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TITLE:

A Two-arm, Open-label, Randomized Phase III Study of Pembrolizumab (MK-3475) Monotherapy versus Standard Chemotherapy in Platinum Pre-treated, Recurrent or Metastatic Nasopharyngeal Cancer (NPC) (Keynote-122)

IND NUMBER: 122325
EudraCT NUMBER: Not Applicable

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
00	20-NOV-2015	Original Protocol
01	05-JUL-2016	To primarily increase the number of trial subjects and to make updates to the following: capecitabine dose, gemcitabine dose, Statistical Analysis Plan (i.e., type I error, sample size, interim analysis, power), and Tables of Dose Modifications for Capecitabine, Gemcitabine and Docetaxel.
02	21-DEC-2016	To primarily include an optional sub-study, remove head/brain imaging requirements, update the MK-3475 Dose Modification Table, and update the Flow Chart for ePRO, tumor imaging, and Anti-pembrolizumab Antibodies.
03	18-AUG-2017	To primarily increase the number of trial subjects, update trial phase number, update duration of trial, and update Statistical Analysis Plan (i.e., sample size, interim analysis, power).
04	17-JAN-2018	To primarily update the MK-3475 Dose Modification Table and survival follow-up language.
05	06-JUN-2019	To primarily update the primary endpoint from dual primary endpoints of PFS and OS to a sole primary endpoint of OS, add newly available clinical trial data to support the update in endpoints, update duration of trial, and update Statistical Analysis Plan (i.e., multiplicity, interim analysis, and power).
06	19-JUL-2021	To update the dose modification and toxicity management guidelines for irAEs in the MK-3475 Dose Modification Table, to allow site Investigators to follow the local/standard imaging schedule, to remove blood collection for Plasma EBV DNA beyond Cycle 80, to remove blood collection for Correlative Studies at the Discontinuation Visit, to remove ePRO administration at the Discontinuation/EOT and 30-Day Safety Follow-Up Visits, and to remove blood collection at time of progression after Cycle 80 for the sub-study.

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.1.2	Dose Modification for Pembrolizumab	The Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab (MK-3475) and Table 4 were updated.	The Dose Modification and Toxicity Management Guidelines for irAEs and table were updated as requested by the U.S. FDA in an effort to harmonize the presentation of safety information across all FDA-approved PD-1/L-1 antibody prescribing information.
6.1 7.1.5.1.2 7.1.5.1.3 7.1.7.3.2	Trial Flow Chart – Initial Treatment Phase – Pembrolizumab (MK-3475) and SOC Arms On Study Tumor Imaging End of Treatment and Follow-up Tumor Imaging Efficacy Follow-up Visits	Updated language (including footnotes k and p) to allow site Investigators to follow the local/standard imaging schedule after Year 1.	As final analysis was completed, frequent imaging is no longer required.
6.2 7.1.5.1.4	Trial Flow Chart – Second Course Phase (Retreatment) – Pembrolizumab (MK-3475) Arm Only Second Course (Retreatment) Tumor Imaging	Updated language (including footnotes g and i) to allow site Investigators to follow the local/standard imaging schedule after Year 1.	As final analysis was completed, frequent imaging is no longer required.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
6.1 7.1.4.2.1	Trial Flow Chart – Initial Treatment Phase – Pembrolizumab (MK-3475) and SOC Arms Plasma Epstein-Barr Virus DNA	Updated language (including footnotes n and r) to confirm that Plasma EBV DNA should not be collected after Cycle 80 Day 1.	As final analysis was completed, biomarker collection is no longer required.
6.1 7.1.4.5	Trial Flow Chart - Initial Treatment Phase – Pembrolizumab (MK-3475) and SOC Arms Blood for Correlative and Biomarker Studies	Removed the sample requirement for blood for correlative studies (DNA and RNA) from the Treatment Discontinuation/EOT Visit.	As final analysis was completed, biomarker collection is no longer required.
6.1	Trial Flow Chart – Initial Treatment Phase – Pembrolizumab (MK-3475) and SOC Arms	Removed EuroQol EQ-5D requirement at the EOT/Discontinuation Visit and Safety Follow-up Visit and edited footnote m.	As final analysis was completed, EuroQol EQ-5D collection is no longer required.
7.1.4.6 12.9.2	Blood for Participation in Optional Sub-Study Optional Sub-Study Trial Flow Chart	Updated language (including footnote d) to confirm that a sample should not be collected at the time of disease progression if disease progression occurs after Cycle 80 Day 1.	As final analysis was completed, biomarker collection is no longer required.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
1.0	Trial Summary	Language added to indicate that 'participant' and 'subject' are equivalent.	For clarification.
4.2.2	Rationale for Dose Selection/Regimen/Modification for Pembrolizumab (MK-3475)	Pembrolizumab language updated for Q3W dosing.	[redacted]
4.2.3.1.1	Primary and Secondary Endpoints	Minor edits to RECIST 1.1 language.	For clarification.
4.2.3.5 7.1.1.1.2 7.1.4.3 7.1.4.4 12.2	Future Biomedical Research Consent and Collection of Specimens for Future Biomedical Research Planned Genetic Analysis Sample Collection Future Biomedical Research Collection and Management of Specimens for Future Biomedical Research	Updated language to remove reference to FBR sub-trial plus minor edits.	Revised to align with current FBR requirements.
5.1.2 5.7.2 12.10	Subject Inclusion Criteria Contraception Contraception Guidance	Male and female contraception language updated. Contraception appendix added.	Revised to align with current contraception requirements.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.7.3 5.7.4	Use in Pregnancy Use in Nursing Women	Sections deleted.	Deleted to reduce repetition because information is now included in other sections.
6.1 6.2 7.1.4.1.1 7.1.4.1.2 7.1.7.1 7.1.7.2.1 7.2.2	Initial Treatment Phase – Pembrolizumab (MK-3475) and SOC Arms Second Course Phase (Retreatment) – Pembrolizumab (MK-3475) Arm Only Pregnancy Testing Hematology, Chemistry, Urinalysis, Other Labs and Coagulation Factors Screening Second Course Phase (Retreatment Period) Reporting of Pregnancy and Lactation to the Sponsor	Pregnancy testing language updated (including additional checkpoints in SoAs and edited footnotes and update to Laboratory Tests table). Pregnancy and infant exposure during breastfeeding language updated.	Revised to align with current pregnancy testing, and pregnancy and infant exposure during breastfeeding requirements.
5.5.2	Prohibited Concomitant Medications	Added the prohibition of live attenuated vaccines and removed examples of live vaccines. Added text to clarify that the concomitant use of licensed COVID-19 vaccines is allowed.	Revised to current prohibited concomitant medication requirements. Revised to clarify the concomitant use of COVID-19 vaccines.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.8	Subject Withdrawal/Discontinuation Criteria	Bulleted list updated to replace 'recurrent Grade 2 pneumonitis' with a reference to any study treatment-related toxicity specified as a reason for permanent discontinuation.	Revised to current requirements for subject withdrawal/discontinuation.
7.1.1.5.2	Concomitant Medications	Sentence added to include Second Course.	For clarification.
7.1.1.8	Trial Compliance (Medication/Diet/Activity/Other)	"Witnessed" changed to "monitored".	Revised to current requirements for trial compliance.
7.1.5.1	Tumor Imaging and Assessment of Disease.	Text moved to Section 7.1.5.1.5 RECIST 1.1 Assessment of Disease.	For clarification.
7.1.5.1.5	RECIST 1.1 Assessment of Disease	Text added from Section 7.1.5.1 Tumor Imaging and Assessment of Disease.	For clarification.
7.2.1	Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor	Updated pembrolizumab overdose text.	Revised to align with current pembrolizumab overdose requirements.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
N/A	Document History	Inserted a row for Amendment 2 with the following information: 1. Date of Issue: 21-Dec-2016. 2. Overall Rationale: To primarily include an optional sub-study, remove head/brain imaging requirements, update the MK-3475 Dose Modification Table, and update the Flow Chart for ePRO, tumor imaging, and Anti-pembrolizumab Antibodies.	The information for Amendment 2 was accidentally deleted during publishing.
N/A	Document History	Added the date of issue for Amendment 5 as 06-Jun-2019.	To confirm the date when Amendment 5 was approved/published.
Entire protocol	Entire protocol	Minor editorial and typographical changes	Not summarized.

1.0 TRIAL SUMMARY

Abbreviated Title	Ph III Trial of MK-3475 (Pembrolizumab) in Platinum Pre-treated, Recurrent/Metastatic Nasopharyngeal Cancer
Trial Phase	Phase III
Clinical Indication	Platinum Pre-treated, Recurrent, or Metastatic Nasopharyngeal Cancer
Trial Type	Interventional
Type of control	Standard of Care (SOC)
Route of administration	Intravenous, Oral
Trial Blinding	Unblinded Open-label
Treatment Groups	Arm 1: MK-3475 (also known as pembrolizumab) 200 mg every 3 weeks (Q3W) OR Arm 2: Investigator's choice of the following SOC: • Capecitabine • Gemcitabine • Docetaxel
Number of trial subjects	Approximately 230 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 4.5 – 5 years from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject[1] will participate in the trial from the time the subject signs the informed consent form (ICF) through the final protocol-specified contact. After a screening phase of 30 days, eligible subjects can be randomized to either pembrolizumab (MK-3475) (experimental arm) or SOC chemotherapy (control arm). The chemotherapy to be used must be chosen before randomization. Subjects will be randomized in a 1:1 fashion to standard chemotherapy per investigator's choice or to pembrolizumab (MK-3475). Treatment on study will continue until disease progression is radiographically documented and verified by blinded independent central review (BICR) per RECIST 1.1 (for subjects treated with SOC chemotherapy) or confirmed by the site per immune-related Response Evaluation Criteria in Solid Tumors ([irRECIST] for subjects treated with pembrolizumab), unacceptable adverse event (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, noncompliance with trial treatment or procedures requirements or administrative reasons requiring cessation of treatment, or until the subject has received 35 administrations of pembrolizumab (approximately 2 years). Subjects who stop trial treatment after receiving 35 administrations of pembrolizumab for reasons other than disease progression or intolerability, or subjects who attain a complete response (CR) and stop trial treatment may be eligible for up to 17 additional administrations of pembrolizumab (approximately 1 year) upon experiencing disease progression (see Section 7.1.7.2.1).

	After the end of treatment, each subject will be followed for the resolution of ongoing select AEs, the occurrence of AEs, OS, and spontaneously reported pregnancy as described in Section 7.2.2. Subjects who discontinue study treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression is documented radiographically and verified by BICR per RECIST 1.1 (subjects treated with SOC chemotherapy) or confirmed by the site per irRECIST (subjects treated with pembrolizumab), initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival until death, withdrawal of consent for survival follow-up, or the end of the study.

[1]The Sponsor has changed the terminology referring to individuals who take part in clinical trials as "Participant" from the previously used term "Subject." For the purpose of any trial-related documents using the previous terminology, the term "Participant" is equivalent to "Subject."

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a two-arm, multi-site, international, randomized, open-label, controlled trial of pembrolizumab (MK-3475) monotherapy versus standard chemotherapy in subjects with platinum pre-treated, recurrent, or metastatic nasopharyngeal cancer to be conducted in conformance with Good Clinical Practices (GCP).

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

2.2 Trial Diagram

The trial design is depicted in Figure 1.

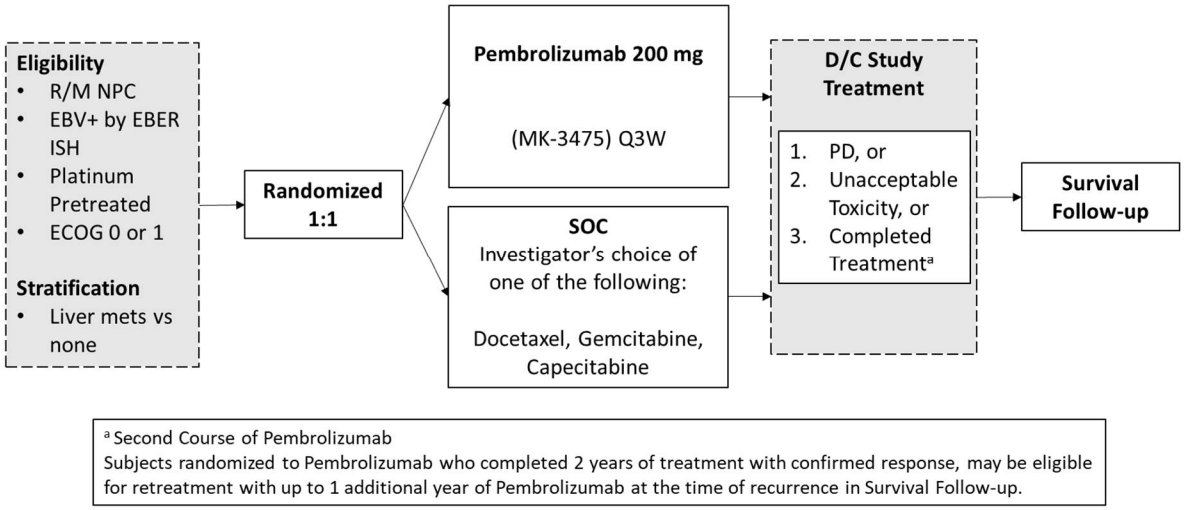

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In subjects with recurrent and/or metastatic (R/M) nasopharyngeal cancer (NPC) treated with pembrolizumab (MK-3475) versus standard of care (SOC) chemotherapy:

(1) **Objective:** To compare overall survival (OS).

Hypothesis: Single agent pembrolizumab (MK-3475) prolongs OS compared to SOC chemotherapy.

The study will be declared a success if OS is shown to be successful.

3.2 Secondary Objective(s)

In subjects with R/M NPC treated with pembrolizumab (MK-3475) versus SOC chemotherapy:

(1) Objective: To compare progression-free survival (PFS) per response evaluation criteria in solid tumors (RECIST) 1.1 as determined by Blinded Independent Central Review (BICR).

Hypothesis: Single-agent pembrolizumab (MK-3475) prolongs PFS per RECIST 1.1 as determined by BICR compared to SOC chemotherapy.

(2) Objective: To compare objective response rate (ORR) per RECIST 1.1 as determined by BICR.

Hypothesis: Single agent pembrolizumab (MK-3475) improves ORR per RECIST 1.1 as determined by BICR compared to SOC chemotherapy.

(3) Objective: To evaluate duration of response (DOR) per RECIST 1.1 as determined by BICR.

(4) Objective: To evaluate survival proportion at 12 months and 24 months.

(5) Objective: To evaluate proportion PFS at 6 months and 12 months per RECIST 1.1 as determined by BICR.

(6) Objective: To evaluate the safety and tolerability profiles of pembrolizumab (MK-3475).

3.3 Exploratory Objectives

In subjects with R/M NPC treated with pembrolizumab (MK-3475) versus SOC chemotherapy:

(1) Objective: To evaluate progression-free survival 2 as defined in Section 8.4.1.

(2) Objective: To evaluate PFS per immune-related RECIST (irRECIST) determined by BICR.

(3) Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments.

(4) Objective: To investigate the relationship between the response to pembrolizumab (MK-3475) treatment and plasma circulating epstein-barr virus (EBV) DNA levels.

(5) Objective: To characterize the quality of life using the European Quality of life (EuroQol) EQ-5D questionnaire.

(6) Objective: To compare the effect of treatment on the level of interferon-γ producing EBV-specific $CD8^+$ T-cells in peripheral blood.

(7) Objective: To investigate the relationship between response to treatment (ORR, PFS and OS) and the increase in levels of interferon-γ producing EBV-specific $CD8^+$ T-cells in peripheral blood.

4.0 BACKGROUND & RATIONALE

4.1 Background

[redacted]

4.1.1 Pharmaceutical and Therapeutic Background

Pembrolizumab (MK-3475), previously known as SCH 9000475 is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between programmed death 1 (PD-1) and its ligands, PD-L1 and programmed death ligand 2 (PD-L2).

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2] [3] [4] [5] [6]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major immune system pathway hijacked by tumors to suppress immune activation. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7] [8]

The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig variable-type domain responsible for ligand binding and a cytoplasmic tail that is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [7] [10] [11] [12]

The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins [13] [14]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, regulatory T-cells and natural killer cells [15] [16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]

The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [1] [14] [18] [19] [20]. 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 [14] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma [21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

4.1.2 Pre-clinical 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 monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [22][23][24][25][26][27]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

4.1.3 Ongoing Clinical Trials

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

Trials evaluating pembrolizumab (MK-3475) in head and neck cancer have demonstrated clinical activity in patients with recurrent and/or metastatic disease. KEYNOTE-012 is a Phase Ib study of pembrolizumab (MK-3475) in patients with human papillomavirus (HPV)-negative and HPV-positive head and neck cancer. This trial enrolled an initial 60 patient cohort with recurrent and/or metastatic squamous cell carcinoma of the head and neck for treatment with single agent pembrolizumab (MK-3475). Preliminary results of this cohort were reported at the Annual Meeting of the American Society of Clinical Oncology in 2014 [28], showing an ORR (confirmed and unconfirmed) of 19.6% (10 partial responses [PRs], 1 complete response [CR] out of 56 patients evaluable for response). An additional 16/56 patients (28.6%) experienced stable disease (SD), with 51% of patients experiencing some numerical decrease in tumor burden from baseline. Seventeen total patients with CR, PR, or SD remain on therapy at the time of the reporting for >6 months. There were no new or unexpected toxicity signals in this patient cohort, with infrequent Grade 3 or 4 drug-related adverse events (DRAEs).

In general, pembrolizumab (MK-3475) was well tolerated with 58.3% reporting a DRAE and 16.7% reporting a Grade 3 to 5 DRAE. The DRAEs with an incidence ≥5% were fatigue (10, 16.7%), pruritus (6, 10%), rash (5, 8.3%), nausea (4, 6.7%), decreased appetite (3, 5.0%), and myalgia (3, 5.0%). Of these DRAEs, Grades 3 to 5 was seen in rash (2, 3.3%). The reported pre-specified adverse events (AEs) were adrenal insufficiency (1, 1.7%); diarrhea (1, 1.7%); pruritus (1, 1.7%); rash (2, 3.3%); rash, macular (1, 1.7%); pneumonitis (0); alanine aminotransferase (ALT) increase (2, 3.3%); and aspartate aminotransferase (AST) increase (2, 3.3%) [26].

