1 discontinued and continued on oxaliplatin or cisplatin alone.

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events. All dose modifications should be based on the AE requiring the greatest dose modification. Dose modifications are detailed in Table 4 through Table 8. Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

Table 4 Dose Modifications for Trial Medications

| | Dose level 0 | Dose level -1 | Dose level -2 | Dose level -3 | Dose level -4 |
|---|---|---|---|---|---|
| **Oxaliplatin** | 130 mg/m$^2$ | 100 mg/m$^2$ | 75 mg/m$^2$ | 50 mg/m$^2$ | Not specified* |
| **Cisplatin** | 60 mg/m$^2$ | 50 mg/m$^2$ | 40 mg/m$^2$ | 30 mg/m$^2$ | Not specified* |
| **TS-1** | 60 mg/dose<br>50 mg/dose<br>40 mg/dose | 50 mg/dose<br>40 mg/dose<br>Not specified* | 40 mg/dose<br>Not specified*<br>Not specified* | Not specified*<br>Not specified*<br>Not specified* | Not specified*<br>Not specified*<br>Not specified* |
| **Pembrolizumab** | 200 mg fixed dose | Dose reductions are not permitted | Dose reductions are not permitted | Dose reductions are not permitted | Dose reductions are not permitted |

*Because there are no further criteria for dose reductions, the treatment may be resumed or started at the lowest dose if the criteria for resuming the treatment in the cycle or for starting the next cycle are met.

If a toxicity is not otherwise specified, investigators should refer to the label or local guidelines for oxaliplatin, cisplatin and TS-1 for dose adjustments.

### 7.2.3 Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 5.

Table 5 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

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

| **Immune-related AEs** | **Toxicity grade or conditions (CTCAEv4.0)** | **Action taken to pembrolizumab** | **irAE management with corticosteroid and/or other therapies** | **Monitor and follow-up** |
|---|---|---|---|---|
| Pneumonitis | Grade 2 | Withhold | • Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper | • Monitor 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 1-2mg/kg prednisone or equivalent) followed by taper | • Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).<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 | | |

General instructions:

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

| **Immune-related AEs** | **Toxicity grade or conditions (CTCAEv4.0)** | **Action taken to pembrolizumab** | **irAE management with corticosteroid and/or other therapies** | **Monitor and follow-up** |
|---|---|---|---|---|
| AST / ALT elevation or Increased Bilirubin | Grade 2 | Withhold | • Administer corticosteroids (initial dose of 0.5- 1mg/kg prednisone or equivalent) followed by taper<br>• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper | • Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable |
| | Grade 3 or 4 | Permanently discontinue | | |
| Type 1 diabetes mellitus (T1DM) or Hyperglycemia | Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure | Withhold | • Initiate insulin replacement therapy for 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 (eg, propranolol) or thionamides as appropriate | • Monitor for signs and symptoms of thyroid disorders. |
| | Grade 3 or 4 | Withhold or Permanently discontinue1 | | |
| Hypothyroidism | Grade 2-4 | Continue | • Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care | • Monitor for signs and symptoms of thyroid disorders. |
| Nephritis and renal dysfunction | Grade 2 | Withhold | • Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper. | • Monitor changes of renal function |
| | Grade 3 or 4 | Permanently discontinue | | |

General instructions:

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

| **Immune-related AEs** | **Toxicity grade or conditions (CTCAEv4.0)** | **Action taken to pembrolizumab** | **irAE management with corticosteroid and/or other therapies** | **Monitor and follow-up** |
|---|---|---|---|---|
| All Other immune-related AEs | Grade 3, or intolerable/ persistent Grade 2 | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology or exclude other causes |
| | Grade 4 or recurrent Grade 3 | Permanently discontinue | | |

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

**NOTE**:
For 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 6.

Table 6 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 participant 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 hrs | **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 participant 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 participant should be premedicated for the next scheduled dose.<br>**Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment** | Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ 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 ventilatory 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 participant 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>**Participant 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 | | |

### 7.2.4 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. Participants 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.

### 7.2.5 Dose Modification for Oxaliplatin, Cisplatin and TS-1

Please refer to criteria for oxaliplatin, cisplatin and TS-1 dose modification included in Table 7, Table 8, and Table 9, respectively.

Table 7 Dose Modification Guidelines for Oxaliplatin Drug-Related Adverse Events

| Category | Toxicity | Hold Oxaliplatin Treatment for Grade | Timing for Restarting Oxaliplatin Treatment | Dose for Restarting Oxaliplatin Treatment |
|---|---|---|---|---|
| **Hematologic**[1] | Neutropenia[5] | 2-3[2] | ≥1,500/mm$^3$ | No Reduction<br>If the criteria for starting the course are not met at Day 22, reduce by 1 DL. |
| | | 4[2] | ≥1,500/mm$^3$ | Reduce by 1 DL |
| | Febrile neutropenia | 3-4[2] | Toxicity resolves | Reduce by 1 DL |
| | Thrombocytopenia | 2-4[2] | ≥75,000/mm$^3$ | Reduce by 1 DL<br>If a platelet count is ≥ 75,000/mm$^3$ to < 100,000/mm$^3$ at Day 22[3] |
| **Non-hematologic** | Creatinine increased | ≥1.5 mg/dL[2] | <1.5 mg/dL | No reduction |
| | Peripheral sensory neuropathy[4] | 2<br>May be interrupted at the discretion of the investigator<br>3-4[2] | Grade 0-2<br>Grade 0-2 | Consider a reduction by 1 DL at the discretion of the investigator<br>Reduce by 1 DL |

[1] Subjects with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.
[2] *Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.*
[3] *If ≥75,000/mm$^3$ and < 100,000/mm$^3$ persist in the next and subsequent courses, a dose reduction is not mandatory.*
[4] Administration may be interrupted or reduced at the discretion of the investigator.
[5] See the package insert of each G-CSF drugs for administration of G-CSF for neutropenia.

Table 8 Dose Modification Guidelines for Cisplatin Drug-Related Adverse Events

| Category | Toxicity | Hold Cisplatin Treatment for Grade | Timing for Restarting Cisplatin Treatment | Dose for Restarting Cisplatin Treatment |
|---|---|---|---|---|
| **Hematologic**[1] | Neutropenia[4] | 2-3[2] | ≥1,500/mm$^3$ | No Reduction<br>If the criteria for starting the course are not met at Day 22, reduce by 1 DL. |
| | | 4[2] | ≥1,500/mm$^3$ | Reduce by 1 DL |
| | Febrile neutropenia | 3-4[2] | Toxicity resolves | Reduce by 1 DL |
| | Thrombocytopenia | 2 | ≥75,000/mm$^3$ | No Reduction |
| | | 3-4[2] | ≥75,000/mm$^3$ | Reduce by 1 DL |
| **Non-hematologic** | Creatinine increased | >1.2 x ULN[2] | ≤1.2 x ULN | Reduce by 1 DL |
| | Ototoxicity or Peripheral sensory neuropathy[3] | 3-4[2] | Grade 0-2 | Reduce by 1 DL |

[1] Subjects with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.
[2] *Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.*
[3] Administration may be interrupted or reduced at the discretion of the investigator.
[4] See the package insert of each G-CSF drugs for administration of G-CSF for neutropenia.

Table 9 Dose Modification Guidelines for TS-1 Drug-Related Adverse Events

| Category | Toxicity | Hold TS-1 Treatment for Grade | Timing for Restarting TS-1 Treatment | Dose for Restarting TS-1 Treatment |
|---|---|---|---|---|
| **Hematologic**[1] | Neutropenia[3] | 3[2] | ≥1,500/mm$^3$ | No Reduction<br>If the criteria for starting the course are not met at Day 22, reduce by 1 DL. |
| | | 4[2] | ≥1,500/mm$^3$ | Reduce by 1 DL |
| | Febrile neutropenia | 3-4[2] | Toxicity resolves | Reduce by 1 DL |
| | Thrombocytopenia | 3-4[2] | ≥75,000/mm$^3$ | Reduce by 1 DL |
| **Non-hematologic** | Diarrhoea, Mucositis, or Hand and foot syndrome | 2-4[2] | Grade 0-1 | Reduce by 1 DL |
| | Creatinine increased | [Cohort 1]<br>≥1.5 mg/dL[2]<br>[Cohort 2]<br>> 1.2 x ULN[2] | [Cohort 1]<br><1.5 mg/dL<br>[Cohort 2]<br>≤ 1.2 x ULN | No Reduction |
| | AST, ALT | > 2.5 x ULN[2]<br>> 5 x ULN for subjects with liver metastases | ≤ 2.5 x ULN<br>≤ 5 x ULN for subjects with liver metastases | Reduce by 1 DL |

[1] Subjects with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.
[2] Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug related AE.
[3] See the package insert of each G-CSF drugs for administration of G-CSF for neutropenia.

### 7.2.6 Timing of Dose Administration

Study treatment in all the cohorts will begin on Day 1 of each 3-week dosing cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatments may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments may be administered on an outpatient basis.

Treatment will be administered in the order presented below:

- Pembrolizumab infusion is administered first followed by the oxaliplatin or cisplatin infusion and then TS-1 administration.
- Treatment may continue with pembrolizumab+chemotherapy until documented confirmed disease progression, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, Investigator's decision to withdraw the subject, subject withdraws consent, subject's request to discontinue, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons requiring cessation of treatment, or until the participant has received 35 administrations of pembrolizumab (approximately 2 years).

Note: Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons (i.e. elective surgery, unrelated medical events, subject vacation, and holidays) not related to study therapy. Subjects should be placed back on study therapy as soon as clinically appropriate per the investigator, and not exceeding 3 weeks from the interrupted dosing. For all study drugs, Day 1 of subsequent cycles should be adjusted accordingly to adhere to every 3 week dosing schedule. Discuss with the Sponsor if subjects cannot restart study medication within 3 weeks. The reason for interruption should be documented in the subject's study record.

#### 7.2.6.1 Pembrolizumab

Regardless of clinical benefit, subjects may only receive 35 administrations (approximately 2 years) with pembrolizumab. Pembrolizumab 200 mg fixed dose 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 the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

#### 7.2.6.2 Oxaliplatin

Oxaliplatin 130 mg/m$^2$ will be administered as a 120 minute IV infusion Q3W on Day 1 of each treatment cycle after all procedures and assessments are completed according to the "TRIAL FLOW CHART in Section 6.0" and pembrolizumab infusion is completed. The administration of oxaliplatin may be interrupted or reduced at the discretion of the investigator because the incidence of neuropathy has been reported to increase with increases in the dose.

#### 7.2.6.3 Cisplatin

Cisplatin 60 mg/m$^2$ will be administered as over 120 minute (120 minute or more is recommended. If it is difficult due to the time, 60 minute or more is allowed.) IV infusion Q3W on Day 1 of each treatment cycle after all procedures and assessments are completed according to the "TRIAL FLOW CHART in Section 6.0" and pembrolizumab infusion is completed. The administration of cisplatin may be interrupted or reduced at the discretion of the investigator because the incidence of hearing impaired has been reported to increase with increases in the dose.

#### 7.2.6.4 TS-1

As tegafur, TS-1 40 to 60 mg/body/dose BID according to the BSA will be administered Q3W at Days 1 to 14 after completion of all procedures and assessments according to the "TRIAL FLOW CHART in Section 6.0," and pembrolizumab and oxaliplatin or cisplatin infusion. An interval of at least 8 hours should be kept between the evening and morning doses of TS-1. The subjects should have a meal and take the drug within 60 minutes after the meal. For additional guidance on the treatment method of TS-1, see the package insert.

Note: If subject is enrolled later in the day, it is acceptable for only 1 dose taken on Day 1, and BID dosing can resume on Days 2-14 and the final dose will be taken in the morning of D15.

### 7.3 Method of Treatment Assignment

Participants participating in this trial will be allocated by non-random assignment. The subjects will be enrolled in the study using web registration system (IWRS). There are 2 cohorts, and the first approximately 45 subjects will be assigned to Cohort 1. After enrollment in Cohort 1 is completed, enrollment in Cohort 2 will be started.

#### 7.3.1 Stratification

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

### 7.4 Blinding

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

### 7.5 Preparation/Handling/Storage/Accountability

#### 7.5.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Concomitant chemotherapeutic agents will be prepared and administered as per the approved product label(s).

### 7.5.2 Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study 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.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

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

## 7.6 Treatment Compliance

Interruptions from the protocol specified treatment plan for more than 12 weeks between pembrolizumab doses for nondrug-related or administrative reason require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

## 7.7 Concomitant Therapy

### 7.7.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids.

All concomitant medications received during the trial through 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 90 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

### 7.7.2 Prohibited Concomitant Medication

Subjects are prohibited from receiving the following therapies during Screening to the day of Treatment discontinuation of this trial:

- Antineoplastic systemic chemotherapy or biological therapy not specified in the protocol
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy; palliative radiation therapy to a symptomatic lesion (e.g. bony metastasis), or to the brain may be permitted after consultation with the Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. The killed virus vaccines used for seasonal influenza vaccines for injection are allowed; however live attenuated intranasal influenza vaccines (e.g. Flu - Mist®) are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or cisplatin supportive care. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor (e.g., for control of acute asthma symptoms).
- For subjects assigned to Cohort 2:
  - Phenytoin should not be started with cisplatin therapy.
- Flucytosine
- Tegafur/Uracil and calcium folinate

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

**Concomitant Medications to be used with caution**

- Warfarin potassium (The effect of warfarin potassium may be enhanced.)
  - When other observation or tests suggested any abnormality, an international normalized ratio (INR), etc. should be measured to pay attention to changes in clotting ability, and the warfarin dose should be, as necessary, adjusted.
- Phenytoin (Phenytoin addiction may occur.)
  - The subject's condition should be monitored if they are on phenytoin. If any abnormality is noted, appropriate therapeutic measures such as a dose reduction and treatment discontinuation should be taken.
- For subjects assigned to Cohort 2:
  - Aminoglycoside antibiotics, vancomycin hydrochloride, and furosemide (concomitant administration of these drugs with cisplatin may enhance renal disorder and ototoxicity).

- Amphotericin B for injection (concomitant administration of the drug with cisplatin may enhance renal disorder).
- Piretanide (concomitant administration of the drug with cisplatin may enhance ototoxicity).