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Nasopharyngeal cancer represents a unique malignancy with a distinct geographic distribution and greater tendency among head and neck cancers for metastasis [29]. Globally, NPC is a relatively rare cancer with approximately 87,000 cases reported and an associated mortality of 50,000 reported for 2012 [29]. While rare in the United States with approximately 3,200 cases expected to be diagnosed in 2015, NPC is endemic in indigenous populations of Southeast Asia, natives of the Arctic region, North Africa, and the Middle East. Even within China, the incidence increases moving from Northern China to Southern China, where for example, in Hong Kong, approximately 1 in 40 people will be diagnosed with NPC before age 75 [30] [31] [32].

Among squamous cell carcinomas of the head and neck, NPC is also distinguished from other head and neck cancers as being an EBV-driven malignancy. Unique among other head and neck cancers, EBV, a member of the herpes virus family, is implicated in the development of NPC.

Upon transmission to the host via saliva, EBV directly infects B lymphocytes of the oropharyngeal epithelium. During the acute phase of infection, EBV causes cellular proliferation of B lymphocytes and induces an EBV-specific cytotoxic lymphocyte response. During this acute phase, integration of the viral genome into host DNA occurs, resulting in the transcription of EBV-encoded RNAs 1 and 2 (EBERs 1 and 2) as well as the expression of EBV nuclear proteins and 2 latent membrane proteins, LMP-1 and LMP-2 [33]. Acute infection is followed by a normal immune response in healthy individuals, resulting in the virus persisting in memory B cells. In contrast, in chronic infection, so-called latent viral infection is associated with continuous expression of various EBV nuclear and latency genes, the specific combination of which is associated with specific malignancies. NPC is distinguished by the type II latency pattern in which EBERs 1 and 2 and the LMP-1s and LMP-2s, are expressed, in addition to Epstein-Barr Nuclear Antigen (EBNA)-1 (but not the other EBNAs) and BARF0 which is expressed in all latency types [33].

EBERs 1 and 2 are nonpolyadenylated, uncapped, noncoding RNAs that are expressed in nearly all EBV-infected cells of NPC [34][35]. While not essential for malignant transformation, EBERS 1 and 2 are expressed in all forms of latency.

LMP-1 is most directly linked to oncogenesis based on its ability to activate multiple oncogenic signaling pathways such as nuclear factor-κB (NF-κB), c-Jun NH_2-terminal kinase, p38 mitogen-activated protein kinase and Janus kinase/signal transducers and activators of transcription. Chief among these diverse signaling pathways, NF-κB is a key transcription factor that controls expression of several cytokines including lymphotoxin, an autocrine growth factor for EBV-transformed cells [36]. Additionally, LMP-1 is able to inhibit apoptosis by increasing levels of *bcl-2* and *a20* as well as by creating membrane aggregation which confers cellular immortalization. The LMP-2 gene encodes 2 proteins (LMP-2A and LMP-2B) which have been demonstrated to drive EBV infection into latency, and is routinely expressed in NPC among other malignancies [37]

Nearly all (>90%) of the population has experienced an acute EBV infection, most with subclinical symptoms; however, few develop chronic infection and subsequent EBV associated malignancy. Although unconfirmed, multiple theories, including environmental exposure, dietary factors, as well as LMP-1 variants which may produce reduced cytotoxic T-cell response, have been postulated to account for what might cause an acute EBV infection to proceed into a chronic latent infection, primarily restricted to specific geographic regions of Southeast Asia [30].

4.2.1.1 Pre-clinical Evidence for the Role of PD-1/PD-L1 in NPC

More recently, evidence has emerged suggesting that prolonged exposure to antigen during chronic viral infections such as EBV result in irreversible functional impairment of memory CD8+ T-cells, causing diminished immunity, a phenomenon known as T-cell exhaustion [38]. A hallmark of the ability to fight infection is that normal differentiation of T-cells results in memory CD8+ T-cells that can persist in the absence of continuing antigen exposure, also known as antigen independent immunity. In contrast to functional CD8+ T-cells in an acute infection, CD8+ T-cells that were chronically exposed to antigen, such as is the case with chronic EBV infection, had impaired proliferation due to decreased cellular cytokine receptors necessary for T-cell proliferation. Additionally, once altered, impaired memory T-cell function could not be restored by subsequent removal of the inciting antigen [38].

During chronic viral infection, PD-1 messenger RNA and protein levels were found to be upregulated, both on the exhausted CD8+ T-cells as well as on the virally infected cells, implicating the immune checkpoint pathway in the development of this phenomenon. Of note, upregulation of PD-1 was a specific response, as was consistent with other reports, and no upregulation of the CTLA-4 was seen [39] [40]. Importantly, anti-PD-L1 blockade restored both virus-specific CD8+ T-cell quantitative and qualitative responses as evidenced by increased cellular proliferation and increased ki-67 levels as well as restoration of cytokine production and lytic degranulation ability [39][40].. Of note, PD-L1 blockade also resulted in substantial reduction of viral levels in the chronically infected host [39].

Given the association between EBV infection and EBV-associated malignancies including NPC, when EBV modulation of the PD-1/PD-L1 checkpoint pathway was further examined, EBV-induced LMP-1 protein was found to increase PD-L1 gene expression [41]. Compared with EBV-negative NPC cell lines, EBV-positive NPC cell lines were found to have increased levels of LMP-1, whether exogenous or endogenous, and EBV-positive NPC cell lines were able to induce PD-L1 expression, which could be abrogated by knocking down LMP1 in EBV-positive cell lines. The differential expression of EBV-positive NPC cell lines (versus EBV-negative) to increase PD-L1 expression was further confirmed by flow-cytometry as well as by visual examination utilizing immunofluorescence. When visually examined, both the cell membrane and cytoplasm of EBV-positive NPC cell lines showed strong PD-L1 fluorescence, while PD-L1 fluorescence within EBV-negative cell lines was significantly weaker. For EBV-positive NPC, the relative expression of PD-L1 correlated with EBV positivity [42]

Taken together, chronic EBV infection leads to increased viral EBV load. This chronically increased virus load results in and correlates with increased expression of PD-1 on cytotoxic memory T-cells, leading to T-cell exhaustion with resultant decreased function and number

of these cells. This upregulation is specific for PD-1 as CTLA-4 levels were unaffected. Of note, increased PD-1 expression also occurs in the virally affected host cells. The relative quantitative and qualitative CD 8+ T-cell decrease leads to altered T-cell immunity, which prevents clearance of the EBV infection and allows further increase of viremia. EBV-latent infection is associated with expression of LMP-1 protein which induces PD-L1 expression. Increased PD-1 and PD-L1 work together to suppress the immune system, leading to decreased EBV cellular immunity. In the laboratory, anti-PD-L1 blockade was demonstrated to restore exhausted CD8+ T-cell function and decrease viral load. This effect was specific for the PD-L1 as virally induced T-cell upregulation of PD-1 did not affect CTLA-4 levels and CTLA-4 blockade had no effect on either CD8+ T-cell function or viral control [39]. Therefore, anti-PD-L1 blockade could be a worthwhile strategy to restore anti-EBV tumor CD-8 positive T-cells, decrease viral load, and target NPC.

4.2.1.2 Preliminary Evidence That Anti-PD-L1 Blockade With Pembrolizumab (MK-3475) Monotherapy has Clinical Activity in Advanced and/or Metastatic NPC

KEYNOTE-028 is a global, non-randomized, multi-cohort trial that has enrolled subjects with a variety of advanced solid tumors in cohorts grouped by tumor type. PD-L1 positivity, defined as PD-L1 expression by immunohistochemistry (IHC) (≥1% PD-L1 membrane staining of tumor cells or stroma by a prototype assay performed at Qualtek CAP/CLIA laboratory), was required for study entry. Pembrolizumab (MK-3475) at a dose of 10 mg/kg intravenous (IV) was administered every 2 weeks as monotherapy until progression of disease.

An advanced NPC cohort that included subjects with metastatic NPC cancer not amenable to curative therapy and whose disease had progressed following at least 1 prior treatment was enrolled. Enrolled subjects were predominantly of Asian ethnicity (67%), male (77.8%), with an Eastern Cooperative Oncology Group (ECOG) performance status of 1 (74%). Of note, approximately two-thirds had received 3 or more prior treatments for metastatic disease. All subjects had received prior platinum-based therapy for their disease. Similar to other reports of high PD-L1 expression among advanced NPC, 98% of screened and 100% of evaluable subjects that enrolled into the NPC cohort (46/47 and 27/27, respectively) were PD-L1 positive.

In this heavily pre-treated population, evidence of clinical activity by investigator assessment was demonstrated, as 22.2% (6/27) subjects had a confirmed ORR (0% CR + 22.2% PR), 25.9% (7/27) had unconfirmed ORR, and 51.9% (14/27) had SD. Thus, only 6 of 27 (22.2%) subjects had progressive disease (PD) as their best response, with approximately three-quarters (75%) of all subjects deriving benefit from pembrolizumab (MK-3475). With a median follow-up of 7.8 months, the median PFS was 5.6 months (95% CI 3.6, 11.0), with a 6-month PFS rate of 49.7% and a 12-month PFS rate of 30.1%. Notably, a 6-month OS rate of 85.2% and 12-month OS rate of 66.7% was demonstrated. Median OS has not been reached at this time.

Of the 27 evaluable and treated subjects, all 27 reported at least 1 AE, with 70.4% (19/27) classifying it as a related AE. Nine subjects (9/27, 33.3%) experienced serious adverse events (SAEs) and 3 subjects (3/27, 11.1%) experienced related SAEs. Overall AEs and related AEs lead to discontinuations in 11.1% (3/27) for both. Additionally, overall SAEs

and related SAEs lead to treatment discontinuation in 7.4% (2/27) for both. Please refer to the IB for additional details.

Thus, encouraging evidence of robust clinical activity coupled with a favorable profile has been observed.

More recently, data from a randomized Phase 2 trial was reported at the American Association for Cancer Research meeting in March 2019. A global, randomized phase 2 study comparing spartalizumab, a humanized anti-PD-1 IgG4 mAb, was compared to the investigator's choice of therapy. In this open-label study, patients were randomized 2:1, to spartalizumab (400 mg every 4 weeks) vs any choice of chemotherapy. The primary endpoint was PFS by independent central review with secondary endpoints of OS, and ORR, and DOR based on independent central review. In total, 82 patients were randomized to spartalizumab (42.7% ECOG PS 0, 54.9% ECOG PS 1) and 40 patients were randomized to chemotherapy (22.5% ECOG PS 0, 75% ECOG PS 1) and the median age of enrolled subjects was 50-51 years of age. Sixteen subjects (19.5%) treated with spartalizumab and 9 subjects (22.5%) in the chemotherapy control arm had received 1 line of prior therapy for the treatment of R/M NPC.

The median PFS for spartalizumab was 1.9 months (95% CI 1.8, 3.6) vs 6.6 months (95% CI 3.7, 9.3) in the chemotherapy arm, thus the primary endpoint was not met with hazard ratio of 1.36 (95% CI 0.87, 2.12). ORR was 17.1% (95% CI 9.7, 27.0) and 35.0% (95% CI 20.6, 51.7) for those treated with spartalizumab and chemotherapy respectively, and 25.9% (7/27) for those treated with monotherapy chemotherapy and 58.3% (7/12) for doublet or triplet chemotherapy regimens. Median DOR in the spartalizumab arm was 10.2 months (95% CI 7.4, NE) compared with 5.7 months (95% CI 3.7, 7.4) for those randomized to chemotherapy. Of note, although the data and follow-up suggest that the OS data are immature, there appeared to be a trend towards superior OS for those randomized to spartalizumab with a median OS of 25.2 months (13.1, NE) compared to 15.5 months (95% CI 8.3 – 21.3) in the chemotherapy arm.

Of the 82 evaluable patients treated with spartalizumab, 79 (96.3%) reported at least 1 AE, with 72% (59/82) classifying it as a related AE. Twenty-seven subjects (32.9%) experienced SAEs and 8 subjects (9.8%) experienced related SAEs. AEs leading to discontinuation or to dose adjustment/interruption were 1.2% (1/82) and 14.6% (12/82), respectively [43].

4.2.1.3 Current Therapies for Advanced and/or Metastatic NPC

Due to the overall low prevalence of NPC, few randomized clinical trials have been conducted in this malignancy, and no randomized Phase III trials have been reported in the metastatic setting. Initially, radiotherapy was viewed as the treatment of choice for NPC until a randomized trial, SWOG 099, reported by Al-Sarraf and colleagues, demonstrated that in the locally advanced population, platinum therapy with adjuvant cisplatin added concurrently to radiotherapy followed sequentially by combination cisplatin and infusional 5-FU improved both disease-free survival and OS compared to adjuvant radiotherapy alone [44].

Unfortunately, among head and neck cancers, NPC has a greater tendency for distant metastasis. Once NPC recurs with incurable and/or metastatic disease, numerous treatments have demonstrated evidence of clinical activity, but with limited durability of response and

no evidence of cure. This evidence comes from multiple single-arm Phase II trials. Several monotherapies have been associated with median ORRs ranging from 3% to 50%, and an approximate time to progression (TTP) of 4 months for those who have progressed following treatment with a platinum-containing regimen [45] [46] [47] [48] [49] [50] [51] [52] [53] [54].

There is no approved agent for NPC, and following a platinum-based chemotherapy regimen, there is no recognized single regimen. Therefore, clinical guidelines have emphasized balancing clinical benefit with tolerable toxicity. Thus, monotherapy regimens are commonly employed following PD after platinum-based therapy. Among the most commonly used monotherapy SOC regimens are gemcitabine, capecitabine, and docetaxel as in Table 1:

Table 1 Monotherapy Regimens Overview

Regimen	Line	Phase	N	ORR	PFS/TTP[#]	OS	Accrual
Gemcitabine[52]	2/3	II	27	48.1%	5.1[#]	10.5	1/99-11/99
Gemcitabine[45]	1+	II	32	43.8%	5.1[#]	16	Prior to 2004
Capecitabine[48]	2-4	II	17	23.5%	4.9[#]	7.6	3/00-2/02
Docetaxel[49]	2-4	II	30	36.7%	5.3	12.8	9/04-7/06

The '#' denotes TTP. The time unit for PFS, TTP and OS are all in months.

Keeping in mind that most of these clinical trial data were acquired and reported prior to the current RECIST assessment guidelines, and one of the higher response rates obtained with gemcitabine [46] included patients treated in the first-line metastatic setting, some of the response rates may represent an overestimation of the true ORR assessed in a contemporary platinum pre-treated metastatic population.

In the effort to increase ORR, several polychemotherapy regimens have been developed and demonstrated increased ORR of 60% to 74%, but with minimal improvement in durability of response with TTP and/or PFS of approximately 5 to 6 months. Despite the addition of increasing numbers of cytotoxic therapies in treatment regimens, DOR was not significantly impacted, although toxicity was increased [55] [56] [57]. Therefore, despite the fact that NPC has historically been described as a radiosensitive and chemosensitive disease, over half of those diagnosed with NPC will ultimately die of their disease.

In summary, the overall low incidence coupled with the Southeast Asian geographic predominance has made it challenging to conduct large randomized clinical trials in patients with NPC. Treatment guidelines refer to the SWOG 099 randomized trial above as the only randomized controlled clinical trial isolating the benefit of a cytotoxic therapy for NPC. Therefore, the inclusion of platinum therapy for locally advanced and/or metastatic recurrence can be taken to represent the SOC for NPC. Following treatment with a platinum-containing regimen, multiple options exist, but without any regulatory approved therapy.

Therefore, we propose to test the clinical activity of pembrolizumab (MK-3475) and compare it to commonly employed monotherapy regimens that might be used for this population. We will seek to ensure that treatment with pembrolizumab (MK-3475) providing targeted PD-L1

blockade is superior to SOC monotherapies in this EBV-driven PD-1/PD-L1 upregulated advanced metastatic NPC disease setting.

4.2.1.4 Quantification of Plasma EBV DNA in Patients With Advanced and/or Metastatic NPC

As noted above, in in vivo animal models, anti-PD-L1 blockade was associated with decreased EBV viral levels in addition to restoration of exhausted memory CD8+ T-cell function [39]. Contemporaneous with this finding, several investigators sought to determine the clinical significance of circulating plasma concentrations of EBV DNA fragments in subjects with NPC. In subjects with locally advanced NPC without evidence of distant disease, paired samples of EBV DNA obtained prior to and upon completion of definitive treatment with cisplatin and 5-fluouracil in conjunction with concurrent radiotherapy were able to be quantified. Circulating EBV DNA from plasma was detectable in over 90% of tested subjects (90 of 94). Importantly, these investigators were able to demonstrate that by genotyping both the plasma EBV DNA as well as the primary tumor samples, the circulating cell-free EBV DNA originated from the primary tumor. Thus, plasma EBV DNA was demonstrated to be a surrogate marker for primary tumor. Median concentrations of plasma EBV DNA increased with increasing stage of disease and disease burden. In subjects who eventually relapsed during follow-up, plasma EBV DNA levels were found to be significantly higher than in those who did not relapse. Additionally, those patients who had persistently detectable plasma EBV DNA were found to have significantly worse relapse-free survival ($P<0.001$) and OS ($P<0.001$) [58].

When evaluated in the recurrent and/or metastatic NPC setting, those subjects with either low pre-treatment or undetectable post-treatment levels of circulating plasma EBV DNA following palliative chemotherapy were found to have superior PFS and OS of 21.7% and 50.6%, respectively [59].