### 7.7.3 Rescue Medications and Supportive Care

#### 7.7.3.1 Supportive Care Guidelines for Pembrolizumab

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

- **Pneumonitis:**
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. See the guidelines shown in Table 5 for recurrent Grade 2 Pneumonitis.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis:**

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4 Hyperglycemia**
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis:**
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism:**

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

- **Hepatic:**
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis:**
  - For Grade 2 events, treat with corticosteroids.
  - For Grade 3-4 events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 6 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

#### 7.7.3.2 Supportive Care Guidelines for Oxaliplatin/ Cisplatin

Prevention and/or treatment of nausea and vomiting should be managed with:

1. IV EMEND (fosaprepitant) 150 mg IV or oral EMEND (aprepitant) 3 day pack 125 mg day 1, 80 mg day 2, 80 mg day 3
2. Plus Aloxi (Palonosetron) 0.25 mg IV

Nausea may also be managed with:

1. Zofran (Ondansetron) 8 mg twice a day
2. Or Compazine (Prochlorperazine) 10 mg 3-4 times per day

Additionally, use of steroids for oxaliplatin/ cisplatin associated anti-emetic support is allowed and is to follow the NCCN guideline, the local guidelines or institutional guidelines.

Please refer to the product label or local standards of care for additional oxaliplatin/ cisplatin supportive measures.

#### 7.7.3.3 Supportive Care Guidelines for TS-1

Please refer to the product label or local standards of care for TS-1 supportive measures.

### 7.7.4 Diet/Activity/Other Considerations

#### 7.7.4.1 Diet

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

#### 7.7.4.2 Contraception

MK-3475 may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm.

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

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

- She is 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.);
- She had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;
- She has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

- practice abstinence[†] from heterosexual activity;
- use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[‡]:

- Single method (one of the following is acceptable):
    - intrauterine device (IUD)
    - vasectomy of a female subject's male partner
    - contraceptive rod implanted into the skin
- Combination method (requires use of two of the following):
    - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
    - cervical cap with spermicide (nulliparous women only)
    - contraceptive sponge (nulliparous women only)
    - male condom or female condom (cannot be used together)

- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. 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.

#### 7.7.4.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment the subject will immediately be discontinued from trial treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the SPONSOR without delay and within 24 hours if the outcome is a SAE (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.

#### 7.7.4.4 Use in Nursing Women

Since many drugs are excreted in human milk, and because of the potential for SAEs in the nursing infant, subjects who are breast-feeding are not eligible for enrollment. Specific additional information follows for individual agents used in this trial.

##### 7.7.4.4.1 Pembrolizumab

It is unknown whether pembrolizumab is excreted in human milk.

##### 7.7.4.4.2 Oxaliplatin

Oxaliplatin has been reported to be excreted in breast milk in an animal experiment (rats). Whether or not oxaliplatin is excreted in human milk is unknown. Subjects who receive oxaliplatin IV infusion should not breast-feed because it inhibits DNA replication and transcription.

##### 7.7.4.4.3 Cisplatin

Cisplatin has been reported to be found in human milk; subjects receiving Cisplatin injection should not breast-feed.

#### 7.7.4.4.4 TS-1

Women who received tegafur/ uracil were reported to have given birth to deformed infants. It is not known whether TS-1 is excreted in human milk. TS-1 inhibits DNA biosynthesis and impairs RNA function so that subjects receiving TS-1 should not breast-feed.

## 7.8 Treatment After the End of the Study

There is no study-specified treatment following the end of the study.

## 7.9 Clinical Supplies Disclosure

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

## 7.10 Standard Policies

### 7.10.1 Study Site Retention Samples

#### 7.10.1.1 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 10.

Table 10 Product Descriptions.

| Product Name & Potency | Dosage Form | Additional Information |
|---|---|---|
| Pembrolizumab (MK-3475), 25 mg/mL | Injection | Provided centrally by the Sponsor or designee |
| Cisplatin, 1 mg/mL | Injection | The drug used in the trial site will be used. |
| Oxaliplatin, 50 mg/mL | Injection | The drug used in the trial site will be used. |
| TS-1 20 mg and 25 mg | Capsule | Provided centrally by the Sponsor or designee |

#### 7.10.1.2 Packaging and Labeling Information

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

MK-3475 will be provided in kits (boxes) containing 2 vials of MK-3475 each.

TS-1 will be provided in a kit (box) containing 56 capsules of TS-1 20 mg or 56 capsules of TS-1 25 mg.

#### 7.10.1.3 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.

For other details, Study Drug Management Procedures must be followed.

#### 7.10.1.4 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, 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.

For other details, Study Drug Management Procedures must be followed.

## 8. Discontinuation/Withdrawal Criteria

### 8.1 Discontinuation of Study Treatment

Discontinuation of study treatment does not represent withdrawal from the study.

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period regimen will still continue to participate in the study as specified in Section 2 - Schedule of Activities and Section 9.1.9 – Withdrawal/Discontinuation, or if available, Protocol Clarification Letter.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.9 – Withdrawal/Discontinuation.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment.
- Unacceptable adverse experiences as described in Appendix 4

- The participant interrupts study treatment administration for more than 12 consecutive weeks.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- Completion of 35 treatments (approximately 2 years) with pembrolizumab
  Note: The number of treatments is calculated starting with the first dose.

For participants who are discontinued from study treatment but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

## 8.2 Withdrawal from the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study is outlined in Section 9.1.9 – Withdrawal/Discontinuation. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 8.3 Lost to Follow Up .

## 8.3 Lost to Follow Up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, phone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the pre-specified statistical data handling and analysis guidelines.

## 9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The Investigator is responsible for assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

### 9.1 Administrative and General Procedures

#### 9.1.1 Informed Consent

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

##### 9.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant'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 participant before participation in the study.

The initial ICF, any subsequent revised written ICF and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use.

The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. 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 participant's dated signature or by the participant's legally acceptable representative's dated signature.

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

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

#### 9.1.1.2 Submitting Tumor Sample

Tumor tissue sample for assessment of PD-L1 status must meet the following requirement:

Either pre-existing archived or newly-obtained (fresh tissue) biopsy specimens from either primary or metastatic tumor of gastric origin, whichever most recent.

- Newly-obtained (fresh tissue) is defined as a specimen obtained up to 42 days prior to administration of study treatment on Day 1 of Cycle 1, and no additional anti-cancer treatment has been given after the specimen was obtained.
- Pre-existing, archived tissue must be obtained prior to time point that any anti-cancer treatment was given.

A fine needle aspirate (FNA) or cytologic specimen will not be acceptable. In the event the most recent available tumor tissue specimen is an FNA or cytologic specimen, a previous specimen obtained prior to any anti-cancer therapy was given may be submitted (provided it is not an FNA or cytologic specimen).

Where available, both newly-obtained (fresh tissue) and pre-existing archived tissues are requested; however, the tissue specimen obtained closest to study treatment initiation on Day 1 of Cycle 1 will be used to determine eligibility for study participation.

Tumor tissue specimen submitted in either formalin solution or FFPE block is acceptable. If submitting unstained cut slides from FFPE block, freshly cut slides should be received by the central laboratory within 14 days from when the slides are prepared. Please refer to the Procedures Manual for additional details.

### 9.1.2 Inclusion/Exclusion Criteria

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

### 9.1.3 Participant Identification Card

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

treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study treatment in emergency situations where the investigator is not available.