Perhaps in response to these important results, an international collaboration to harmonize the quantitation of plasma EBV DNA assay for development of future biomarker-guided trials in NPC cancer is underway [60] and treatment guidelines for NPC have been updated to recommend quantification of EBV DNA during treatment of NPC [61]. Therefore, in this clinical trial, we propose to evaluate paired samples of plasma EBV DNA at baseline, on treatment, as well as at PD, to see if pre-treatment levels as well as post-treatment levels can predict response to anti-PD-L1 blockade with pembrolizumab (MK-3475).

4.2.1.5 Rationale for Evaluation of Interferon-γ Producing EBV-specific T-cells in Peripheral Blood

4.2.1.5.1 T-cell Responses Against EBV in NPC Patients

The levels of functional interferon-γ producing EBV-specific T-cells are reduced in NPC patients and it is hypothesized that loss of EBV-specific CD8+ T-cell immune surveillance may be involved in the development or progression of NPC [62]. This is founded on the observation that peripheral blood CD8+ T-cell responses for two of the EBV proteins found in tumor cells, EBNA-1 and LMP-2, are detected in EBV-positive healthy individuals but are decreased in NPC patients [62] [63]. These reduced EBV-specific CD8+ T-cell responses in NPC patients are not due to a lack of CD8+ T-cells able to recognize the viral antigens, but

rather that these cell have become unresponsive [63]. A number of mechanisms have been proposed to explain the limited effectiveness of these cells, as noted above. Additionally, a number of studies have reported increased regulatory T-cells (Tregs) in the peripheral blood of NPC patients as potential suppressors of the CD8+ T-cell response [64] [65] [66]. Alternatively the unresponsiveness of these cells could be due to the inhibitory PD-1-PD-L1 interaction between CD8+ T-cells and tumor cells. Treatment with anti-PD-1 therapy could potentially relieve this inhibition and result in an increase in active interferon-γ producing EBV-specific T-cells.

4.2.1.5.2 Evidence That EBV-specific T-cell Responses are Important for Survival From NPC

Compelling evidence that EBV-specific T-cells are important for survival from NPC is provided by a number of clinical studies that treated advanced EBV-associated NPC with EBV-specific T-cells. In these studies, autologous EBV-specific T-cells were expanded in-vitro and re-introduced into the patient. Prominent amongst these approaches is a phase II trial in untreated patients that received 6 doses of EBV-specific T-cells following treatment with gemcitabine and carboplatin[67] This combination demonstrated a response rate of 71.4% with 3 complete and 22 partial responses. Furthermore, the authors concluded that the median overall survival of 29.9 months and the 2- and 3- year overall survival rates of 62.9 % and 37 %, respectively, were significantly higher than those observed in historical controls receiving chemotherapy alone (11-22 months). A multicenter Phase III randomized control trial using this protocol is currently underway (NCT 02578641). Other studies with this approach reported response rates of 60% [68] (2 partial responses and 4 with stable disease) and 67% [69] (5 complete responses, 2 partial responses and 3 with stable disease). In the latter study, 8 additional patients were treated in their second or subsequent remission and 5 remained free of disease after 6 years. It is notable that in all these studies an association between measurable benefit of treatment with EBV-specific T-cells and the presence of T-cells specific for the EBV antigen LMP2 was observed [67] [68] [69].

4.2.1.5.3 Evaluation of Interferon-γ Producing EBV-specific T-cells in Peripheral Blood of NPC Patients Receiving Anti-PD1 Therapy

In this currently on-going, KEYNOTE-122, we propose in this sub-study to evaluate paired samples of PBMC from baseline (cycle 1) and after 1-, 2-, 3-, and 4- cycles, as well as at the time of disease progression, to see if levels of EBV-specific T-cells are increased following treatment with pembrolizumab and SOC chemotherapy. We propose to evaluate whether increases in EBV-specific T-cell levels are predictive of response to treatment. A previous study in NSCLC identified a subject who demonstrated a > 40 fold increase in tumor-specific T-cell responses after a single cycle of anti-PD-1 therapy [70]. This response was maintained after a second cycle and returned to levels just above background in the subsequent months. In this sub-study, patients, regardless of HLA type, will have cryopreserved peripheral blood mononuclear cells (PBMC) tested using EBV-specific T-cell biomarker assays that measure the T-cell Interferon-γ response following stimulation with peptides specific for EBV antigens. Various approaches may be used for measuring the immune reactivity of these PBMCs to EBV antigens found in the tumor. Key questions that this sub-study will address include (1) Whether interferon-γ producing EBV-specific T-cells can be measured in peripheral blood following anti-PD-1 therapy? (2) Whether interferon-γ

producing EBV-specific T-cells increase after anti-PD-1 therapy i.e., whether EBV-specific T-cells are more active following anti-PD-1 therapy? (3) Whether levels of interferon-γ producing EBV-specific T-cells are increased in responsive patients (as compared to non-responders)?

4.2.2 Rationale for Dose Selection/Regimen/Modification for Pembrolizumab (MK-3475)

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and non-small cell lung cancer (NSCLC) indications demonstrating flat dose- and exposure- efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5- to 7-fold exposure range (refer to IB Section 5.2.2)
- Population pharmacokinetic (PK) analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically based PK analysis) at 200 mg Q3W

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary and Secondary Endpoints

Based on the recently presented spartalizumab data, where the primary PFS endpoint was not met for spartalizumab with a median PFS of 1.9 months vs 6.6 months with a hazard ratio of 1.36 (95% CI 0.87, 2.12), we are amending the primary and efficacy endpoints from dual primary endpoints of PFS and OS to a single primary endpoint of OS. Of note, early data from the spartalizumab trial suggested a potential trend for superior OS with a median OS of 25.2 months (13.1, NE) compared to 15.5 months (95% CI 8.3 – 21.3) in the chemotherapy arm (HR not provided).

The primary efficacy objective to evaluate the anti-tumor activity of pembrolizumab (MK-3475) will be based on the primary endpoint of OS in this randomized, open-label trial. To further support the robustness of the primary endpoint of OS, key secondary endpoints of PFS and ORR as assessed per RECIST 1.1 by the independent central review, blinded to treatment assignment to minimize bias in the response assessments, will also be analyzed as part of a complete assessment of the anti-tumor and clinical utility of pembrolizumab (MK-3475) compared to SOC chemotherapy in R/M NPC.

Because one of the key secondary efficacy objectives is ORR, measurable disease assessed by the site will be required at baseline for eligibility prior to treatment allocation/randomization. Retrospective confirmation of measurable disease will be assessed by central imaging vendor on a rolling basis. In addition, because PFS is an important supportive endpoint, final determination of radiologic PD will be based on the BICR of progression rather than local site investigator/radiology assessment. Expedited assessment by central imaging in instances of suspected radiologic progression identified at the site (verification of PD) will be communicated to the site study team. RECIST 1.1 will be used to determine the dates of progression as this methodology is accepted by regulatory authorities (see Appendix Section 12.7).

In order to more fully characterize the endpoints OS and PFS, secondary efficacy objective of DOR, as well as evaluation of progression-free survival proportion at 6- and 12-months per RECIST 1.1 and survival proportion at 12-and 24-months will be analyzed.

RECIST 1.1 will also be used by the local site for treatment decisions. However, RECIST 1.1 will be adapted to account for the unique tumor response profile seen with treatment of pembrolizumab (MK-3475) as below (see Section 4.2.3.1.1.1), and is referenced as irRECIST.

4.2.3.1.1.1 Immune-related RECIST

Immunotherapeutic agents such as pembrolizumab (MK-3475) may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may, thus, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab (MK-3475). Based on an analysis of patients with melanoma enrolled in KEYNOTE-001, 7% of evaluable patients experienced delayed or early tumor pseudoprogression. Of note, patients who had progressive disease by RECIST 1.1, but not by immune-related response criteria, had longer OS than patients with PD by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab (MK-3475) in approximately 15% of patients. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enable treatment beyond initial radiographic progression.

Immune-related RECIST is RECIST 1.1 adapted to account for the unique tumor response seen with immunotherapeutics as described in Nishino et al.[71]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, Merck has implemented an adaptation related to new lesions, non-target, and tumor burden assessment in order to confirm radiographic progression. Immune-related RECIST will be used by local site investigators to assess tumor response and progression, and make treatment decisions (for subjects in treated with pembrolizumab [MK-3475]) as well as by central imaging vendor in support of PFS endpoint.

4.2.3.2 Safety Endpoints

The safety objective of this trial is to characterize the safety and tolerability of pembrolizumab (MK-3475) in subjects with R/M NPC. The safety analysis will be based on subjects who experience toxicities as defined by National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.0. Safety will be assessed by summarizing the toxicities and grades experienced by subjects who have received pembrolizumab (MK-3475), including serious SAEs and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related ECIs as described in Section 7.2.3.2.

4.2.3.3 Patient-Reported Outcomes

The EuroQol EQ-5D is not for pure efficacy or safety endpoint because it is affected by both disease progression and treatment tolerability.
The eEuroQol-5D (eEQ-5D) is a standardized instrument for use as a measure of health outcome. The eEQ-5D will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life-years. The 5 health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 3-point scale from 1 (extreme problem) to 3 (no problem). The eEQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the assessment. The eEQ-5D (or paper EQ-5D, if necessary) is to be completed at time points as specified in the Section 6.0 - Trial Flow Chart.

4.2.3.4 Planned Exploratory Biomarker Research

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

Germline (blood) genetic analyses (e.g., SNP analyses, whole exome sequencing, whole genome sequencing)

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

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (i.e., mutations, methylation status, microsatellite instability). Key molecular changes of interest to immune-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort in addition to tumor-specific mutations in specific target genes. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (i.e., colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and blood RNA analyses

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

Proteomics and immunohistochemistry (IHC) using blood or tumor

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

novel protein biomarkers that could aid in patient selection for immunotherapy and/or treatments.

Other biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins, RNA and/or DNA can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay (ELISA) that measure proteins, those assessing circulating tumor DNA, RNA and/or exosomes may also be evaluated from blood samples. Correlation of these biomarkers with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

Other molecular changes of interest include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated.

Induction of EBV antigen-specific T cells in peripheral blood in response to pembrolizumab (MK-3475) therapy.

PBMC isolated from peripheral blood will be assessed for antigen specificity using EBV-specific T-cell biomarker assays following stimulation with overlapping pools of peptides from known EBV antigenic proteins. Various approaches for measuring immune reactivity of these PBMCs may be utilized.

4.2.3.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research (FBR) on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Section 12.2 – Collection and Management of Specimens for FBR. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

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

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects with recurrent and/or metastatic nasopharyngeal carcinoma who are ≥18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be ≥18 years of age on day of signing informed consent.
3. Have histologically confirmed non-keratinizing differentiated NPC (World Health Organization [WHO] Type II) or undifferentiated NPC (WHO Type III).
4. Have locally or centrally determined EBV-positive NPC by EBV-encoded small RNA in situ hybridization (EBER in situ hybridization [ISH]) assay [72] If EBV-positive status has been previously determined by EBER ISH assay, then no re-testing is required.

   Note: If EBV status by EBER ISH assay has not been previously determined and cannot be tested locally, tumor tissue from a newly obtained core or excisional biopsy or archival tissue may be submitted for central EBV determination.
5. Have metastatic disease defined as either disseminated disease and/or locally recurrent disease that is not amenable to curative treatment.
6. Subjects must have had prior receipt of platinum-containing regimen, ***either***:
   a. For the treatment of recurrent or metastatic disease, ***or***
   b. Experienced progression of disease within 6 months following completion of a platinum-based combination therapy as part of (neo)adjuvant chemotherapy

   Note: Patients who had only concurrent chemoradiation therapy without (neo)adjuvant therapy and then recurred/metastasized must have progressed on at least 1 platinum-containing regimen for their recurrent/metastatic disease before study entry.
7. Have measurable disease based on RECIST 1.1 imaging criteria.
8. Have an ECOG performance status of 0 or 1.
9. Demonstrate adequate organ function as defined in Table 2. Specimens must be collected within 10 days prior to the start of trial treatment.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (CrCl) (Glomerular filtration rate [GFR] can also be used in place of creatinine or CrCl)	≤1.5 x upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels >1.5 x institutional ULN
Hepatic	
Total bilirubin	≤1.5 x ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 x ULN
AST (serum glutamic oxaloacetic transaminase [SGOT]) and ALT (serum glutamic pyruvic transaminase [SGPT])	≤2.5 x ULN **OR** ≤5 x ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 x ULN unless subject is receiving anticoagulant therapy and PT, partial thromboplastin time (PTT) or INR is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 x ULN unless subject is receiving anticoagulant therapy and PT, PTT or aPTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

10. Provide a tissue sample for PD-L1 biomarker analysis from a newly obtained core or excisional biopsy or archival tissue.

    Note: If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut. See Section 7.1.3.2 for further explanation.

11. Please refer to inclusion criterion number 12 for pregnancy testing of WOCBP.

12. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

    • Is not a WOCBP

    OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Section 12.10 – Contraceptive Guidance during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows:
  - MK-3475: at least 120 days
  - Chemotherapy: at least 180 days

  The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.
  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours for a urine test and 72 hours for a serum test before the first dose of study intervention.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
  - Additional requirements for pregnancy testing during and after study intervention are in Section 7.1.4.1.1 – Pregnancy Testing.
  - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
  - Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

13. Male participants are eligible to participate if they agree to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows:
    - MK-3475: no contraception requirements
    - Chemotherapy: at least 95 days
    - Refrain from donating sperm

    PLUS either:
    - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Section 12.10 – Contraceptive Guidance]) as detailed below:
  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP 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-vaginal penetration.
- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

14. Have a life expectancy of greater than 3 months.

5.1.2.1 Optional Sub-study Additional Subject Inclusion Criteria (Appendix 12.9)

1. Provide written informed consent for this sub-study clinical trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial as well as the additional sub-study without participating in Future Biomedical Research.
2. In the Investigator's assessment, be physically able and willing to donate the extra required tubes of whole blood throughout the course of this study. See Procedures Manual for sub-study.

5.1.3 Subject Exclusion Criteria

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

1. Has disease that is suitable for local therapy administered with curative intent.
2. Has a histological diagnosis of keratinizing squamous cell carcinoma (WHO Type I) or basaloid squamous cell nasopharyngeal carcinoma.
3. Patients who have received platinum therapy only as part of a concurrent chemoradiotherapy regimen (i.e., have not received platinum as part of (neo)adjuvant platinum-based combination therapy either prior to or following definitive concurrent chemoradiation, or as a platinum-containing regimen for the treatment of recurrent or metastatic disease) are excluded.
4. Patients previously treated in the recurrent/metastatic setting with any one of the 3 SOC therapies in this trial (i.e., docetaxel, capecitabine, or gemcitabine) may not receive the same therapy if randomized to the SOC arm. Additionally, patients previously treated in the recurrent/metastatic setting with all 3 SOC therapies are excluded from this trial.

5. Is currently participating in and receiving trial treatment or has participated in a study of an investigational agent and received trial treatment or used an investigational device within 4 weeks of the first dose of treatment.

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

6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Study Day 1 or who has not recovered (i.e., ≤Grade 1 or at baseline) from adverse events due to a previously administered agent.

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

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

7. Has had a diagnosed additional malignancy within 5 years prior to treatment allocation/randomization with the exception of curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin and/or curatively resected in situ cervical and/or breast cancers.

8. Has known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability.

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

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) is not considered a form of systemic treatment and is permitted.

11. Has a history of non-infectious pneumonitis that required steroids or current pneumonitis.

12. Has an active infection requiring systemic therapy.

13. 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.

14. Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).

15. Has known active hepatitis B (e.g., hepatitis B surface antigen-reactive) or known active hepatitis C (e.g., hepatitis C virus RNA [qualitative] is detected; subjects who have been treated and now have a viral load that is undetectable are eligible).

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

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

18. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 180 days after the last dose of trial treatment for the chemotherapy arm or 120 days after the last dose of trial treatment for the pembrolizumab (MK-3475) arm.

19. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or has previously participated in Merck pembrolizumab (MK-3475) clinical trials.

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

5.1.3.1 Optional Sub-study Additional Subject Exclusion Criteria

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

5.2 Trial Treatment(s)

The study drug dose and schedule to be used in this trial are outlined below in Table 3.

Table 3 Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab (MK-3475)	200 mg	Q3W	Intravenous (IV) infusion	Day 1 of each cycle (3 week cycles)	Experimental
Capecitabine	1000 mg/m^2 See Note	BID	Oral (tablet)	Days 1-14 twice daily, followed by 7 days with no dosing per 3 week cycle	Standard of Care
Gemcitabine	1250 mg/m^2	QW	IV infusion	Days 1 and 8 per 3 week cycle	Standard of Care
Docetaxel	75 mg/m^2	Q3W	IV infusion	Day 1 per 3 week cycle	Standard of Care
Note: For capecitabine, based on labeling and local SOC, countries may increase the dose to 1250 mg/m^2 from Cycle 2 onwards based upon tolerability and local practices.					

For Cycle 1, Day 1, trial treatment should be given on the day of treatment allocation/randomization, but up to 3 days after treatment allocation/randomization is permitted. For all subsequent cycles, +/-3 days of Day 1 are permitted.

All supplies indicated in Table 3 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. Per local guidelines, the trial site may be responsible for recording the lot number, manufacturer, and expiry date of any locally purchased product. If the same potency/strength of the SOC specified in the protocol is not available, then the potency/strength that is available may be used.

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

5.2.1 Dose Selection/Modification for Pembrolizumab (MK-3475)

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of dose of pembrolizumab (MK-3475) to be used in this trial is provided in Section 4.0 – Background & Rationale. Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

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

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

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 4.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

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

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

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

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

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

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

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

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to trial treatment (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). If a subject interrupts the treatment plan for more than 3 weeks for a non-drug related reason, the site should consult with the Sponsor (see section 7.1.1.8). The reason for interruption should be documented in the subject's study record.

Refer to Section 5.6.1 for management of infusion reactions for pembrolizumab (MK-3475).

5.2.2 Timing of Dose Administration

5.2.2.1 Pembrolizumab (MK-3475) Administration

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

All trial treatments will be administered on an outpatient basis.

Trial treatment of pembrolizumab (MK-3475) should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in Section 6.0 - Trial Flow Chart. In general, the window for each visit is ± 3 days unless otherwise noted.