### 9.1.4 Medical History

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

Please note that if the subject has lost at least 15 lbs. (6.8 kg.) over the three months prior to screening, "weight loss" should be entered as an active condition on the Medical History. As well, any autoimmune disorders, regardless of onset date, should be recorded.

### 9.1.5 Prior and Concomitant Medications Review

#### 9.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record details regarding the subject's gastric or GEJ adenocarcinoma separately.

#### 9.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study from the day of first dose until the Safety Follow-up visit.

### 9.1.6 Assignment of Screening Number

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

Any participant 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 9.10.1.

A screening numbers is a "XX (trial site number)-1-" and 2-digit number in Cohort 1, and "XX (trial site number)-2-" and 2-digit number in Cohort 2.The 2-digit numbers are serial numbers in each trial site.

### 9.1.7 Assignment of Treatment/Randomization Number

At the time of confirmation of subjects' eligibility, the subjects will be assigned to Cohort 1 or 2 one by one, by Interactive Web Response System (IWRS). For detailed procedures for assignment, see procedures which are provided separately.

All eligible subjects will receive a patient number. The patient number identifies the subject for all procedures occurring after enrollment. Once a patient number is assigned to a subject, it can never be re-assigned to another subject.

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

Trial treatment should begin within 8 days after the day of enrollment.

A patient number is a "659-1-" and 2-digit number in Cohort 1, and "659-2-" and 2-digit number in Cohort 2. The 2-digit numbers are serial numbers in each cohort of the trial (not each trial site).

### 9.1.8 Treatment Administration

Administration of Pembrolizumab, Oxaliplatin and Cisplatin will be witnessed by the investigator and/or trial staff. Study Treatment should begin within 8 days after the day of enrollment.

#### 9.1.8.1 Timing of Dose Administration

Refer to section 7.2.6 for details regarding administration of the study treatment.

### 9.1.9 Discontinuation and Withdrawal

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final trial visit should be performed (at the time of withdrawal). Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 Adverse Events (AE), Serious Adverse Events (SAE) and Other Reportable Safety Events.

### 9.1.10 Participant Blinding/Unblinding

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

### 9.1.11 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 study 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 study site.

Critical Equipment for this study includes:

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

See protocol-specified guidance in the Administrative Binder, Procedures Manual, Site Imaging Manual (SIM) and iRECIST Tip Sheet.

## 9.2 Efficacy Assessments

### 9.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the BICR can be found in the Site Imaging Manual (SIM). Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

All scheduled images for all study participants from the sites will be submitted to the BICR. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but captures radiologic progression based on investigator assessment, should also be submitted to the BICR.

When the investigator identifies radiographic progression per RECIST 1.1, the BICR will perform expedited verification of radiologic PD and communicate the results to the trial site and Sponsor (See [Section 9.2.1.4] and Figure 2). Treatment should continue until PD has been verified. Regardless of whether PD is verified, if the investigator considers the participant has progressed, but elects to implement iRECIST, the investigator will assess for confirmation of progression by iRECIST at subsequent time points. Images should continue to be submitted to the BICR.

#### 9.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 21 days prior to the date of allocation. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

#### 9.2.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed within 21 days prior to the date of allocation. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After 6 weeks, participants who remain on treatment will have imaging performed every 6 weeks. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator (unless the investigator elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death, or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the BICR.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for

confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Note: Response does not typically need to be verified in real time by the BICR.

Per iRECIST (Section 9.2.1.5), disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site, provided they have met the conditions detailed in Section 9.2.1.5. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 9.2.1.5.

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

For participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging if the investigator elects not to implement iRECIST.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (every 6 weeks in Year 1 or every 6 weeks after Year 1) until the start of a new anticancer treatment, disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first.

#### 9.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by BICR as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

#### 9.2.1.5 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 2. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent in to the BICR for potential retrospective BICR.

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 7, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 2 and submitted to the BICR.

A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 11 and illustrated as a flowchart in Figure 2.

Table 11 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

| | Clinically Stable | | Clinically Unstable | |
|---|---|---|---|---|
| | Imaging | Treatment | Imaging | Treatment |
| First radiologic evidence of PD by RECIST 1.1 | Repeat imaging at 4 to 8 weeks to confirm PD. | May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST. | Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only. | Discontinue treatment |
| Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment | No additional imaging required. | Discontinue treatment (exception is possible upon consultation with Sponsor). | No additional imaging required. | Not applicable |
| Repeat tumor imaging shows iUPD by iRECIST per investigator assessment | Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit. | Continue study treatment at the investigator's discretion. | Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only. | Discontinue treatment |
| Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment. | Continue regularly scheduled imaging assessments. | Continue study treatment at the investigator's discretion. | Continue regularly scheduled imaging assessments. | May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule. |

iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1.
Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the BICR, but no rapid review will occur.

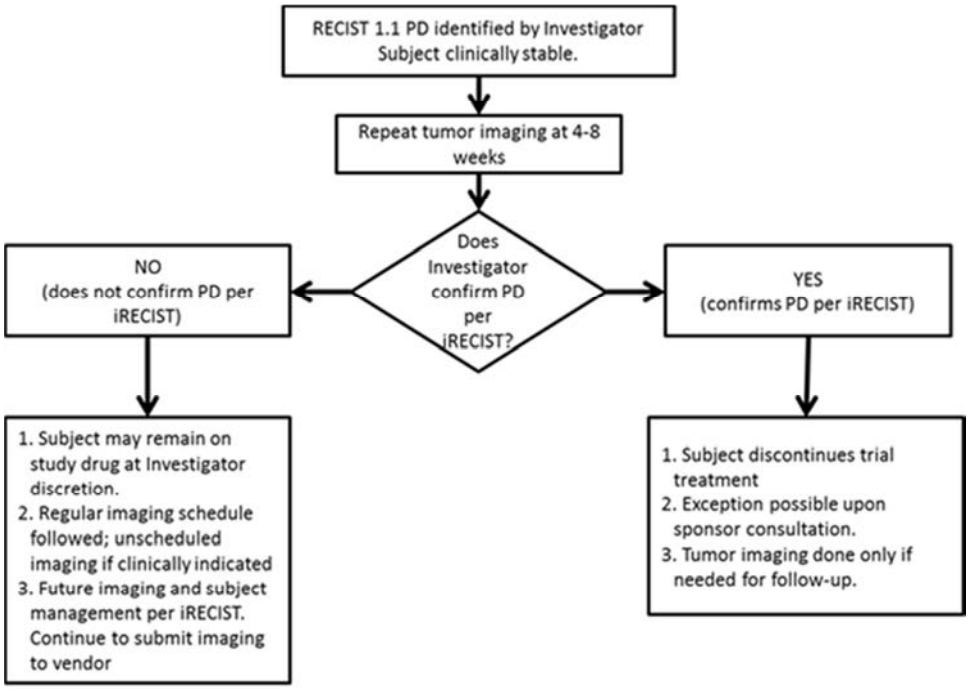



Figure 2 Imaging and Treatment for Clinically Stable Participants Treated with Pembrolizumab after First Radiologic Evidence of PD Assessed by the Investigator

## 9.3 Adverse Events (AE), Serious Adverse Events (SAE) and Other Reportable Safety Events

The definitions of an adverse event (AE) or serious adverse event (SAE), as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE and other reportable safety event reports can be found in Appendix 4.

Progression of the cancer under study is not considered an adverse event as described in Section 9.3.5 – Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs, and Appendix 4.

AE, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

### 9.3.1 Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the sponsor or designee within the timeframes as indicated in Table 12.

Table 12 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

| Type of Event | | Reporting Time Period: Consent to Randomization/ Allocation | Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period | Reporting Time Period: After the Protocol Specified Follow-up Period | | Timeframe to Report Event and Follow-up Information to SPONSOR: |
|---|---|---|---|---|---|---|
| **Non-Serious Adverse Event (NSAE)** | | Report if:<br>- due to protocol-specified intervention<br>- causes exclusion<br>- participant is receiving placebo run-in or other run-in treatment | Report all | Not required | | Per data entry guidelines |
| **Serious Adverse Event (SAE) including Cancer and Overdose** | | Report if:<br>- due to protocol-specified intervention<br>- causes exclusion<br>- participant is receiving placebo run-in or other run-in treatment | Report all | Report if:<br>- drug/vaccine related.<br>(Follow ongoing to outcome) | | Within 24 hours of learning of event |
| **Pregnancy/Lactation Exposure** | | Report if:<br>- due to intervention<br>- causes exclusion | Report all | Previously reported – Follow to completion/termination; report outcome | | Within 24 hours of learning of event |
| **Event of Clinical Interest (require regulatory reporting)** | | Report if:<br>- due to intervention<br>- causes exclusion | Report<br>- Potential DILI<br>- Require regulatory reporting | Not required | | Within 24 hours of learning of event |
| **Event of Clinical Interest (Do not require regulatory reporting)** | | Report if:<br>- due to intervention<br>- causes exclusion | Report<br>- non-DILI ECIs and those not requiring regulatory reporting | Not required | | Within 5 calendar days of learning of event |

### 9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AE and/or SAE and other reportable safety events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

### 9.3.3 Follow-up of AE, SAE and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

### 9.3.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

### 9.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Progression of the cancer under study is not considered a reportable event.

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

### 9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

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.

### 9.3.7 Events of Clinical Interest (ECI)

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

Events of clinical interest for this study include:

1. an overdose of Sponsor's product, as defined in Section 9.4 – Treatment of Overdose, 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 study site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

## 9.4 Treatment of Overdose

For this study, an overdose will be defined as any dose exceeding the prescribed dose for the standard treatments by ≥20% and as 1000 mg or greater (≥5 times the indicated dose) of pembrolizumab.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant 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, the adverse event(s) is reported as a SAE, even if no other seriousness criteria are met.

If a dose of Sponsor's product 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 paper. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

## 9.5 Safety

Details regarding specific safety 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 participant can be found in Procedures Manual.

Planned time points for all safety assessments are provided in the SoA.

### 9.5.1 Physical Examinations

#### 9.5.1.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 2. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

#### 9.5.1.2 Directed Physical Exam

For cycles that do not required a full physical exam as defined in Section 2, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to the administration of the study treatment. New clinically significant abnormal findings should be recorded as AEs.

### 9.5.2 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart- Section 2. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

### 9.5.3 Electrocardiograms

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.

### 9.5.4 Clinical Safety Laboratory Assessments

Refer to Appendix 5 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 5, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

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

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 5.

#### 9.5.4.2 Pregnancy Test

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal (defined as: a woman who is ≥45 years of age and has not had menses for greater than 1 year), must be tested for pregnancy at the timing of enrollment. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result.

### 9.5.5 Performance Assessments

#### 9.5.5.1 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 6) at screening, prior to the administration of each dose of study treatment and during the follow-up period as specified in the Study Flow Chart (Section 2).

### 9.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

### 9.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

### 9.8 Biomarkers

Biomarkers are not evaluated in this study except for PD-L1 to confirm the eligibility.

### 9.9 Future Biomedical Research Sample Collection

Future Biomedical Research Samples will not be collected in this study.

### 9.10 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

#### 9.10.1 Screening

Within 21 days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6. Screening procedures may be repeated after consultation with the Sponsor.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the protocol SOA, including consent review. Rescreen procedures cannot be conducted the day prior to treatment allocation if there are Day -1 procedures planned per protocol.

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant 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 21 days prior to the first dose of study treatment except for the following:

- Laboratory tests are to be performed within 21 days prior to the first dose of study treatment. An exception is hepatitis testing which may be done up to 28 days prior to the first dose of study treatment.
- Evaluation of ECOG is to be performed within 3 days prior to date of allocation.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- Archival tumor sample collection is not required to be obtained within 28 days prior to the first dose of study treatment. Newly obtained tumor tissue may be obtained within 90 days of treatment initiation.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat

screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

### 9.10.2 Treatment Period Visit

Visit requirements are outlined in the Study Flow Chart (Section 2). Specific procedure-related details are provided in Section 9.1.

### 9.10.3 Post-Treatment Visits

#### 9.10.3.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever comes first.

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer therapy, whichever occurs first. Serious AEs and ECI that occur within 30 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

#### 9.10.3.2 Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (± 7 days) until PD. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of study. Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

#### 9.10.3.3 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone every 12 weeks (± 14 days) to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

The Sponsor will request survival status to be assessed at additional time points during the course of the trial. All participants who are in the Survival Follow-Up Phase and not known to have died prior to the request for these additional survival status time points will be contacted at that time.

## 10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to data lock, changes made to the statistical methods related to the primary analysis for the primary endpoint, 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 data lock, will be documented in a

supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

## 10.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 10.2 to Section 10.12.

| | |
|---|---|
| **Study design Overview** | Phase IIb study of Pembrolizumab in combination with TS-1+Cisplatin or TS-1+Oxaliplatin in GC |
| **Treatment Assignment** | Approximately 90 participants will be enrolled. First, 45 subjects will be assigned to Cohort 1, pembrolizumab + oxaliplatin + TS-1 combination therapy, and then, 45 subjects will be assigned to Cohort 2, pembrolizumab + cisplatin + TS-1 combination therapy. |
| **Analysis Populations** | Efficacy: All Subjects as Treated (ASaT)<br>Safety: All Subjects as Treated (ASaT) |
| **Primary Endpoints** | Overall Response Rate (ORR) based on RECIST 1.1 as assessed by BICR |
| **Secondary Endpoints** | • Duration of Response (DOR), per RECIST 1.1 and per iRECIST based on BICR<br>• ORR, per iRECIST by BICR<br>• Disease Control Rate (DCR) , per RECIST 1.1 and per iRECIST based on BICR<br>• Progression Free Survival (PFS) , per RECIST 1.1 and per iRECIST based on BICR<br>• Time To Response (TTR) , per RECIST 1.1 and per iRECIST based on BICR<br>• Overall survival (OS)<br>• Safety and tolerability |
| **Statistical Methods for Key Efficacy Analyses** | The main analytical objective of the trial is to estimate ORR of Cohort 1 and Cohort 2 assessed by the BICR to estimate the magnitude of add-on effect of pembrolizumab co-administered with TS-1 + oxaliplatin and TS-1 + cisplatin in PD-L1 positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. 95% CI for ORR will be calculated using Exact method based on binomial distribution. |
| **Statistical Methods for Key Safety Analyses** | Count and percentage of AE will be provided. |
| **Interim Analyses** | No efficacy interim analysis is planned. |
| **Multiplicity** | This is an estimation study. No multiplicity adjustment will be applied. |
| **Sample Size and Power Calculations** | A total of 80 subjects (Cohort 1, 40 subjects; Cohort 2, 40 subjects) will be included in the ASaT. A total of 90 subjects (Cohort 1, 45 subjects; Cohort 2, 45 subjects) will be enrolled. |

## 10.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the sponsor and the statistics department of the contracted third party.