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

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab (MK-3475) infusion fluid and administration of infusion solution.

5.2.2.2 Standard of Care Administration

Doses of SOC chemotherapy below should be based upon actual body weight, not ideal body weight. If the subject's weight increases or decreases by >10% from baseline during the course of the study, the drug dose should be re-calculated.

5.2.2.3 Dose Selection for Capecitabine (Preparation)

The preparation and administration of capecitabine should follow local treatment guidelines. However, the following recommendations should be taken into account.

Capecitabine is administered at 1000 mg/m^2 twice daily orally (i.e., total daily dose of 2000 mg/m$^{2)}$, for 14 days continuously, followed by 7 days with no dosing in a 3-week cycle. Dosage may need to be individualized to optimize patient management. Based on labeling and local SOC, countries may increase the dose to 1250 mg/m^2 twice daily orally from Cycle 2 onwards. Capecitabine dosing is repeated for every 3-week cycle.

The morning dose of capecitabine should be taken with approximately 200 ml of water within 30 minutes after a meal.

The evening dose of capecitabine should be taken approximately 12 hours after the morning dose and should be taken with food, or within 30 minutes after food/meal, with approximately 200 ml of water.

*If a subject vomits after taking capecitabine, the subject should be instructed **not** to retake the dose. If vomiting persists, then the subject should notify the investigator. If the complete tablets are clearly visualized in the vomiting incident, follow local label instructions as per SOC.*

Capecitabine can induce diarrhea, sometimes severe, including the rare reporting of necrotizing enterocolitis (typhlitis). Therefore, for subjects who experience capecitabine-associated diarrhea, aggressive supportive management with anti-diarrheals, including loperamide and lomotil, according to local SOC treatment guidelines are indicated. Additional supportive measures should include aggressive hydration with electrolyte replacement as indicated, and could also include implementation of the American Dietetic Association BRAT diet as clinically indicated.

5.2.2.4 Dose Modification for Capecitabine

Table 5 Dose Modification Guidelines for Capecitabine Drug-Related Events or (Drug-Related) Adverse Events

Toxicity Grades	During a Course of Therapy	Dose Adjustment for Next Treatment (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
• 1st appearance	Interrupt until resolved to Grade 0-1	100%
• 2nd appearance		75%
• 3rd appearance	Interrupt treatment	50%
• 4th appearance	Discontinue treatment permanently	-
Grade 3		
• 1st appearance	Interrupt until resolved to Grade 0-1	75%
• 2nd appearance		50%
• 3rd appearance	Discontinue treatment permanently	-
Grade 4		
• 1st appearance	Discontinue permanently OR If physician deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0-1	50%

For additional guidance regarding treatment modification of capecitabine, please refer to the United States package insert (or local prescribing information) for dose modifications for hematologic and other non-hematologic toxicities.

Drug-induced Liver Injury

If the AE of elevated liver enzymes (i.e., ALT, AST or total bilirubin) meets the following laboratory criteria for potential Drug-induced Liver Injury (DILI) as defined below, the event must be reported as a DILI as well as an ECI:

- An elevated ALT or AST lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and
- At the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,
- As a result of within-protocol-specific testing or unscheduled testing.

For capecitabine-related diarrhea supportive care guidelines, please see Section 5.6.2 – Supportive Guidelines for SOC Chemotherapy.

5.2.2.5 Dose Selection for Gemcitabine (Preparation)

The preparation and administration of gemcitabine should follow local treatment guidelines. However, the following recommendations should be taken into account.

Gemcitabine is administered by IV infusion at a dose of 1250 mg/m^2 over 30 minutes on Days 1 and 8, of a 3-week cycle. Pre-medication with steroids prior to IV infusion is permitted as per local SOC.

5.2.2.6 Dose Modification for Gemcitabine

Table 6 Dose Modification Guidelines for Gemcitabine Hematologic Drug-Related Events or (Drug-Related) Adverse Events

Absolute neutrophil count (x 10^6/L)		**Platelet count**	**% of Full Dose**
>1000	and	≥100,000	100%
500-999	or	50,000-99,000	75%
<500	or	<50,000	Hold until resolves to Grade 0-1

Dose Modification Guidelines for Gemcitabine Non-Hematologic Drug-Related Events or (Drug-Related) Adverse Events

- Withhold gemcitabine or reduce dose by 50% of full dose for other severe (Grade 3 or 4) non-hematologic toxicities until resolved to Grade 0-1.
- No dose modifications are recommended for alopecia, nausea, or vomiting.
- Permanently discontinue gemcitabine for the following:
  - Unexplained dyspnea or other evidence of severe pulmonary toxicity
  - Severe hepatic toxicity
  - Hemolytic-uremic syndrome

- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

For additional guidance regarding treatment modification of gemcitabine, please refer to the United States package insert (or local prescribing information) for dose modifications for hematologic and other non-hematologic toxicities.

5.2.2.7 Dose Selection for Docetaxel (Preparation)

The preparation and administration of docetaxel should follow local treatment guidelines. However, the following recommendations should be taken into account.

Docetaxel is administered by IV infusion over 1 hour every 3 weeks at a dose of 75 mg/m^2.

Corticosteroid Use with Docetaxel

In order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions, all patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days, starting 1 day prior to docetaxel administration.

Growth Factor Support Use with Docetaxel

For docetaxel, pegfilgrastim 6 mg subcutaneous (SQ) on Day 2 of each treatment cycle or filgrastim 5 µg/kg SQ on Days 2 through 11 of each treatment cycle may be used according to local treatment standards; however, discontinue for ANC >10,000/mm^3. See also Section 5.6.2 – Supportive Guidelines for SOC Chemotherapy.

Docetaxel should not be given to subjects with bilirubin >1 x ULN, or to subjects with AST and/or ALT >1.5 x ULN with concomitant ALP >2.5 x ULN as subjects with laboratory values above these limits are at increased risk of SAEs [refer to local product label].

5.2.2.8 Dose Modification for Docetaxel

Table 7 Dose Modification for Docetaxel Drug-Related Events (or Drug-Related) Adverse Events)

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
Liver dysfunction	AST/ALT >2.5 to ≤5 × ULN and AP ≤2.5 × ULN, or AST/ALT >1.5 to ≤5 × ULN and AP >2.5 to ≤5 × ULN		Yes	Restart treatment at 60 mg/m^2	N/A
	AST/ALT >5 × ULN and/or AP >5 × ULN		Yes	N/A	Discontinue upon onset
Peripheral Neuropathy	Grade 3, 4		Yes	N/A	Discontinue upon onset
Oral Mucositis	Grade 3, 4	1st,2nd occurrence	Hold until resolved	55 mg/m^2	

Note: Patients who develop >Grade 3 peripheral neuropathy should have docetaxel treatment permanently discontinued.

For additional guidance regarding treatment modification of docetaxel, please refer to the United States package insert (or local prescribing information) for dose modifications for hematologic and other non-hematologic toxicities as recommended for monotherapy with docetaxel in patients with non-small cell lung cancer).

5.2.3 Trial Blinding/Masking

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

5.3 Treatment Allocation

Treatment allocation/randomization will occur centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). There are 2 treatment arms; subjects will be assigned randomly in a 1:1 ratio to pembrolizumab (MK-3475) or SOC, respectively. The choice of SOC for a subject must be identified and documented prior to randomization. The choice of the SOC therapy will be input in the IVRS/IWRS prior to the randomized allocation schedule generation. Patients randomized to SOC therapy who discontinue will not be crossed-over to pembrolizumab (MK-3475).

5.4 Stratification

Randomization will be stratified according to the presence or absence of liver metastasis(es) (presence of any liver metastasis versus absence of all liver metastasis).

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

All concomitant medications taken by the subject from the date of first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant

medications administered >30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2 – Assessing and Recording AEs.

Bisphosphonate or denosumab therapy is allowed as long as it is begun at least 2 weeks prior to randomization. If started after randomization, it will be determined to be consistent with symptomatic progression of disease and clinical progression will be declared at that time followed by discontinuation of study treatment.

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol (with the exception of denosumab as noted above in Section 5.5.1)
- Investigational agents other than pembrolizumab (MK-3475)
- Radiation therapy
- Live or live attenuated vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Note: Killed vaccines are allowed.

  Note: Any licensed COVID-19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Investigational vaccines (i.e., those not licensed or approved for Emergency Use) are not allowed.

5.5.2.1 Prohibited Concomitant Medications for Pembrolizumab (MK-3475)

- Glucocorticoids (inhaled steroids as part of a stable regimen for the treatment of asthma/chronic obstructive pulmonary disease are permitted) for any purpose other than to modulate symptoms from an AE. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Additionally, a short limited course of steroids may be used to treat medical conditions and/or AEs during the study after Sponsor notification and consultation (Sponsor consultation is not required for topical steroid administration or for any other non-parenteral steroid administration).

  Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., IV contrast dye) is permitted.

5.5.2.2 Prohibited Concomitant Medications for SOC

- For subjects receiving docetaxel, strong inhibitors of the CYP3A4 enzymes (a common list of such agents may be found in Section 12.8 for subjects receiving docetaxel)

  Note: For subjects randomized to the standard treatment arm that require treatment with a strong inhibitor of CYP3A4, docetaxel may not be chosen as the standard treatment.

- For subjects receiving capecitabine, rare, unexpected severe toxicity (e.g., stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with 5-fluorouracil has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity. A link between decreased levels of DPD and increased, potentially fatal toxic effects of 5-fluorouracil/capecitabine therefore, cannot be excluded. Therefore, capecitabine may not be chosen as the standard treatment for any subject with a known DPD deficiency.

- For subjects being treated with warfarin, capecitabine may not be chosen as the standard treatment.

  Note: Concomitant treatment with low-molecular weight heparin therapy may be instituted instead.

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

The Exclusion Criteria describe other medications that are prohibited in this trial.

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Pembrolizumab (MK-3475)

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. **Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Section 5.2.1.2 (Table 4).** Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab (MK-3475).

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined in Section 5.2.1.2; Table 4).

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

Management of Infusion Reactions:

Pembrolizumab (MK-3475) 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 (MK-3475) associated infusion reaction are shown in Table 8.

Table 8 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	**Treatment**	**Premedication at Subsequent Dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs [NSAIDS], narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: • Diphenhydramine 50 mg po (or equivalent dose of antihistamine). • Acetaminophen 500 to 1000 mg PO (or equivalent dose of antipyretic).

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

5.6.2 Supportive Care Guidelines for Standard of Care Chemotherapy

5.6.2.1 Growth Factor Support

Docetaxel should not be given to subjects with neutrophil counts of <1500 without growth factor support.

- For docetaxel, pegfilgrastim 6 mg SQ on Day 2 of each treatment cycle or filgrastim 5 µg/kg SQ on Days 2 through 11 of each treatment cycle may be used according to local treatment standards; however, discontinue for ANC >10,000/mm^3.
- For gemcitabine, filgrastim 5 µg/kg SQ on Days 2 through 5 following each infusion, may be used according to local treatment standards; however, discontinue for ANC >10,000/mm^3.

5.6.2.2 Prophylactic Steroid Administration

For subjects randomized to gemcitabine:

Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome, have been reported rarely following 1 or more doses of gemcitabine administered to patients with various malignancies. Some patients experienced the onset of pulmonary symptoms up to 2 weeks after the last gemcitabine dose.

Respiratory failure and death occurred very rarely in some patients despite discontinuation of therapy. Therefore, prophylactic steroids may be administered prior to gemcitabine infusions as per the local treatment standards.

For subjects randomized to docetaxel:

Hypersensitivity reactions, especially during the first and second infusions, as well as severe fluid retention, have been reported following docetaxel infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, as well as very rarely, fatal anaphylaxis, have been reported.

Therefore, in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reaction, all subjects randomized to receive docetaxel must be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to docetaxel administration.

5.6.2.3 Steroid Administration for Treatment of Adverse Events or Medical Conditions

A short course of steroids may be used as concomitant medication for either treatment of an adverse event or medical condition with Sponsor approval (Sponsor consultation is not required for topical steroid administration or for any other non-parenteral steroid administration).

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

Capecitabine can induce diarrhea, sometimes severe, including the rare reporting of necrotizing enterocolitis (typhlitis). Therefore, for subjects who experience capecitabine-associated diarrhea, aggressive supportive management with anti-diarrheals, including loperamide and lomotil, according to local SOC treatment guidelines are indicated. Additional supportive measures should include aggressive hydration with electrolyte replacement as indicated, and could also include implementation of the American Dietetic Association BRAT diet as clinically indicated.

5.7.2 Contraception

Details regarding contraception are outlined in Section 5.1.2 - Subject Inclusion Criteria and Section 12.10 - Contraceptive Guidance.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding

withdrawal from Future Biomedical Research, are provided in Section 7.1.6 – Other Procedures.

In this trial, a subject may discontinue from treatment but continue in the study in survival follow-up, as long as the subject does not withdraw consent. Once a subject has discontinued treatment, even though he/she continues to be monitored in the trial, he/she may be allowed to begin treatment again if deemed medically appropriate, as outlined in Section 7.1.7.2.1.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

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

- The subject or legal representative (such as a parent or legal guardian) requests to discontinue treatment
- Confirmed radiographic disease progression outlined in Section 7.1.5 (exception if the Sponsor approves treatment continuation).

  Note: For unconfirmed radiographic disease progression, please see Section 7.1.5.1.6.
- Unacceptable AEs as described in Section 7.2
- Any progression or recurrence of any malignancy, or occurrence of another malignancy that requires active treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Any study treatment-related toxicity specified as a reason for permanent discontinuation as defined in Section 5.2.1.2.1
- Investigator's decision to discontinue treatment for the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 35 administrations of pembrolizumab (MK-3475) (approximately 2 years)

  Note: Subjects who stop pembrolizumab (MK-3475) after 35 administrations (approximately 2 years) may be eligible for up to 17 additional administrations of pembrolizumab (MK-3475) (approximately 1 year) if they progress after stopping trial treatment provided they meet the requirements detailed in Section 7.1.7.2.1.
- Administrative reasons

The End of Treatment and Follow-up Visit procedures are listed in Section 6.0 – Trial Flow Chart and Section 7.1.7 – Visit Requirements. After the end of treatment, each subject will be followed for the occurrence of AEs and spontaneously reported pregnancy as described in

Section 7.2. See Section 7.2.2 for complete details of reporting requirements of AEs and pregnancy/lactation.

Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. After documented disease progression, each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Trial Treatment After CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have received at least 8 administrations of pembrolizumab (MK-3475) and had at least 2 treatments with pembrolizumab (MK-3475) beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to 17 additional administrations of pembrolizumab (MK-3475) (approximately 1 year) at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab (MK-3475), the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose as at the time of initial discontinuation. Additional details are provided in Section 7.1.7.2.1. Response or progression in this Second Course Phase will not count towards the ORR and PFS of the key secondary endpoint in this trial.

5.8.2 Subject Withdrawal/Discontinuation Criteria from the Optional Sub-Study

Subjects may withdraw consent at any time for any reason or discontinue from this sub-study at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the sub-study is inappropriate, the sub-study plan is violated, or for administrative and/or other safety reasons. Subjects may withdraw from the sub-study without withdrawing from the main study.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

The overall 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 telephone-call or visit, withdraws from the study or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

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

6.0 TRIAL FLOW CHART

6.1 Initial Treatment Phase – Pembrolizumab (MK-3475) and SOC Arms

Details regarding the procedures listed in this table are outlined in Section 7.0.