## 10.3 Hypotheses/Estimation

This is an estimation study. Objectives and hypotheses of the study are stated in Section 4.0.

## 10.4 Analysis Endpoints

The definition of the efficacy and safety endpoints is shown below.

### 10.4.1 Efficacy Endpoints

#### 10.4.1.1 Primary Efficacy Endpoint

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

Objective response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR).

#### 10.4.1.2 Secondary Efficacy Endpoints

- Objective response rate (ORR) - per iRECIST assessed by BICR.
- Duration of Response (DOR) – per RECIST 1.1 assessed by BICR and per iRECIST assessed by BICR.

For subjects who demonstrated CR or PR, response duration is defined as the time from the date of first response (CR or PR) until the date of disease progression or death.

- Disease Control Rate (DCR): - per RECIST 1.1 assessed by BICRand per iRECIST assessed by BICR.

DCR is defined as proportion of subjects in the analysis population who have CR or PR or stable disease (SD).

- Time to Response (TTR) - per RECIST 1.1 assessed by BICR and per iRECIST assessed by BICR.

Time to response is defined as a time from the date of enrollment day to the first date of confirmed CR or PR.

- Progression-free Survival (PFS) - per RECIST 1.1 assessed by BICR and per iRECIST assessed by BICR.

PFS is defined as the time from the date of enrollment day to the first documented disease progression or death due to any cause, whichever occurs first.

- Overall survival (OS)

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

### 10.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, fatal AEs, laboratory tests, and vital signs as described in Section 9.5.

Furthermore, specific events will be collected and designated as ECIs as described in Section 9.3.7.

## 10.5 Analysis Populations

### 10.5.1 Efficacy Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of ORR, DCR, TTR, PFS, and OS. ASaT population consists of all subjects who received at least one dose of study treatment.

The analysis population for DOR consists of responders who have best response of CR or PR in the ASaT.

### 10.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study.

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.

## 10.6 Statistical Methods

### 10.6.1 Statistical Methods for Efficacy Analyses

The main analytical objective of the trial is to estimate ORR of TS-1 + oxaliplatin + pembrolizumab therapy (Cohort 1) and TS-1 + cisplatin + pembrolizumab therapy (Cohort 2) assessed by the BICR to estimate the magnitude of add-on effect of pembrolizumab co-administered with TS-1 + oxaliplatin and TS-1 + cisplatin in PD-L1 positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. The point estimate and 95% confidence interval will be provided using exact binomial method proposed by Clopper and Pearson (1934). Subjects in the primary analysis population (ASaT) without ORR data will be counted as non-responder.

For DOR. PFS, TTR and OS, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate.

Censoring rules for DOR are summarized in Table 13.

Table 13 Censoring Rules for 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) |
| Patients are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anti-cancer therapy and have not been determined to be lost to follow-up. | | |

For each Cohort, the efficacy endpoints, analysis population, and statistical methods (including missing data handling) that will be employed for the efficacy analyses are presented in Table 14.

Table 14 Summary of Analysis Strategy for Efficacy Endpoints

| Endpoint | Statistical Method | Analysis Population | Missing data approach |
|---|---|---|---|
| **Primary Endpoint** | | | |
| ORR<br>• RECIST 1.1 by BICR | Exact method based on binomial distribution | ASaT in all below populations:<br>Cohort 1<br>Cohort 2 | Subjects with missing data are considered non-responders |
| **Secondary Endpoints** | | | |
| ORR<br>• iRECIST by BICR | Exact method based on binomial distribution | ASaT in all below populations:<br>Cohort 1<br>Cohort 2 | Subjects with missing data are considered non-responders |
| DCR<br>• RECIST 1.1 by BICR<br>• iRECIST by BICR | Exact method based on binomial distribution | ASaT in all below populations:<br>Cohort 1<br>Cohort 2 | Subjects with missing data are considered as disease not under control |
| TTR<br>• RECIST 1.1 by BICR<br>• iRECIST by BICR | Summary statistics using Kaplan-Meier method | ASaT in all below populations:<br>Cohort 1<br>Cohort 2 | Censored at last assessment date |
| PFS<br>• RECIST 1.1 by BICR<br>• iRECIST by BICR<br>OS | Summary statistics using Kaplan-Meier method | ASaT in all below populations:<br>Cohort 1<br>Cohort 2 | Censored at last assessment date |
| DOR<br>• RECIST 1.1 by BICR<br>• iRECIST by BICR | Summary statistics using Kaplan-Meier method | Responders in below populations:<br>Cohort 1<br>Cohort 2 | Censored at last assessment date |

### 10.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, vital signs. Count and percentage of AE will be provided.

### 10.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of subjects screened, enrolled, the primary reasons for screening failure, and the primary reason for 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 for all enrolled subjects.

## 10.7 Interim Analyses

No interim analysis is planned in this study.

## 10.8 Multiplicity

No multiplicity adjustment will be applied.

## 10.9 Sample Size and Power Calculations

A total of 80 subjects (TS-1 + oxaliplatin + pembrolizumab group [Cohort 1], 40 subjects; TS-1 + cisplatin + pembrolizumab group [Cohort 2], 40 subjects) will be included in the all participants as treated (ASaT). A total of 90 subjects (Cohort 1, 45 subjects; Cohort 2, 45 subjects) will be enrolled.

The sample size set with 90 subjects (Cohort 1 45 subjects; Cohort 2 45 subjects) that can expect a similar confidence interval of ORR to the previous studies of the first line treatment for gastric cancer for the purpose of the estimation of the ORR.

Considering approximately 10% of untreated subjects excluded, a total of 90 subjects (Cohort 1, 45 subjects; Cohort 2, 45 subjects) will be enrolled and a total of 80 subjects (Cohort 1, 40 subjects; Cohort 2, 40 subjects) will be included as ASaT.

Table 15 show the two-sided 95% confidence interval of ORR when the number of subjects is 80 (40 subjects in Cohort 1 and 40 subjects in Cohort 2).

Table 15 Two sided 95% Confidence interval of ORR with 40 subjects as ASaT

| Number of Observed Responders | ORR Estimates | 95% CI of ORR (%) |
|---|---|---|
| 16 | 40.0% | (24.9, 56.7) |
| 17 | 42.5% | (27.9, 59.) |
| 18 | 45.0% | (29.3, 61.5) |
| 19 | 47.5% | (31.5, 63.9) |
| 20 | 50.0% | (33.8, 66.2) |
| 21 | 52.5% | (36.1, 68.5) |
| 22 | 55.0% | (38.5, 70.7) |
| 23 | 57.5% | (40.9, 73.0) |
| 24 | 60.0% | (43.3, 75.1) |
| 25 | 62.5% | (45.8, 77.3) |
| 26 | 65.0% | (48.3, 79.4) |
| 27 | 67.5% | (50.9, 81.4) |
| 28 | 70.0% | (53.5, 83.4) |
| 29 | 72.5% | (56.1, 85.4) |
| 30 | 75.0% | (58.8, 87.3) |
| 31 | 77.5% | (61.5, 89.2) |
| 32 | 80.0% | (64.4, 90.9) |

There will be approximately 40 subjects enrolled for each cohort, Table 16 shows the two-sided 95% CI of AE rate with 40 subjects.

Table 16 Two-sided 95% CI of AE incidence rate with 40 Subjects

| Number of AE | AE incidence rate estimates | 95% CI of incidence rate (%) |
|---|---|---|
| 1 | 2.5% | (0.00, 13.2) |
| 2 | 5.0% | (0.61, 16.9) |
| 3 | 7.5% | (1.57, 20.4) |
| 4 | 10.0% | (2.8, 23.7) |
| 5 | 12.5% | (4.2, 26.8) |
| 6 | 15.0% | (5.7, 29.8) |
| 7 | 17.5% | (7.3, 32.8) |
| 8 | 20.0% | (9.1, 35.7) |
| 9 | 22.5% | (10.8, 38.5) |

| Number of AE | AE incidence rate estimates | 95% CI of incidence rate (%) |
|---|---|---|
| 10 | 25.0% | (12.7, 41.2) |
| 11 | 27.5% | (14.6, 43.9) |
| 12 | 30.0% | (16.6, 46.5) |
| 13 | 32.5% | (18.6, 49.1) |
| 14 | 35.0% | (20.6, 51.7) |
| 15 | 37.5% | (22.7, 54.2) |

### 10.10 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 selected factors (e.g., analyses for each patient background factors). The details will be described in the sSAP.

### 10.11 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

### 10.12 Extent of Exposure

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

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# 12. Appendices

## 12.1 Appendix 1: Study Governance Considerations

## 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 participant 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 (eg, 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 participant preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research participants 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 participants, 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. Participant Protection**

**A. IRB/IEC review**

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

**B. Safety**

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants 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. Participants are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Participants are enrolled only after providing informed consent for participation. Participants 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 participant 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 participant 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 participants 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 participant referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

**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/IEC 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 (eg, 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."

**Financial Disclosure**

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.

**Data Protection**

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

**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/IEC) 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 study 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.

**Confidentiality of Participant Records**

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of

verifying worksheet/case report form information, the participant 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 participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

**Confidentiality of IRB/IEC Information**

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. 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.

**Publication Policy**

The results of this study may be published or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the sponsor, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

**Compliance with Study Registration and Results Posting Requirements**

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

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

**Compliance with Law, Audit and Debarment**

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, 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 study.

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

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

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

The Investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection, and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

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

**Data Quality Assurance**

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study 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 or regulatory authority as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/case report forms.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

**Source Documents**

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

**Study and Site Closure**

The sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

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

## 12.2 Appendix 2: Description of the iRECIST Process for Assessment of Disease Progression

*Assessment at Screening and Prior to RECIST 1.1 Progression*

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

*Assessment and Decision at RECIST 1.1 Progression*

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 11 and Figure 2). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent in to the BICR for potential retrospective BICR.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

*Assessment at the Confirmatory Imaging*

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

*Confirmation of Progression*

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new non-target lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

*Persistent iUPD*

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

*Resolution of iUPD*

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

*Management Following the Confirmatory Imaging*

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 2 and submitted to the BICR.

*Detection of Progression at Visits after Pseudo-progression Resolves*

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear

- Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
- Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication [Seymour, L., et al 2017].

## 12.3 Appendix 3: Contraceptive Guidance and Pregnancy Testing

### Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

### Contraception Requirements

### Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 6.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 18 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

**Female Participants**

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 17 during the protocol-defined time frame in Section 6.1.

Table 17 Highly Effective Contraception Methods

| |
|---|
| **Highly Effective Contraceptive Methods That Are User Dependent** [a]<br>*Failure rate of <1% per year when used consistently and correctly.* |
| ● Combined (estrogen- and progestogen- containing ) hormonal contraception [b, c]<br>○ Oral<br>○ Intravaginal<br>○ Transdermal<br>○ Injectable |
| ● Progestogen-only hormonal contraception [b, c]<br>○ Oral<br>○ Injectable |
| **Highly Effective Methods That Have Low User Dependency**<br>*Failure rate of <1% per year when used consistently and correctly.* |
| ● Progestogen- only contraceptive implant [b, c]<br>● Intrauterine hormone-releasing system (IUS) [b]<br>● Intrauterine device (IUD)<br>● Bilateral tubal occlusion |
| ● Vasectomized partner<br>A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. |
| ● Sexual abstinence<br>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.) |
| Notes:<br>Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.<br>a) Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly).<br>b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [X days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment .<br>c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. |

**Pregnancy Testing**

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. This test should be repeated a maximum of 24-hours before the first dose/vaccination.

Following initiation of treatment additional pregnancy testing will be performed at monthly intervals during the treatment period and at [X days/weeks (corresponding to time needed to eliminate any study treatment(s) (MK and or any active comparator/combination) plus 30 days (a menstruation cycle) for study treatments with risk of evidence of genotoxicity at any dose)] after the last dose of study treatment and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

## 12.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

**Definition of AE**

| **AE Definition** |
|---|
| • An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.<br>• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.<br>• NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the sponsor for human use in this study. |

| **Events <u>Meeting</u> the AE Definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator.<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication.<br>• For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose of study treatment without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."<br>• Any new cancer (that is not a condition of the study).<br>Note: Progression of the cancer under study is not a reportable event. Refer to Section 9.3.5 for additional details. |

| **Events NOT Meeting the AE Definition** |
|---|
| • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.<br>• Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.<br>• Refer to section 9.3.5 for protocol specific exceptions |

**Definition of SAE**

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met

| **A SAE is defined as any untoward medical occurrence that, at any dose:** |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br>• The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br>• 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 an MSD product and is documented in the patient's medical history. |
| **d. Results in persistent or significant disability/incapacity**<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| **e. Is a congenital anomaly/birth defect**<br>• in offspring of participant taking the product regardless of time to diagnosis |

**f. Other important medical events:**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

**Additional Events reported in the same manner as SAE**

**Additional Events which require reporting in the same manner as SAE**

- 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.

**Recording AE and SAE**

**AE and SAE Recording**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the Adverse Event case report forms/worksheets at each examination.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Intensity**

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

**Assessment of Causality**

- 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 product and the adverse event based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:
    - **Exposure:** Is there evidence that the participant 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 studies 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
- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study); or (4) Sponsor's product(s) is/are only used one time.)
- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study 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.
- 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: Participant 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 participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements

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

**Follow-up of AE and SAE**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

**Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor**

| **AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool** |
|---|
| • The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.<br>  • Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).<br>  • If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.<br>  • Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information for reporting time requirements<br>• The site will enter the SAE data into the electronic system as soon as it becomes available.<br>• After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.<br>• If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).<br>• Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent). |
| **SAE Reporting to the Sponsor via Paper CRF** |
| • If the electronic data collection tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.<br>• In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.<br>• Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.<br>• Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent). |

## 12.5 Appendix 5: Clinical Laboratory Tests

- The tests detailed in Table 18 will be performed by the local laboratory.