Trial Period	Screening Phase	Treatment Cycles (3-Week Cycles)						End of Treatment	Post-Treatment Visits		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 6 cycles[r] 5	6	Discon	Safety Follow-up	Efficacy Follow-up[p]	Survival Follow-up[a]
Scheduling Window (Days)[b]:	-30 to -1	+3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose	Every 6 weeks post discon	Every 12 weeks
Administrative Procedures											
Informed Consent	X										
Informed Consent for Future Biomedical Research	X										
Inclusion/Exclusion Criteria	X										
Subject Identification Card	X										
Demographics and Medical History	X										
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X		
Post-study Anti-cancer Therapy Status										X	X
Obtain Randomization Number Using IVRS/IWRS		X									
Study Medication Administration (Pembrolizumab [MK-3475] or SOC)		X	X	X	X	X	X				
Survival Status[a]		<- ->									X
Clinical Procedures/Assessments											
12-Lead ECG (Local)	X										
Visits on Day 1 of each Cycle for all treatments, and additionally on Day 8 for Subjects treated with Gemcitabine											
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X							X			
Directed Physical Examination		X	X	X	X	X	X		X		
Vital Signs	X[c]	X	X	X	X	X	X	X	X		
ECOG Performance Status	X[d]	X	X	X	X	X	X	X	X		
Visits on Days 8 & 15 of Cycles 1, 2, 3 & 4 for all treatments											
Review Adverse Events		X	X	X	X						
Directed Physical Examination		X	X	X	X						

Trial Period	Screening Phase	Treatment Cycles (3-Week Cycles)						End of Treatment	Post-Treatment Visits		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 6 cycles[r] 5	6	Discon	Safety Follow-up	Efficacy Follow-up[p]	Survival Follow-up[a]
Scheduling Window (Days)[b]:	-30 to -1	+3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose	Every 6 weeks post discon	Every 12 weeks
Vital Signs		X	X	X	X						
ECOG Performance Status		X	X	X	X						
Tumor Tissue Collection											
Archival or Newly Obtained Tissue Collection for EBV Status	X										
Archival or Newly Obtained Tissue Collection for PD-L1 Biomarker Analysis	X										
Laboratory Procedures/Assessments: Analysis Performed by LOCAL Laboratory											
Pregnancy Test (Serum or Urine)[e]	X		X	X	X	X	X	X	X	X	X
Hematology[f]	X[d]		X	X	X	X	X	X	X		
Chemistry Panel[f]	X[d]		X	X	X	X	X	X	X		
Urinalysis[f]	X[d]		X		X		X[g]		X		
T3 or FT3, FT4, TSH, Other Labs[o]	X[d]		X		X		X[g]		X		
Coagulation Factors (PT/INR, aPTT)	X[q]										
Laboratory Procedures/Assessments: Analysis Performed by CENTRAL Laboratory											
Plasma EBV DNA[n]		X	X	X	X	X	X				
Pharmacokinetics[h,] (Pembrolizumab [MK-3475] Arm Only)		X	X		X		X[i]				
Anti-pembrolizumab (MK-3475) Antibodies[h] (Pembrolizumab [MK-3475] Arm Only)		X	X		X		X[i]				
Blood for Genetics (DNA)[j]		X									
Blood for Correlative Studies (DNA and RNA)[j]		X	X	X							
Blood for Biomarker Studies (Plasma and Serum)[j]		X									
Efficacy Measurements											
Tumor Imaging	X			X		X[k]		X[l]		X	
Patient-Reported Outcomes											
EuroQol EQ-5D[m]		X	X	X		X					

Trial Period	Screening Phase	Treatment Cycles (3-Week Cycles)						End of Treatment	Post-Treatment Visits		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 6 cycles[r] 5	6	Discon	Safety Follow-up	Efficacy Follow-up[p]	Survival Follow-up[a]
Scheduling Window (Days)[b]:	-30 to -1	+3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose	Every 6 weeks post discon	Every 12 weeks

a. After documented disease progression, or the start of new anti-cancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded). The investigator should make every attempt to follow the subject's AE(s) during the Survival Follow-Up Phase if the AE is in the reporting timeframe. See Section 7.1.7.3.3 for details.
b. In general, the window for each visit is ± 3 days unless otherwise noted.
c. Height will be measured at visit 1 only.
d. ECOG and laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment.
e. For women of reproductive potential, a urine pregnancy test should be performed within 24 hours or a serum pregnancy test should be performed within 72 hours prior to first dose of trial treatment and repeated at every cycle, at the time of treatment discontinuation, at the safety follow-up visit, and at least 120 days after the last dose of pembrolizumab or at least 180 days after the last dose of chemotherapy. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Monthly pregnancy testing should be conducted as per local regulations where applicable.
f. After Cycle 1, Hematology and Chemistry lab samples can be collected up to 3 days prior to Day 1 of every cycle for all treatment groups and additionally up to 3 days prior to Day 8 for subjects assigned to gemcitabine. Urinalysis is **only** required at Day 1 of Cycle 2 and then Day 1 of every other cycle after Cycle 2, for all treatment groups, and additionally on Day 8 of every other cycle for subjects assigned to gemcitabine. For Urinalysis, samples can be obtained up to 3 days prior to the scheduled time points.
g. To be repeated every other cycle after Cycle 6.
h. Pre-dose trough PK and anti-pembrolizumab (MK-3475) antibody samples will be collected at Cycles 1, 2, 4, 6 and 8. All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab (MK-3475).
i. To be repeated every 4 cycles after Cycle 8, until discontinuation of study drug (or until the subject starts new anti-cancer therapy).
j. Details for collection can be found in Section 7.1.4, Laboratory Procedures/Assessments.
k. Tumor imaging assessments are to be every 6 weeks as per Section 7.1.5.2. After 1 year in the treatment period, imaging should be performed every 9 weeks (63 days ± 7 days). After Year 1, it will be at the site Investigator's discretion to follow the protocol-specified imaging schedule or to follow the imaging schedule per local/standard practice.
l. If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. Refer to Section 7.1.5.1.3 for details.
m. It is a best practice and strongly recommended that ePROs are administered to randomized subjects prior to drug administration, AE evaluation, and disease status notification. The EQ-5D is to be performed prior to dosing on only Day 1 of Cycle 1, Cycle 2, Cycle 3 and every 2 cycles thereafter (e.g., Cycle 5, Cycle 7, Cycle 9) up to 1 year from treatment initiation (i.e., Cycle 17). If the subject does not complete the EQ-5D for any reason, the Miss Mode form must be completed to capture the reason the assessment was not performed.
n. Plasma EBV DNA to be collected weekly during Cycle 1, and then up to 3 days prior to dosing at all subsequent cycles. Plasma EBV DNA should not be collected beyond Cycle 80 Day 1.
o. After Cycle 1, lab samples can be collected up to 3 days prior to the scheduled time point. Note: weekly collection of Serum human chorionic gonadotropin (hCG) is not required for any subject. See footnote e regarding pregnancy test requirements.
p. In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring disease status by radiologic imaging using the same imaging schedule used while on treatment (every 6 weeks in Year 1 and every 9 weeks after Year 1) to monitor disease status until (1) the start of new anti-

Trial Period	Screening Phase	Treatment Cycles (3-Week Cycles)						End of Treatment	Post-Treatment Visits		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 6 cycles[r] 5	6	Discon	Safety Follow-up	Efficacy Follow-up[p]	Survival Follow-up[a]
Scheduling Window (Days)[b]:	-30 to -1	+3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose	Every 6 weeks post discon	Every 12 weeks

cancer treatment, (2) disease progression, (3) pregnancy, (4) death, (5) withdrawal of consent, or (6) the end of the study, whichever occurs first. Follow-up visits may be adjusted to coincide with the Follow-up imaging schedule. After Year 1, it will be at the site Investigator's discretion to follow the protocol-specified imaging schedule or to follow the imaging schedule per local/standard practice.

q. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. PTT may be performed if the local lab is unable to perform aPTT. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

r. Subjects on the SOC arm may continue study treatment beyond Cycle 35 until they meet a discontinuation criterion. For subjects on the SOC arm who are dosed beyond Cycle 35, procedures (i.e., imaging) should continue.

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

Details regarding the procedures listed in this table are outlined in Section 7.0.

Trial Period:	Treatment Cycles (3-Week Cycles)						End of Treatment	Post-Treatment Visits		
Treatment Cycle/Title:	1	2	3	4	To be repeated beyond 6 cycles 5	6	Discon	Safety Follow-up	Efficacy Follow-up[i]	Survival Follow-up[a]
Scheduling Window (Days)[b]:	+ 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose	Every 6 weeks post discon	Every 12 weeks
Administrative Procedures										
Eligibility Criteria	X									
Concomitant Medication Review	X	X	X	X	X	X	X	X		
Pembrolizumab (MK-3475) Administration	X	X	X	X	X	X				
Post-study Anti-cancer Therapy Status									X	X
Survival Status[a]	<- ->									X
Clinical Procedures/Assessments										
Review Adverse Events	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X						X			
Directed Physical Examination		X	X	X	X	X		X		
Vital Signs	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X		
Laboratory Procedures/Assessments: Analysis Performed by LOCAL Laboratory										
Pregnancy Test (Serum or Urine)[c]	X	X	X	X	X	X	X	X	X	X
Hematology[d]	X[e]	X	X	X	X	X	X	X		
Chemistry Panel[d]	X[e]	X	X	X	X	X	X	X		
Urinalysis[d]	X[e]		X		X[f]					
T3 or FT3, FT4, TSH, Other Labs[h]	X[e]		X		X[f]			X		
Coagulation Factors (PT/INR, aPTT)	X[j]									
Efficacy Measurements										
Tumor Imaging	X[g]		X		X[g]		X		X	

a. After documented disease progression, or the start of new anti-cancer treatment; contacts are approximately every 12 weeks (± 3 weeks) by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded). Investigator should make every attempt to follow the subject's AEs during the Survival Follow-Up Phase if the AE is in the reporting timeframe. See Section 7.1.7.3.3 for details.
b. In general, the window for each visit is ± 3 days unless otherwise noted.
c. For women of reproductive potential, a urine pregnancy test should be performed within 24 hours or a serum pregnancy test should be performed within 72 hours prior to first dose of trial treatment and repeated at every cycle, at the time of treatment discontinuation, at the safety follow-up visit, and at least 120 days after the last dose of pembrolizumab. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Monthly pregnancy testing should be conducted as

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

per local regulations where applicable.
d. After Cycle 1, Hematology and Chemistry lab samples can be collected up to 3 days prior to Day 1 of every cycle at the scheduled time point. Urinalysis is **only** required at Day 1 of every other cycle after Cycle 1. Urinalysis samples can be scheduled up to 3 days prior to the scheduled time point.
e. Laboratory tests for determining eligibility for retreatment are to be performed within 10 days prior to the first retreatment dose of pembrolizumab (MK-3475).
f. To be repeated every other cycle after Cycle 5.
g. A scan must be performed within 30 days prior to restarting treatment with pembrolizumab (MK-3475). Subjects who obtain a confirmation scan for CR, PR, or disease progression do not need to undergo scheduled tumor imaging if it is <4 weeks later and may wait until the next scheduled imaging time point, unless clinical disease progression is suspected or subject is deemed to be clinically unstable. In the Re-treatment phase tumor assessments are to be every 6 weeks/every 3 cycles as outlined in Section 7.1.5.1.4. Subjects who discontinue without documented disease progression will continue scans every 6 weeks for the first year and every 9 weeks in Year 2. After Year 1, it will be at the site Investigator's discretion to follow the protocol-specified imaging schedule or to follow the imaging schedule per local/standard practice.
h. After Cycle 1, lab samples can be collected up to 3 days prior to the scheduled time point. Note: weekly collection of Serum human chorionic gonadotropin (hCG) is not required for any subject. See footnote c for pregnancy test requirements.
i. In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring disease status by radiologic imaging using the same imaging schedule used while on treatment (every 6 weeks in Year 1 and every 9 weeks after Year 1) to monitor disease status until (1) the start of new anti-cancer treatment, (2) disease progression, (3) pregnancy, (4) death, (5) withdrawal of consent, or (6) the end of the study, whichever occurs first. Follow-up visits may be adjusted to coincide with the Follow-up imaging schedule. After Year 1, it will be at the site Investigator's discretion to follow the protocol-specified imaging schedule or to follow the imaging schedule per local/standard practice.
j. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. PTT may be performed if the local lab is unable to perform aPTT. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

The optional sub-study flow chart can be found in Section 12.9.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related

to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.2.1 Inclusion/Exclusion Criteria for Optional Participation in the Sub-Study

All additional inclusion and exclusion criteria as noted in Sections 5.1.2.1 and 5.1.3.1 will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinical significant by the investigator. Details regarding the subject's nasopharyngeal cancer 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 3 months prior to screening, "weight loss" should be entered as an active condition on the Medical History. In addition, any autoimmune disorders, feeding tube placement, and tracheotomy, regardless of onset date, should be recorded.

7.1.1.4.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding the subject's nasopharyngeal cancer.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject during the screening period (Day -30 through Day -1 of trial treatment start). Prior anti-cancer treatment for NPC will be recorded separately and not listed as a prior medication.

7.1.1.5.1.1 Prior Treatment Details for Nasopharyngeal Cancer

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

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject from the date of first dose of trial treatment through the Safety Follow-up visit. In addition, new medications started during the Second Course through the Second Course Safety Follow-up Visit should be recorded. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2 – Assessing and Recording Adverse Events. Additionally, please see Section 5.5.1 – Acceptable Concomitant Medications and Section 5.5.2 – Prohibited Concomitant Medications.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-cancer therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up Visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated, the subject will move into Survival Follow-up.

7.1.1.6 Assignment of Screening Number

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

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

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.7.1.

7.1.1.7 Assignment of Treatment/Randomization Number

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

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

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

Details regarding administration of trial treatment are outlined in Section 5.2 – Trial Treatment.

Interruptions from the protocol specified treatment plan for greater than 3 weeks between pembrolizumab (MK-3475) doses for non-drug-related or administrative reasons (see Section 5.2.1.2 for drug-related modifications) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial treatment will be monitored by the investigator and/or trial staff. The total volume of pembrolizumab (MK-3475) infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab (MK-3475) administered.

The instructions for preparing and administering pembrolizumab (MK-3475) will be provided in the Pharmacy Manual.

7.1.1.9 Survival Status

Details regarding survival status follow-up are outlined in Section 7.1.7.3.3 – Survival Follow-up and Section 7.1.7.4 – Survival Status.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event Monitoring

The investigator or qualified designee will assess each subject weekly during the first 4 cycles, followed by Day 1 of each subsequent cycle to evaluate for potential new or worsening AEs, and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the Follow-up Period according to NCI CTCAE Version 4.0 (see Section 12.6). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab (MK-3475), all AEs of unknown etiology associated with pembrolizumab (MK-3475) exposure should be evaluated to determine if it is possibly an ECI of a potentially irAE; see Section 7.2.3.2 regarding the identification, evaluation and management of potential irAEs.

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

7.1.2.2 Electronic Patient-Reported Outcomes

The EuroQol EQ-5D questionnaire will be administered by trained site personnel and completed electronically (eEQ-5D) or by paper (EQ-5D), if necessary, by subjects at the time points specified in the Trial Flow Chart. It is a best practice and strongly recommended that electronic patient-reported outcomes (ePROs) are administered to randomized subjects prior to drug administration, AE evaluation, and disease status notification.

7.1.2.3 Physical Exam

7.1.2.3.1 Full Physical Exam

The investigator or clinical designee will perform a complete physician exam during the screening period and at the time of treatment discontinuation. Clinically significant

abnormal findings should be recorded as medical history. A full physical exam should be performed as specified in Section 6.0 - Trial Flow Chart. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3.2 Directed Physical Exam

The investigator or qualified designee will perform a directed physical exam weekly for the first 4 cycles in the Initial Treatment Phase only and prior to all dosing visits. On dosing visits, the directed physical exam will be performed prior to dosing ± 3 days of Day 1 of each treatment cycle. For subjects assigned to gemcitabine with dosing visits on Day 1 and Day 8 of each cycle, a directed physical exam will be performed prior to dosing ± 3 days of Day 1 and ± 3 days of Day 8. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, weekly for the first 4 cycles in the Initial Treatment Phase only, and ± 3 days of Day 1 of each subsequent treatment cycle, as well as at treatment discontinuation as specified in the Trial Flow Chart. For subjects assigned to gemcitabine with dosing visits on Day 1 and Day 8 of each cycle, vital signs will be taken prior to dosing ± 3 days of Day 1 and ± 3 days of Day 8. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 12-Lead Electrocardiogram

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

7.1.2.6 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG status (see Section 12.5) at screening, weekly for the first 4 cycles in the Initial Treatment Phase only, prior to dosing ± 3 days of Day 1 of each treatment cycle, and at discontinuation of trial treatment as specified in the Trial Flow Chart. For subjects assigned to gemcitabine with dosing visits on Day 1 and Day 8 of each cycle, ECOG will be assessed prior to dosing ± 3 days of Day 1 and ± 3 days of Day 8.

7.1.3 Tumor Tissue Collection

7.1.3.1 Epstein-Barr Virus Status

All subjects must have assessment of EBV status from tumor tissue prior to treatment allocation/randomization (see Section 5.1.2). Baseline tumor tissue from an archival tissue sample or newly obtained core or excisional biopsy (fine needle aspirate [FNA] not adequate for archival and new tissue samples) must be evaluated for EBV status (if EBV status is not already known) by local assessment by means of EBER ISH testing. If EBV status has previously been tested using EBER ISH, no retesting is required.

Note: Subjects without available local EBER ISH testing results may submit tumor tissue for central EBER ISH testing.

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

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

7.1.3.2 PD-L1 Status

All subjects should submit either a newly obtained core or excisional biopsy or archival tissue (FNA not adequate for both archival and new tissue samples) to a central lab for characterization of PD-L1 status prior to treatment allocation/randomization.

Note: Submission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; if submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory within 14 days from site slide section date, otherwise a new specimen will be requested.

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

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

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

7.1.4 Laboratory Procedures/Assessments

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

7.1.4.1 Local Laboratory Evaluations

7.1.4.1.1 Pregnancy Testing

Details regarding pregnancy testing are outlined in Section 5.1.2 - Subject Inclusion Criteria, Section 7.1.7.1 - Screening and Section 7.1.4.1.2 - Hematology, Chemistry, Urinalysis and Other Labs.

Pregnancy tests are required within 24 hours for a urine pregnancy test and within 72 hours for a serum pregnancy test prior to each cycle.

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.2.

- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention(s) as noted in Section 5.1.2. The length of time required to continue pregnancy testing for each study intervention is as follows:
  - MK-3475: at least 120 days
  - Chemotherapy: at least 180 days
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

7.1.4.1.2 Hematology, Chemistry, Urinalysis, Other Labs and Coagulation Factors

All required laboratory tests are specified in Table 9.

Table 9 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other	Coagulation Factors (Hemostatic Tests)
Hematocrit	Albumin	Blood	Highly sensitive serum human chorionic gonadotropin (hCG)[c]	PT (INR)
Hemoglobin	Alkaline phosphatase	Glucose		aPTT or PTT
Platelet count	Alanine aminotransferase (ALT)	Protein		
White Blood Cell Count (WBC) (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3) or Free T3 (FT3)[d]	
Red Blood Cell Count (RBC)	Carbon dioxide (CO_2 or bicarbonate)[b]	Microscopic exam, if abnormal results are noted	Free thyroxine (FT4)	
Absolute Neutrophil Count[a]	Calcium	Urine pregnancy test[c]	Thyroid stimulating hormone (TSH)	
Absolute Lymphocyte Count	Chloride			
	Creatinine			
	Glucose			
	Potassium			
	Sodium			

Hematology	Chemistry	Urinalysis	Other	Coagulation Factors (Hemostatic Tests)
	Total Bilirubin			
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal			
	Total protein			
	Blood Urea Nitrogen or Urea[e]			
	Lactate dehydrogenase (LDH)			
	Uric acid			

[a] Absolute is required, % is considered optional.
[b] If these tests are not done as part of standard of care in your region, then these tests do not need to be performed.
[c] As needed for women of childbearing potential. Serum pregnancy test is preferred but urine test can be considered if serum not appropriate.
[d] T3 or FT3 can be assayed based on local standards.
[e] Blood Urea Nitrogen is preferred: if not available urea may be tested

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. After Cycle 1, pre-dose laboratory procedures (hematology and chemistry) must be conducted up to 3 days prior to Day 1 of each cycle. In addition, laboratory procedures must be performed within 3 days prior to Day 8 dosing for all subjects assigned to gemcitabine.

Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. PTT may be performed if the local lab is unable to perform aPTT. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

After screening, urinalysis and thyroid function tests should be performed within 3 days prior to Day 1 of every other cycle (e.g., Cycles 2, 4, 6, 8).

Note: Weekly collection of Serum hCG is not required for any subject.

With the exception of thyroid tests that are obtained after the baseline testing, laboratory results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment. Unresolved abnormal labs that are DRAEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.

7.1.4.2 Central Laboratory Evaluations

7.1.4.2.1 Plasma Epstein-Barr Virus DNA

Blood for plasma EBV DNA analysis is to be drawn weekly during Cycle 1, and then up to 3 days prior to dosing at all subsequent cycles. Plasma EBV DNA should not be collected beyond Cycle 80 Day 1. Hence, there will be 3 collections for plasma EBV DNA analysis in

Cycle 1 and 1 collection in all subsequent cycles. All samples are to be submitted for central testing. Collection, storage, and shipment instructions for this sample will be provided in the Procedures Manual.

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

7.1.4.2.2 Pharmacokinetic Evaluations

To further evaluate pembrolizumab (MK-3475) immunogenicity and pembrolizumab (MK-3475) exposure in this indication, and also to evaluate exposure of the 200 mg fixed dosing regimen, sample collections for analysis of anti-drug antibodies (ADA) and PK are currently planned as shown in the Trial Flow chart (Section 6.1). Blood samples will be obtained to measure PK of serum pembrolizumab (MK-3475) as monotherapy. Blood samples for PK and ADA collected will be stored and analysis will be performed only if required. If ongoing ADA and/or PK results continue to be consistent with existing ADA and/or PK data from other pembrolizumab (MK-3475) clinical trials, it may be decided to discontinue or reduce further sample collection in this study.

7.1.4.2.2.1 Blood Collection for Serum Pembrolizumab (MK-3475)

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

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

Sample collection, storage and shipment instructions for serum samples will be provided in the Procedures Manual. Anti-pembrolizumab (MK-3475) antibody samples should be drawn according to the ADA collection schedule for subjects who receive pembrolizumab (MK-3475). Simultaneous PK sampling is required for interpretation of ADA analysis.

7.1.4.3 Planned Genetic Analysis Sample Collection

A sample should be drawn at the Cycle 1 Visit for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant provides documented informed consent for Future Biomedical Research consent. If the planned genetic analysis is not approved, but Future Biomedical Research is approved and consent is given, this sample will be collected for the purpose of Future Biomedical Research.

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

7.1.4.4 Future Biomedical Research

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover DNA for future research
- Leftover main study tumor tissue for future research
- Leftover main study plasma from EBV DNA analyses stored for future research
- Leftover DNA and RNA from correlative studies
- Leftover plasma and serum from biomarker studies

Detailed instructions for the collection and management of specimens for Future Biomedical Research are provided in the Procedures Manual and Section 12.2 – Collection and Management of Specimens for Future Biomedical Research.

7.1.4.5 Blood for Correlative and Biomarker Studies

Blood for correlative studies (RNA and DNA) should be collected pre-dose for each of the following: Day 1, Cycle 1; Day 1, Cycle 2; Day 1, Cycle 3. Blood for biomarker studies (plasma and serum) should be collected pre-dose on Day 1, Cycle 1 only. Detailed instructions with specific time points per sample are provided in the Procedures Manual. Any leftover samples from the correlative and biomarker studies will be stored for future biomedical research if the subject signs the Future Biomedical Research consent.

7.1.4.6 Blood for Participation in Optional Sub-Study

Blood for this translational sub-study should be collected pre-dose for each of the following: baseline sample obtained prior to or on Day 1, Cycle 1. Additional samples will also be collected prior to Day 1 of Cycle 2, Day 1 of Cycle 3, Day 1 of Cycle 4, Day 1 of Cycle 5, and at the time of disease progression. If disease progression occurs after Cycle 80 Day 1, a sample should not be collected at the time of disease progression. Detailed instructions are provided in the Procedures Manual. Please see Appendix 12.9 for details. Any leftover samples from the optional sub-study will be stored for future biomedical research if the subject signs the FBR consent.

7.1.5 Efficacy Measurements

7.1.5.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual. Tumor imaging should be acquired by computed tomography (CT) (strongly preferred). Magnetic resonance imaging (MRI) should only be used when CT is contraindicated or for imaging of the brain. The same imaging technique regarding modality and use of contrast should be used in a subject throughout the trial to optimize the visualization of existing and new tumor burden.

Imaging should include the neck, chest, and abdomen at all time points specified in Section 6.0 – Trial Flow Chart. Imaging of the pelvis is considered optional, and should be

acquired if clinically indicated. A CT from the vertex of the head or a brain CT is preferred but not required. A soft tissue neck CT (starting from orbital line) plus CT of chest and abdomen are required. For an individual subject, imaging should be consistent at all time points (i.e., follow-up scans should image the same area as the baseline area, using the same imaging modality).

A dedicated brain MRI is only needed at baseline to document stability in subjects with previously treated brain metastasis (see Section 5.1.3). A dedicated brain MRI is to be acquired at follow-up only if there is clinical suspicion of brain metastasis. This imaging should be submitted to the central imaging vendor.

Confirmation of measurable disease based on RECIST 1.1 by central imaging vendor at screening will be reviewed retrospectively on a rolling basis. All scheduled images from the sites should be submitted to the central imaging vendor for evaluation and should be submitted in a timely fashion. In addition, additional imaging (including other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons but captures radiologic progression, should be submitted to the central imaging vendor as well.

7.1.5.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 30 days prior to the date of treatment allocation/randomization. The site study team must review screening images to confirm the subject has measurable disease per RECIST 1.1. The screening images must be submitted immediately to the central imaging vendor for retrospective confirmation of measurable disease per RECIST 1.1. Subject eligibility will be based on the site assessment.

Scans performed as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 30 days prior to the date of treatment allocation/randomization and can be assessed by the central imaging vendor.

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

7.1.5.1.2 On Study Tumor Imaging

The first on study imaging assessment should be performed at 6 weeks (42 days ± 7 days) after the date of first dose regardless of treatment delays. Subsequent tumor imaging should be performed every 6 weeks up to the first year of treatment (42 days ± 7 days), or more frequently if clinically indicated. After 1 year, subjects who remain on treatment will have imaging performed every 9 weeks up to completion of the second year of treatment (63 days ± 7 days), or more frequently if clinically indicated. After Year 1, it will be at the site Investigator's discretion to follow the protocol-specified imaging schedule or to follow the

imaging schedule per local/standard practice. 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 (unless site PI elects to continue treatment and follow irRECIST), the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

Per RECIST 1.1, PR or CR should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated. Subjects will then return to regularly scheduled imaging every 6 weeks in the first year (42 days ± 7 days), or every 9 weeks after 1 Year (63 days ± 7 days), depending on weeks from date of first dose, starting with the next scheduled imaging time point. After Year 1, it will be at the site Investigator's discretion to follow the protocol-specified imaging schedule or to follow the imaging schedule per local/standard practice. Subjects who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is <4 weeks later and may wait until the next scheduled imaging time point.

Per irRECIST (Section 7.1.5.1.6), disease progression in subjects treated with pembrolizumab (MK-3475) should be confirmed by the site at least 4 weeks after central verification of site-assessed first radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment at the discretion of the site investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 7.1.5.1.6 – irRECIST Assessment of Disease. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Subjects who have confirmed disease progression as assessed by the site will discontinue the treatment. Exceptions are detailed in Section 7.1.5.1.6 – irRECIST Assessment of Disease.

7.1.5.1.3 End of Treatment and Follow-up Tumor Imaging

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

In subjects who discontinue trial treatment without documented disease progression, continuous monitoring of their disease status must be completed by tumor imaging using the same imaging schedule used while on treatment (every 6 weeks in Year 1 or 9 weeks after Year 1) to monitor disease status until (1) the start of new anti-cancer treatment, (2) disease progression, (3) pregnancy, (4) death, (5) withdrawal of consent, or (6) the end of the study, whichever occurs first. After Year 1, it will be at the site Investigator's discretion to follow the protocol-specified imaging schedule or to follow the imaging schedule per local/standard practice.

For subjects who stopped treatment prior to the maximum time of 2 years/35 treatments due to confirmed CR or who completed 2 years/35 treatments of treatment, a less frequent imaging schedule of 12 weeks can be considered with Sponsor approval; this applies only to subjects prior to initiation of second course (retreatment).

7.1.5.1.4 Second Course (Retreatment) Tumor Imaging

A scan must be performed within 30 days prior to restarting treatment with pembrolizumab (MK-3475). Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. Imaging should be submitted to the central imaging vendor for retrospective verification.

The first on study imaging assessment should be performed at 6 weeks (42 days ± 7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 6 weeks (42 days ± 7 days) or more frequently if clinically indicated. After Year 1, it will be at the site Investigator's discretion to follow the protocol-specified imaging schedule or to follow the imaging schedule per local/standard practice.

Per RECIST 1.1, PR or CR should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated. Subjects will then return to regular scheduled imaging every 6 weeks (42 days ± 7 days), starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is <4 weeks later and may wait until the next scheduled imaging time point. After Year 1, it will be at the site Investigator's discretion to follow the protocol-specified imaging schedule or to follow the imaging schedule per local/standard practice.

Per irRECIST (Section 7.1.5.1.6), if tumor imaging shows initial PD in subjects treated with pembrolizumab (MK-3475), tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Subjects who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is <4 weeks later and may wait until the next scheduled imaging time point if clinically stable.

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

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

In subjects who discontinue trial treatment without documented disease progression, continuous monitoring of their disease status must be completed by radiologic imaging every 6 weeks (42 days ± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, (4) withdrawal of consent, or (5) the end of the study, whichever occurs first. After Year 1, it will be at the site Investigator's discretion to follow the protocol-specified imaging schedule or to follow the imaging schedule per local/standard practice.

7.1.5.1.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 (Section 12.7) will be applied by the central imaging vendor as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of trial 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.

For subjects treated with pembrolizumab (MK-3475) or SOC chemotherapy, initial tumor imaging showing site-assessed PD should be submitted to the central imaging vendor immediately. The site will be notified if the central imaging vendor verifies progressive disease (PD) using RECIST 1.1. Figure 2 illustrates the imaging flow involving verification of PD for clinically stable subjects.

7.1.5.1.6 irRECIST Assessment of Disease

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

When feasible, subjects treated with pembrolizumab (MK-3475) should not be discontinued until progression is confirmed by the local site investigator/radiology assessment. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

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

In subjects treated with pembrolizumab (MK-3475) who have shown initial evidence of radiological PD by RECIST 1.1 as verified by central imaging vendor, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained (using irRECIST for subject management, see Table 10 and Figure 2). This clinical judgment decision by the site investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects

may receive study treatment and tumor assessment should be repeated ≥4 weeks later in order to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

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

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

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

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

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

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

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

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

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

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

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

Table 10 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Tumor Imaging	Treatment	Tumor Imaging	Treatment
1st radiologic evidence of PD by RECIST 1.1 which has been verified by the central imaging vendor	Repeat imaging at ≥4weeks at site to confirm PD	May continue study treatment at the site Investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST	Repeat imaging at ≥4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional tumor imaging required*	Discontinue treatment*	No additional tumor imaging required	N/A
Repeat tumor imaging shows SD, PR or CR by irRECIST at the local site	Continue regularly scheduled tumor imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled tumor imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

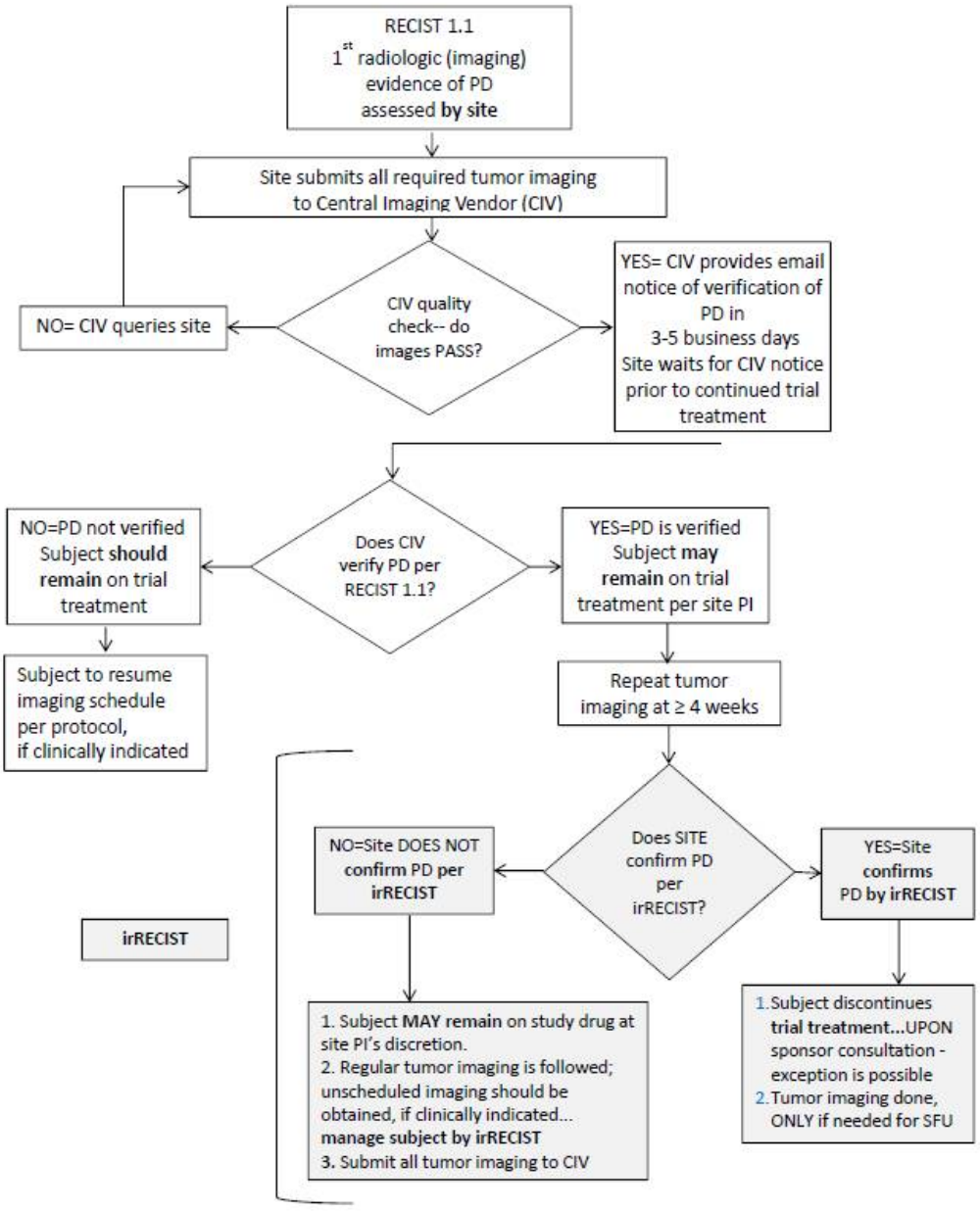

Figure 2 Imaging and Treatment for Clinically Stable Subjects in Subjects Treated With Pembrolizumab (MK-3475) After First Radiologic Evidence of Progressive Disease Assessed by the Site

7.1.6 Other Procedures

7.1.6.1 Withdrawal/Discontinuation

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the End of Treatment Visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who 1) attain a CR or 2) complete 35 administrations of pembrolizumab (MK-3475) (approximately 2 years) may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.7.2.1 – Second Course Phase (Retreatment Period). After discontinuing treatment following assessment of CR or 35 administrations of pembrolizumab (MK-3475), these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.7.3.1) and then proceed to the Follow-up Period of the study (described in Section 7.1.7.3.2).

7.1.6.1.1 Withdrawal From Future Biomedical Research

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

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

7.1.6.2 Blinding/Unblinding

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

7.1.6.3 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical trial that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible.

Documentation of equipment calibration must be retained as source documentation at the trial site.

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, and Site Imaging Manual.

7.1.7 Visit Requirements

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

7.1.7.1 Screening

Approximately 30 days prior to allocation/randomization number assignment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1 – Entry Criteria. Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Screening procedures may be repeated.

Visit requirements for the Optional Sub-Study are outlined in Appendix 12.9 – Trial Flow Chart for participation in the Optional Sub-Study. During screening procedures ongoing for the main trial, potential subjects will be identified and evaluated for additional entry requirements as set forth in Sections 5.1.2.1 and 5.1.3.1.

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 (i.e., within 30 days prior to the date of treatment allocation/randomization).

Screening procedures are to be completed within 30 days prior to the first dose of trial treatment except for the following:

- Laboratory tests and ECOG Performance Scale are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. A urine test within 24 hours prior to the first dose of trial treatment may be considered if serum test is not appropriate.

  Note: A pregnancy test must be repeated at time points post screening if required by local guidelines.
- Archival tumor collection is not required to be obtained within 30 days prior to the first dose of trial treatment. Newly obtained tumor tissue may be obtained within 30 days of treatment allocation/randomization.

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

of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria are met.

Study personnel will access IVRS/IWRS to obtain the allocation/randomization number and study drug assignment.

7.1.7.2 Treatment Period

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

7.1.7.2.1 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab (MK-3475) with SD, PR or CR, may be eligible for up to 1 year of additional pembrolizumab (MK-3475) therapy if they progress after stopping trial treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
  - Stopped initial treatment with pembrolizumab (MK-3475) after attaining an investigator-determined confirmed CR according to RECIST 1.1
    - Was treated for at least 8 administrations of pembrolizumab (MK-3475) before discontinuing therapy
    - Received at least 2 treatments with pembrolizumab (MK-3475) beyond the date when the initial CR was declared

  OR

  - Had SD, PR or CR and stopped pembrolizumab (MK-3475) treatment after 35 administrations (approximately 2 years) for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab (MK-3475)
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab (MK-3475)
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2 – Subject Inclusion Criteria
- WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours for a urine test and 72 hours for a serum test prior to receiving retreatment with study medication.