Table 18 Protocol-Required Safety Laboratory Assessments

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| Hematocrit | Albumin | Blood | Serum β-human chorionic gonadotropin (β-hCG)[a] |
| Hemoglobin | Alkaline phosphatase | Glucose | PT (INR) |
| Platelet count | Alanine aminotransferase (ALT) | Protein | aPTT |
| WBC count | Aspartate aminotransferase (AST) | Specific gravity | Total triiodothyronine (T3) or Free T3 |
| Percentages of Neutrophils | Calcium | Microscopic exam, if abnormal results are noted | Free thyroxine (T4) |
| Percentages of Eosinophils | Chloride | Urine pregnancy testa | Thyroid stimulating hormone (TSH) |
| Percentages of Basophiles | Creatinine | | |
| Percentages of Lymphocytes | Glucose | | |
| Percentages of Monocytes | Phosphorus | | |
| | Potassium | | |
| | Sodium | | |
| | Total Bilirubin | | |
| | Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal | | |
| | Total protein | | |
| | Blood Urea Nitrogen/Urea[b] | | |
| | Uric acid | | |
| | Creatinine clearance | | |

a. Perform on women of childbearing potential only. Serum pregnancy test is preferred but urine test can be considered if serum not appropriate.
b. Blood Urea Nitrogen is preferred; if not available urea may be tested.

Laboratory tests for screening should be performed within 7 days of enrollment. For Cycle 1 and 2, laboratory tests should be performed within 72 hours prior to dosing and every week (accepted if performed within 3 days before and after a reference day) after dosing. After Cycle 3, 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.

**Serum/Urine β-hCG**

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal (defined as: a woman who is ≥45 years of age and has not had menses for greater than 1 year), will be tested for pregnancy within 72 hours prior to each cycle of trial treatment and 30 days post treatment. Subjects must be excluded/discontinued in the event of a positive or borderline-positive test result. If a urine test is positive or borderline a serum β -HCG test will be required.

## 12.6 Appendix 6: ECOG Performance Status

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

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

http://ecog-acrin.org/resources/ecog-performance-status

## 12.7 Appendix 7: Abbreviations and Trademarks

| Abbreviation/Term | Definition |
|---|---|
| 1L | First Line |
| 2L | Second Line |
| 5-FU | 5-fluorouracil |
| AE | Adverse Event |
| ADA | Anti-Drug Antibodies |
| ALT | Alanine Aminotransferase |
| ANC | Absolute Neutrophil Count |
| AP | Alkaline Phosphatase |
| APaT | All Patients as Treated |
| aPTT | Activated Partial Thromboplastin Time |
| ASCO | American Society of Clinical Oncology |
| AST | Aspartate Aminotransferase |
| AUC | Area Under the Curve |
| BICR | Blinded Independent Central Review |
| BID | Twice a Day |
| ß-HCG | Beta Human Chorionic Gonadotropin |
| BSA | Body Surface Area |
| CBC | Complete Blood Count |
| CI | Confidence Interval |
| CNS | Central Nervous System |
| CR | Complete Response |
| CrCl | Calculated Creatinine Clearance |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| CT | Computed Tomography |
| CTCAE | Common Toxicity Criteria for Adverse Events |
| CTLA-4 | Cytotoxic T-Lymphocyte-Associated Antigen-4 |
| CTU | Computed Tomography Urography |
| DCR | Disease Control Rate |
| DMC | Data Monitoring Committee |
| DNA | Deoxyribonucleic acid |
| DOR | Duration of Response |
| DR | Drug Related |
| ECI | Events of Clinical Interest |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| FA | Final Analysis |
| FBR | Future Biomedical Research |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act |
| FDAMA | Food and Drug Administration Modernization Act |
| FFPE | Formalin-Fixed, Paraffin-Embedded |
| FNA | Fine Needle Aspirate |
| FP | Cisplatin + 5-fluoruracil |
| GCP | Good Clinical Practice |
| GEJ | Gastroesophageal Junction |
| GFR | Glomerular Filtration Rate |
| HBsAg | Hepatitis B surface Antigen |
| HCV | Hepatitis C Virus |
| HER2/neu | Human Epidermal Growth Factor Receptor 2 |

| Abbreviation/Term | Definition |
|---|---|
| HIV | Human Immunodeficiency Virus |
| HNSCC | Head and Neck Squamous Cell Carcinoma |
| HPV | Human Papillomavirus |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IHC | Immunohistochemistry |
| iCPD | iRECIST confirmed progressive disease |
| iCR | iRECIST complete response |
| INR | International Normalized Ratio |
| iPR | iRECIST partial response |
| irAEs | Immune-related Adverse Events |
| iRECIST | modified RECIST for immune-based therapeutics |
| IRB | Institutional Review Board |
| iSD | iRECIST stable disease |
| ITIM | Immunoreceptor Tyrosine-based Inhibition Motif |
| ITSM | Immunoreceptor Tyrosine-based Switch Motif |
| ITT | Intention To Treat |
| iUPD | iRECIST unconfirmed progressive disease |
| IV | Intravenous |
| IVRS | Interactive Voice Response System |
| IWRS | Integrated Web Response System |
| Kg | Kilogram |
| KN | KEYNOTE |
| LDH | Lactate Dehydrogenase |
| mAb | Monoclonal Antibody |
| mcL | Microliters |
| MEL | Melanoma |
| Mg | Milligram |
| Mg/kg | Milligram per Kilogram |
| mL | Milliliter |
| MRI | Magnetic Resonance Imaging |
| MSD | Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. |
| MTD | Maximum Tolerated Dose |
| NA or N/A | Not Applicable |
| NCI | National Cancer Institute |
| NSAID | Non-Steroidal Anti-inflammatory Drug |
| NSCLC | Non-Small Cell Lung Cancer |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| OTC | Over-the-counter |
| PD | Progressive Disease |
| PD-1 | Programmed Death-1 |
| PD-L1 | Programmed Death-Ligand 1 |
| PFS | Progression Free Survival |
| PGt | Pharmacogenetic |
| PIN | Personal Identification Number |
| PK | Pharmacokinetic |
| PK/PD | Pharmacokinetic/Pharmacodynamic |
| PO | Oral Administration |
| PR | Partial Response |
| PRO | Patient Reported Outcomes |

| Abbreviation/Term | Definition |
|---|---|
| PT | Prothrombin Time |
| PS | Performance Status |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | Ribonucleic Acid |
| RR | Response Rate |
| Q2W | Every 2 Weeks |
| Q3W | Every 3 Weeks |
| SAC | Scientific Advisory Committee |
| SAE | Serious Adverse Events |
| SAP | Statistical Analysis Plan |
| SFU | Survival Follow-Up |
| SGOT | Serum Glutamic Oxaloacetic Transaminase |
| SGPT | Serum Glutamic Pyruvic Transaminase |
| siDMC | Standing Internal Data Monitoring Committee |
| SOC | Standard of Care |
| SOP | Standard Operating Procedures |
| T1DM | Type 1 Diabetes Mellitus |
| TIL | Tumor Infiltrating Lymphocytes |
| TSH | Thyroid Stimulating Hormone |
| ULN | Upper Limit of Normal |
| WBC | White Blood Cell |