If a urine pregnancy test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Additional requirements for pregnancy testing are in Section 7.1.4.1.1 – Pregnancy Testing.

- Female subject of childbearing potential should be willing to follow contraception requirements in Section 5.1.2 – Subject Inclusion Criteria and Section 12.10 – Contraceptive Requirements.
- Male subjects should agree to follow contraception requirements in Section 5.1.2 – Subject Inclusion Criteria and Section 12.10 – Contraceptive Requirements.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose frequency as when they last received pembrolizumab (MK-3475). Treatment will be administered for up to 17 additional administrations (approximately 1 year).

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

7.1.7.3 Post-Treatment Visits

7.1.7.3.1 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0 or 1 or until the beginning of a new anti-cancer therapy, whichever occurs first. Each subject will be followed for the occurrence of SAEs and ECIs for 90 days after the end of treatment, or 30 days following cessation of treatment if the subject initiates new anti-cancer therapy, whichever is earlier.

The Discontinuation and 30-day Safety Follow-up visits may be performed simultaneously if the Discontinuation visit is conducted at least 3 weeks after last dose or if the subject starts new anti-cancer therapy shortly after the End of Treatment.

Subjects who are eligible for retreatment with pembrolizumab (MK-3475) (as described in Section 7.1.7.2.1) may have up to 2 safety follow-up visits, 1 after the Initial Treatment or First Course and 1 after the Second Course.

7.1.7.3.2 Efficacy Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will begin the Efficacy Follow-Up and should be assessed radiographically every 6 weeks in Year 1 and every 9 weeks after Year 1 to monitor disease status. After Year 1, it will be at the site Investigator's discretion to follow the protocol-specified imaging schedule or to

follow the imaging schedule per local/standard practice. Follow-up visits may be adjusted to coincide with the Follow-up imaging schedule. The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks). Every effort should be made to collect information regarding disease status in the follow-up period (see Section 7.1.5.1.3) until the start of new anti-cancer therapy, disease progression, death, end of study, or if the subject begins retreatment with pembrolizumab (MK-3475) as detailed in Section 7.1.7.2.1 – Second Course Phase (Retreatment Period).

Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab (MK-3475) according to the criteria in Section 7.1.7.2.1 – Second Course Phase (Retreatment Period) will move from the Efficacy Follow-Up Phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.0 – Trial Flow Chart for retreatment with pembrolizumab (MK-3475).

7.1.7.3.3 Survival Follow-up

Once a subject experiences disease progression as determined by the site per RECIST 1.1 or irRECIST or starts a new anti-cancer therapy, the subject moves into the Survival Follow-Up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. The investigator should make every attempt to follow the subject's AE(s) during the Survival Follow-Up Phase if the AE is in the reporting timeframe. If the AE occurred prior to the Safety Follow-Up Visit, subjects with an AE of Grade > 1 should be followed until the resolution of the AE to Grade 0 or 1 or until the beginning of a new anti-cancer therapy, whichever occurs first.

7.1.7.4 Survival Status

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

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

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

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

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

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

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

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 serious adverse event, 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 electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

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

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

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

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

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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

7.2.4 Evaluating Adverse Events

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

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

Table 11 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

This trial was developed in collaboration with both Sponsor and non-Sponsor scientific experts who provided input with respect to the trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

7.3.1 Executive Oversight Committee

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

7.3.2 Data Monitoring Committee

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

The eDMC will make recommendations to the EOC regarding steps to ensure subject safety, efficacy, and continued ethical integrity of the trial. The eDMC will be convened twice a year to monitor subject safety in this trial.

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

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to the conduct of any analysis, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study (this includes the exploratory analyses for the Optional Sub-Study protocol which will also be documented in a separate sSAP). Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2 – Responsibility for Analyses/In-House Blinding to Section 8.12 – Extent of Exposure.

Study Design Overview	A Phase III Study of Pembrolizumab (MK-3475) vs. Standard Chemotherapy in Subjects with Platinum Pre-treated, Recurrent or Metastatic Nasopharyngeal Cancer (KEYNOTE-122)
Treatment Assignment	This is an open-label study. Approximately 230 subjects will be randomized in a 1:1 ratio to receive pembrolizumab (MK-3475) or one of the 3 standard of care (SOC) treatments.
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoint	Overall Survival (OS)
Key Secondary Endpoint(s)	Progression-free Survival (PFS) per RECIST 1.1 by BICR Objective Response Rate (ORR) per RECIST 1.1 by BICR
Statistical Methods for Key Efficacy Analyses	The primary hypothesis for OS will be evaluated by comparing pembrolizumab (MK-3475) to SOC using a stratified log-rank test. Estimation of the hazard ratio will be performed using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the non-parametric Kaplan-Meier method. The same approach will be applied to the secondary hypothesis for PFS per RECIST 1.1 by BICR. The secondary hypothesis for ORR per RECIST 1.1 by BICR will be evaluated by comparing pembrolizumab (MK-3475) to SOC using Stratified Miettinen and Nurminen method. The same stratification factors used for randomization (see Section 5.4) will be applied to the stratified log-rank test, stratified Cox model and the stratified Miettinen and Nurminen method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. There are no events of interest that warrant elevation as Tier 1 event in this study. Point estimates and 95% CIs for between-treatment comparisons via the Miettinen and Nurminen method will be provided for Tier 2 safety endpoints; only point estimates by treatment group will be provided for Tier 3 safety endpoints.

Interim Analyses	**Efficacy** One IA will be performed in this study. Results will be reviewed by an external data monitoring committee. The IA and final analysis (FA) are summarized below. Details are provided in Section 8.7. • IA: o Timing: [redacted] OS events and all subjects have been followed up for at least [redacted] months (estimated to be approximately [redacted] months after the first subject is randomized). If OS events accrue slower than expected and fewer than [redacted] events are observed [redacted] months after the first participant is randomized, then the Sponsor may conduct the interim analysis at that time. o Testing: Inferential analyses for OS will be provided. If superiority of OS is declared, then inferential analysis for PFS will be conducted. Furthermore, if superiority of PFS is also declared then inferential analysis for ORR will be conducted. • FA: o Timing: [redacted] OS events and all subjects have been followed up for at least [redacted] months (estimated to be approximately [redacted] months after the first subject is randomized). If OS events accrue slower than expected and fewer than [redacted] events are observed [redacted] months after the first participant is randomized, then the Sponsor may conduct the final analysis at that time. The efficacy boundaries will be adjusted accordingly in such a situation. o Testing: Inferential analysis for OS will be provided if superiority is not declared at the IA. Note: If superiority of OS is declared at the FA, and not at the IA, the test statistics computed for PFS at the IA will be used to conduct inferential analysis. Similarly, the test statistics computed for ORR at the IA will be used to conduct inferential analysis if superiority of both OS and PFS is declared at the FA and not at the IA. **Safety:** Every 6 months since first subject is randomized.
Multiplicity	The type I error rate for this study is strongly controlled at 2.5% (one-sided) with full alpha allocated to the OS hypothesis. A group sequential approach will be used to allocate alpha between the interim and final analyses of OS. The study will be declared a success if OS is shown to be successful. If the statistical criterion for success in OS hypothesis is met at an interim analysis or final analysis, the key secondary endpoint of PFS will be tested at the alpha level determined by the alpha shifting schema that follow the graphical approach of Maurer and Bretz (2013) [73] as described in Section 8.8. Similarly, if the PFS hypothesis is successful, alpha will be shifted to the key secondary endpoint of ORR using the same graphical approach of Maurer and Bretz.

Sample Size and Power	The planned sample size is approximately 230 subjects. For the primary endpoint OS, the trial provides approximately [redacted] power to demonstrate that pembrolizumab (MK-3475) is superior to SOC at a one-sided 2.5% alpha-level, if the true underlying hazard ratio of OS is [redacted] For the key secondary endpoint PFS, the trial provides approximately [redacted] power to demonstrate that pembrolizumab (MK-3475) is superior to SOC at a one-sided 2.5% alpha-level, if the true underlying hazard ratio of PFS is [redacted] For the secondary endpoint ORR, the trial provides approximately [redacted] power to demonstrate that pembrolizumab (MK-3475) is superior to SOC at a one-sided [redacted] alpha-level, assuming response rate in the SOC arm is 15% and 20% true treatment difference between two arms.

8.2 Responsibility for Analyses/In-House Blinding

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

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IVRS. Although the trial is open label, analyses or summaries generated by randomized treatment assignment, or actual treatment received will be limited and documented. Further documentation will be provided in the sSAP. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment.

Planned IA is described in Section 8.7. The results of the IA will not be shared with the investigator prior to the completion of the study. Subject-level unblinding will be restricted to the external unblinded statistician and scientific programmer performing the IA, who will have no other responsibilities associated with the study.

Treatment-level results of the IA will be provided by the external unblinded statistician to the eDMC. The eDMC will serve as the primary reviewer of the treatment-level results and will make recommendations for discontinuation of the study or modification to an Executive Oversight Committee of the SPONSOR. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the eDMC Charter.

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

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0 – Objectives and Hypotheses.

The study will be declared a success if the primary endpoint OS is shown to be successful.

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

Primary

- **Overall Survival**

  Overall Survival is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of analysis will be censored at the date of last known contact.

Secondary

- **Progression-free Survival – RECIST 1.1 by BICR**

  Progression-free survival is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs earlier. See Section 8.6.1 – Statistical Methods for Efficacy Analyses for definition of censoring.

- **Objective Response Rate – RECIST 1.1 by BICR**

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

- **Duration of Response – RECIST 1.1 by BICR**

  For subjects who demonstrated confirmed CR or PR, response duration is defined as the time from the date of first response (CR or PR) until the date of first documented disease progression or death. Duration of response for subjects who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment.

- **Survival Proportion at 12 Months and 24 Months**

  The survival proportion at 12 months and at 24 months is defined as the Kaplan-Meier estimate of the survival function for OS at 12 months and 24 months respectively.

- **Proportion Progression-free survival at 6 Months and 12 Months – RECIST 1.1 by BICR**

  The proportion progression free survival at 6 months and at 12 months is defined as the Kaplan-Meier estimate of the survival function for PFS at 6 months and 12 months, respectively. The progression-free status is based on BICR per RECIST 1.1.

8.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.3.2 – Safety Endpoints.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The Intention-to-Treat (ITT) population will serve as the population for primary efficacy analysis. All randomized subjects will be included in this population. Subjects will be included in the treatment group to which they are randomized. The ITT population consists of all randomized subjects whether or not treatment was administered. Any subject who receives a treatment randomization number will be considered to have been randomized.

Details on the approach to handling missing data are provided in Section 8.6 – Statistical Methods.

8.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least 1 dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any subject who receives the incorrect study medication for 1 cycle but receives the correct treatment for all other cycles will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the subject is incorrectly dosed.

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

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

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

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8 – Multiplicity.

8.6.1.1 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model.

Since subjects in the SOC arm are expected to discontinue treatment earlier compared to subjects in the pembrolizumab arm, and they may switch to another anti PD-1 treatment following confirmation of PD, adjustment for the effect of crossover on OS may be performed based on recognized methods, [redacted] based on an examination of the appropriateness of the data to the assumptions required by the methods [74].

8.6.1.2 Progression-free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model.

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

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 2 sensitivity analyses with a different set of censoring rules will be performed. The first sensitivity analysis is the same as the primary analysis except that the data for any subject who misses more than 1 disease assessment (with or without a subsequent death or progression) are censored at the last disease assessment prior to missing visits. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of an anti-cancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for subjects without documented PD or death. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 12.

Table 12 Censoring Rules for Primary and Sensitivity Analyses of Progression-free Survival

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

Further details of sensitivity analyses will be described in the sSAP.

8.6.1.3 Objective Response Rate

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

8.6.1.4 Duration of Response

For subjects who demonstrate CR or PR, duration of response is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

Censoring rules for DOR are summarized in Table 13.

For each DOR analysis, a corresponding summary of the reasons responding subjects are censored will also be provided. Subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~5 months of the data cutoff date are considered

ongoing responders at the time of analysis. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 13 Censoring Rules for Duration of Response

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anti-cancer therapy, if any	Censor (non-event)
Death or progression after ≤1 missed disease assessments and before new anti-cancer therapy, if any	PD or death	End of response (event)
Note: A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

8.6.1.5 Summary of Efficacy Analysis Methods

Table 14 summarizes the primary analysis approach for primary and secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint.

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

Table 14 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Endpoint			
OS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Key Secondary Endpoints			
PFS per RECIST 1.1 by BICR	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule‡ • Sensitivity analysis 1‡ • Sensitivity analysis 2‡
ORR per RECIST 1.1 by BICR	Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered as non-responders.

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Response duration per RECIST 1.1 by BICR	Summary statistics using Kaplan-Meier method	All responders in ITT	Non-responders are excluded in analysis

† Statistical models are described in further detail in the text.

‡ Additional details are located in Table 12

8.6.2 Statistical Methods for Safety Analyses

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

Adverse Events

Adverse events will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and grouped system organ class. AEs will be graded by the investigator according to the CTCAE, version 4.0.

The analysis of safety results will follow a tiered approach (Table 15). The tiers differ with respect to the analyses that will be performed. Adverse experiences (specific terms as well as system organ class terms) that are not pre-specified as Tier 1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed.

Tier 1 Events

Safety parameters or adverse events of interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance. For this protocol, there are no Tier 1 events as acceptable and manageable safety/tolerability profile of pembrolizumab monotherapy has been established.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events using the Miettinen and Nurminen method, an unconditional, asymptotic method [75].

Membership in Tier 2 requires that at least 10% of subjects in any treatment group exhibit a specific AE; all other AEs will belong to Tier 3. The threshold of at least 10% of subjects was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of subjects would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, specific Grade 3 to 5 AEs (≥5% of subjects in 1 of the treatment groups) and specific SAEs (≥5% of subjects in 1 of the treatment groups) will be considered Tier 2 endpoints. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful

descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, any DRAE, any Grade 3 through 5 AE, any serious AE, any AE which is both drug-related and Grade 3 through 5, any AE that is both serious and drug-related, due to AE, discontinued due to an AE, and death that are not pre-specified as Tier 1 endpoints will be considered Tier 3 endpoints. Laboratory test toxicity grade shift from baseline is considered a Tier 3 event. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Table 15 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Specific Grade 3-5 AEs (incidence ≥5% of subjects in one of the treatment groups)	X	X
	Specific serious AEs (incidence ≥5% of subjects in one of the treatment groups)	X	X
	Specific AEs (incidence ≥10% of subjects in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Any SAE		X
	Any Grade 3-5 AE		X
	Any DRAE		X
	Any Serious and DRAE		X
	Any Grade 3-5 and DRAE		X
	Discontinuation due to AE		X
	Death		X
	Specific AEs, SOCs (incidence >0% of subjects in all of the treatment groups)		X
	Change from Baseline Results (lab toxicity grade)		X

Abbreviations: AE = adverse event; CI = confidence interval; DRAE = drug-related adverse event; SAE = serious adverse event; SOC = System Organ Class; X = results will be provided
† Adverse Experience references refer to both Clinical and Laboratory AEs.

8.6.3 Summaries of Baseline Characteristics, and Demographics

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

8.7 Interim Analyses

8.7.1 Efficacy Interim Analysis

There will be 1 IA for efficacy. The endpoints, timing, and purpose of the interim and final analyses are summarized in Table 16.

Table 16 Summary of Interim and Final Analyses Strategy for Efficacy

Analyses	Key Endpoints	Timing	Estimated Months after First Participant Randomized	Primary Purpose of Analysis
Efficacy IA	• OS • PFS • ORR	[redacted] OS events and all subjects have been followed up for at least [redacted] months. If OS events accrue slower than expected and fewer than [redacted] events are observed [redacted] is randomized, then the Sponsor may conduct the interim analysis at that time.	[redacted]	Demonstrate OS superiority. If successful, then test PFS superiority. If PFS is also successful, then test ORR superiority.
Efficacy FA	• OS	[redacted] OS events and all subjects have been followed up for at least [redacted] months. If OS events accrue slower than expected and fewer than [redacted] events are observed [redacted] months after the first participant is randomized, then the Sponsor may conduct the final analysis at that time.	[redacted]	Demonstrate OS superiority if not declared at IA.
Abbreviations: FA = final analysis; IA = interim analysis; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.				

In the event that superiority of OS is not declared at the IA, the study will continue to follow subjects for OS. The study may stop early if superiority of OS is declared at the IA. Decisions to stop the study early will be made by the Executive Oversight Committee, based on DMC recommendations.

Type I error control for the efficacy analyses as well as efficacy bounds are described in Section 8.8 Multiplicity.

8.7.2 Safety Interim Analyses

Table 17 Summary of Interim Analysis Strategy for Safety

Key Endpoints	Timing	Estimated Months after First Participant Randomized	Primary Purpose of Analysis
percentage of participants with AEs	Every 6 months since first subject is randomized	~ 6, 12, 18, 24, 30, 36, 42, 48, 54 months	Safety evaluation
Abbreviations: AE = adverse event.			

8.8 Multiplicity

8.8.1 Multiplicity Control for Efficacy Interim Analyses

The study uses the graphical method of Maurer and Bretz (2013) [73] to provide strong multiplicity control for multiple hypotheses. Figure 3 shows the initial one-sided α-allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses. This is further explained below.

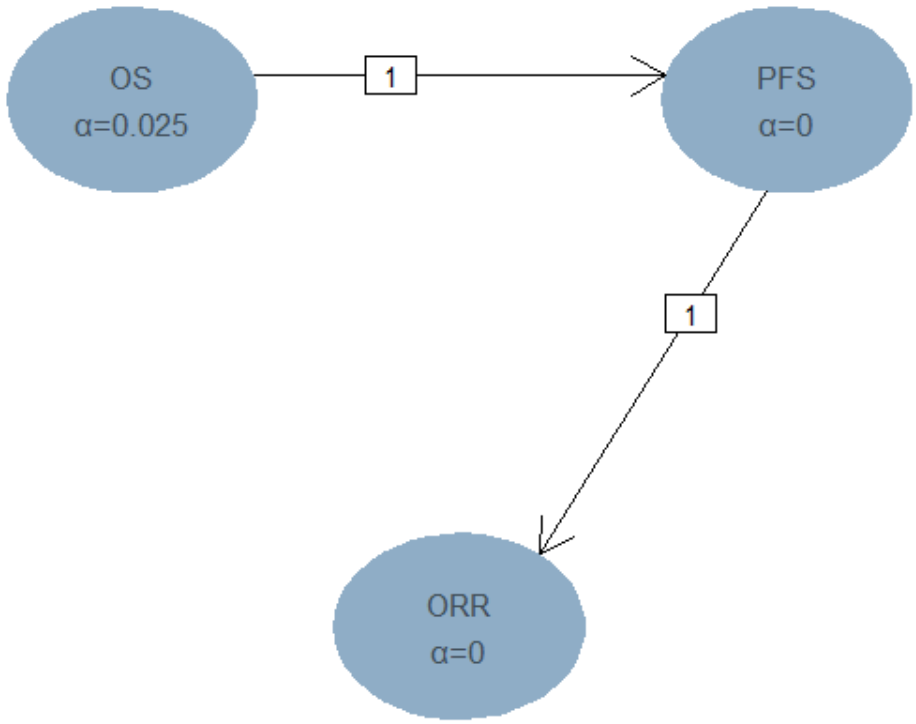

Figure 3 Multiplicity Strategy

8.8.1.1 Overall Survival

The OS hypothesis will be tested at the interim and the final analyses. The OS hypothesis will be tested at α=0.025. Table 18 below, demonstrates the bounds and boundary properties for OS hypothesis testing which were derived using a Lan-DeMets O'Brien-Fleming α spending function. The nominal α for testing is shown in the rows labeled "p (1-sided)". The approximate hazard ratio required to reach an efficacy bound is in the row labeled "HR at bound". The probability of crossing a bound is shown under the null hypothesis "P(Cross if HR=1)" and alternative hypothesis [redacted] Note that at the final analysis, these are the probabilities of crossing either at the interim or final analysis; e.g., the final row indicates that the total power to reject the null hypothesis for OS is [redacted] if the α -level for testing is 0.025. If the actual number of events at the OS analyses differ from those specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming spending function accordingly. If the OS hypothesis is rejected at any analysis, the corresponding α=0.025 level (1-sided) will be rolled over to the PFS test.

[redacted]

Abbreviations: HR=hazard ratio; IA=interim analysis.

8.8.1.2 Progression-Free Survival

The PFS hypothesis will be tested only once at the interim analysis. Note that if superiority of OS is declared at the final analysis and not at the interim analysis, the test statistics computed for PFS at the interim analysis will be used to conduct inferential analysis.

The PFS hypothesis will be tested at α=0.025 (if the OS null hypothesis is rejected). Table 19 below, analogous to the OS table explained above, shows the bound and boundary properties for the analysis of PFS. If the actual number of events at the PFS analysis differs from that specified in the table, the bound will be adjusted accordingly. If the PFS hypothesis is rejected, the α=0.025 level (1-sided) will be rolled over to the ORR hypothesis testing.

8.8.1.3 Objective Response Rate

ORR will be tested only once at the interim analysis. Note that, if superiority of OS is declared at the final analysis and not at the interim analysis, and furthermore superiority of PFS is also declared, the test statistics computed for ORR at the interim analysis will be used to conduct inferential analysis.

The ORR null hypothesis will be tested at α=0.025 (if both the PFS and OS null hypotheses are rejected). Power, as well as the approximate treatment difference required to reach the bound (ΔORR), are shown in Table 20, assuming underlying [redacted] and [redacted] response rates in the SOC and pembrolizumab arms, respectively.

8.8.2 Multiplicity Control for Safety Interim Analyses

To account for any multiplicity concerns raised by the DMC review of unplanned efficacy data when prompted by safety concerns, a sensitivity analysis for OS will be pre-specified in the sSAP. This analysis will be performed if requested by the DMC. However, DMC review of OS data beyond the planned efficacy analysis to assess the overall risk/benefit to study participants will not require multiplicity assessment typically associated with a planned efficacy IA because these analyses are not to declare a positive efficacy finding.

8.9 Sample Size and Power Calculations

Enrollment of approximately [redacted] subjects will occur over [redacted] months.

The OS hypothesis testing was designed for α=0.025 and power of [redacted] to detect a hazard ratio of [redacted] with [redacted] deaths at the final analysis. The duration of OS in the SOC arm is assumed to follow an exponential distribution with a median of 12 months based on historical

data. The assumed follow-up time after last participant enrolled is 30 months. An exponential dropout rate of 6% per year is assumed.

The PFS hypothesis testing was designed for α=0.025 and power of [redacted] to detect a hazard ratio of [redacted] with [redacted] PFS events at IA. The duration of PFS in the SOC arm is assumed to follow an exponential distribution with a median of 5 months based on historical data. The assumed follow-up time after last subject enrolled is 18 months. An exponential dropout rate of [redacted] per year is assumed.

The sample size of [redacted] for ORR testing at the α=0.025 level yields [redacted] power to detect a difference from an underlying [redacted] response rate in the SOC arm to [redacted] in the pembrolizumab arm.

8.10 Subgroup Analyses and Effect of Baseline Factors

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

- Age category (<65 versus ≥65 years)
- PD-L1 expression levels (CPS<10 vs. CPS ≥ 10)
- Liver metastasis(es): Present versus Absent
- Pembrolizumab (MK-3475) versus comparator therapies. Subjects will be analyzed according to the comparator identified by the site prior to randomization.

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above. In addition, a Forest plot will be produced, which provides the estimated point estimates and CIs for the treatment effect across the categories of subgroups listed above.

8.11 Compliance (Medication Adherence)

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

8.12 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.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 21.

Table 21 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Pembrolizumab (MK-3475) 50 mg	Lyophilized powder for IV injection/infusion	Provided centrally by the Sponsor
Pembrolizumab (MK-3475) 100 mg/4 mL	Solution for infusion	Provided centrally by the Sponsor; however, solution will not be supplied at initiation of the trial. It is considered a backup formulation.
Capecitabine 150 mg and 500 mg	Tablets	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee.
Gemcitabine 1000 mg	Lyophilized powder for IV infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee.
Docetaxel 80 mg/4 mL	Solution for infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee.
IV = intravenous Note: If the standard of care is locally sourced, the potency/strength that is available may be used		

All supplies indicated in Table 21 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 21 will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

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

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 7.1.4.4 – Future Biomedical Research will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

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

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens

will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Participants

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

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be

identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

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

12. Questions

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

13. References

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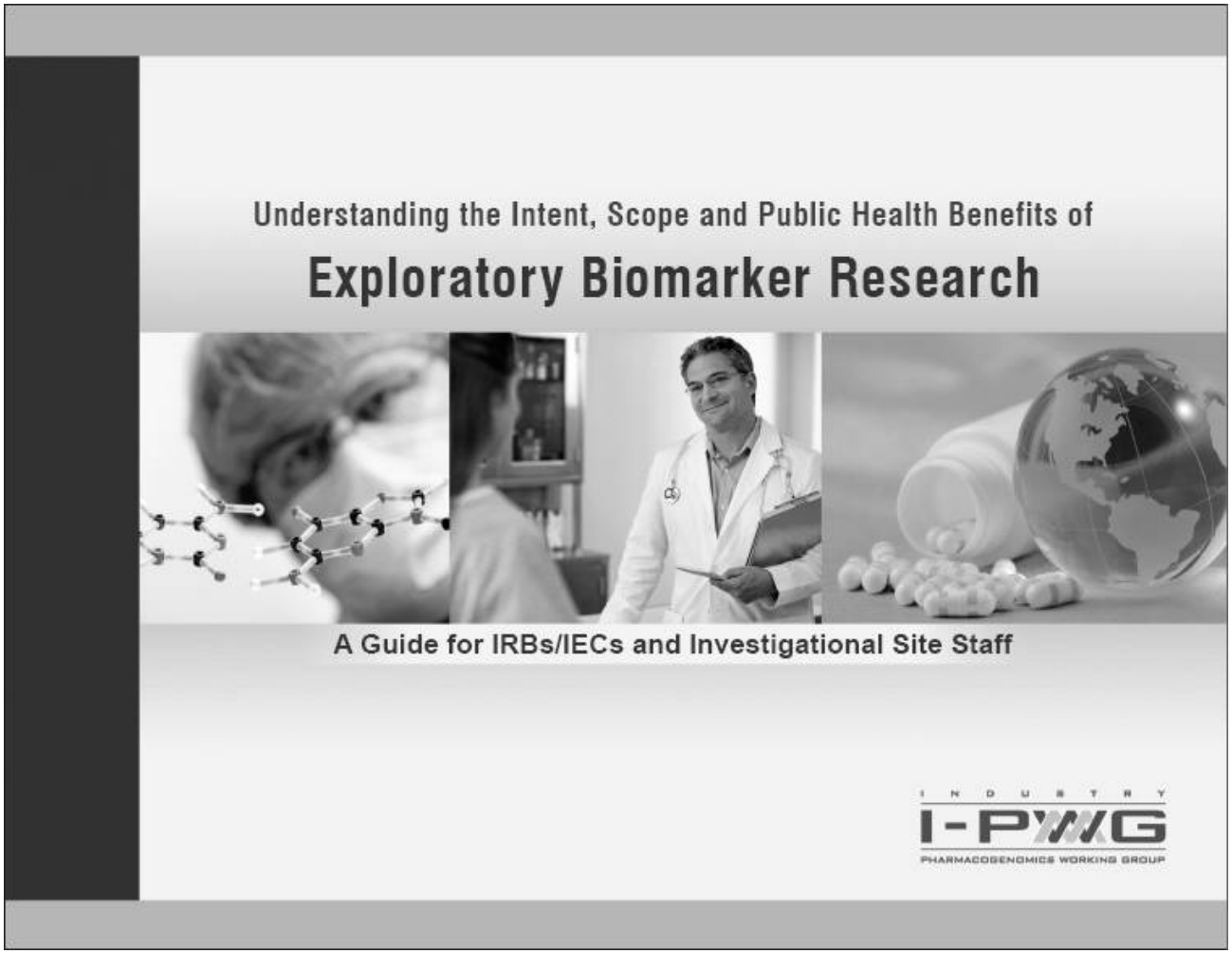
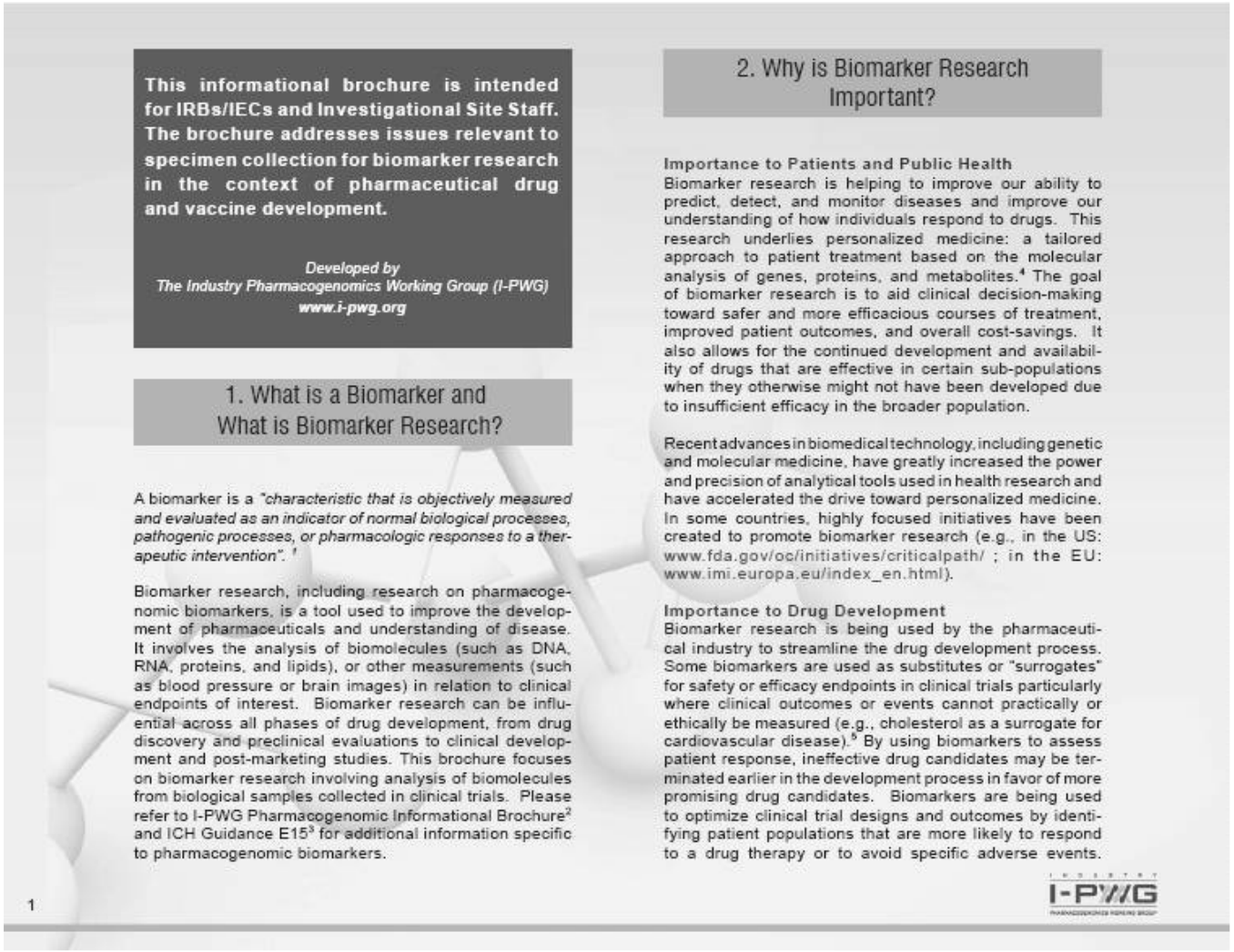
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

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





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

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

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

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

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

2. Why is Biomarker Research Important?

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

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

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

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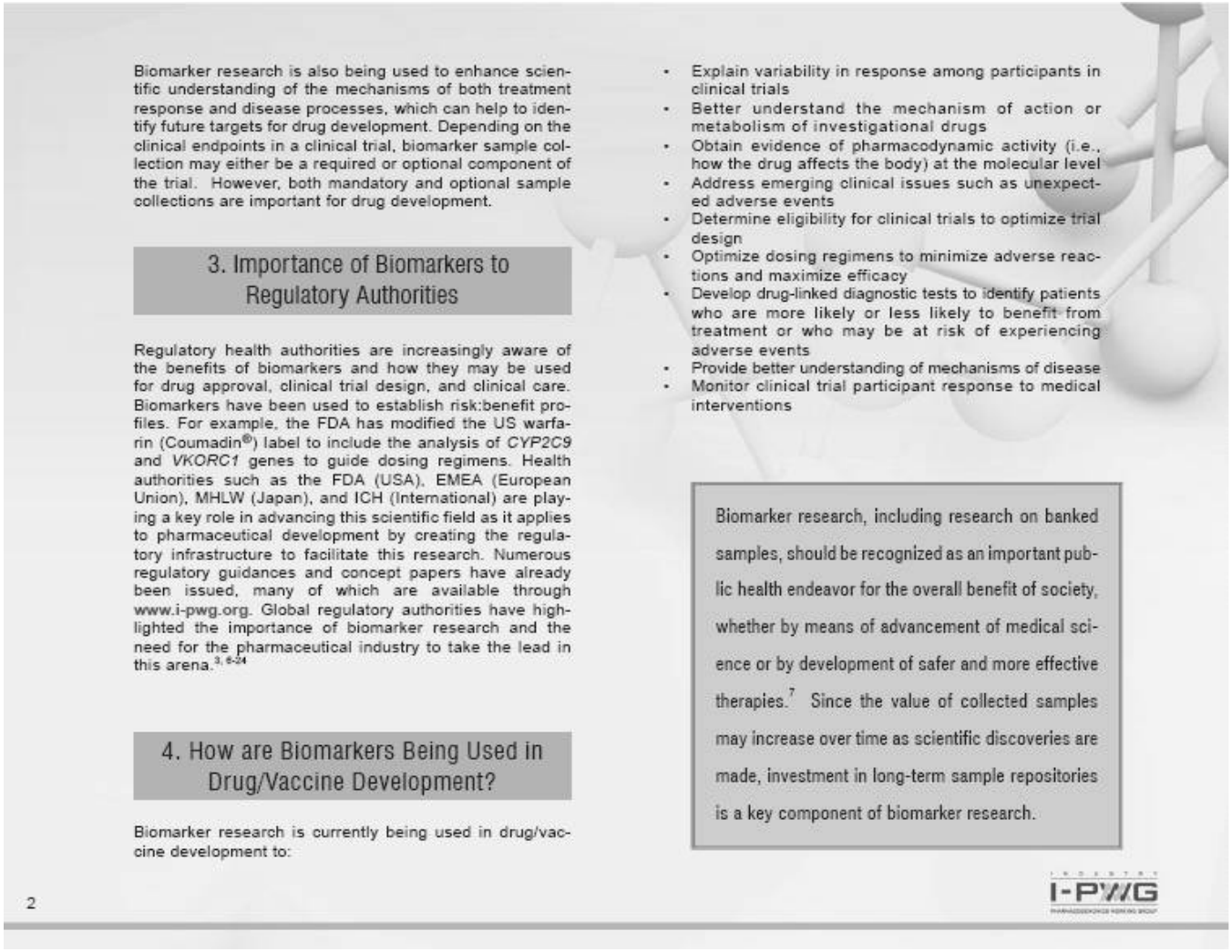

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]

4. How are Biomarkers Being Used in Drug/Vaccine Development?

Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.

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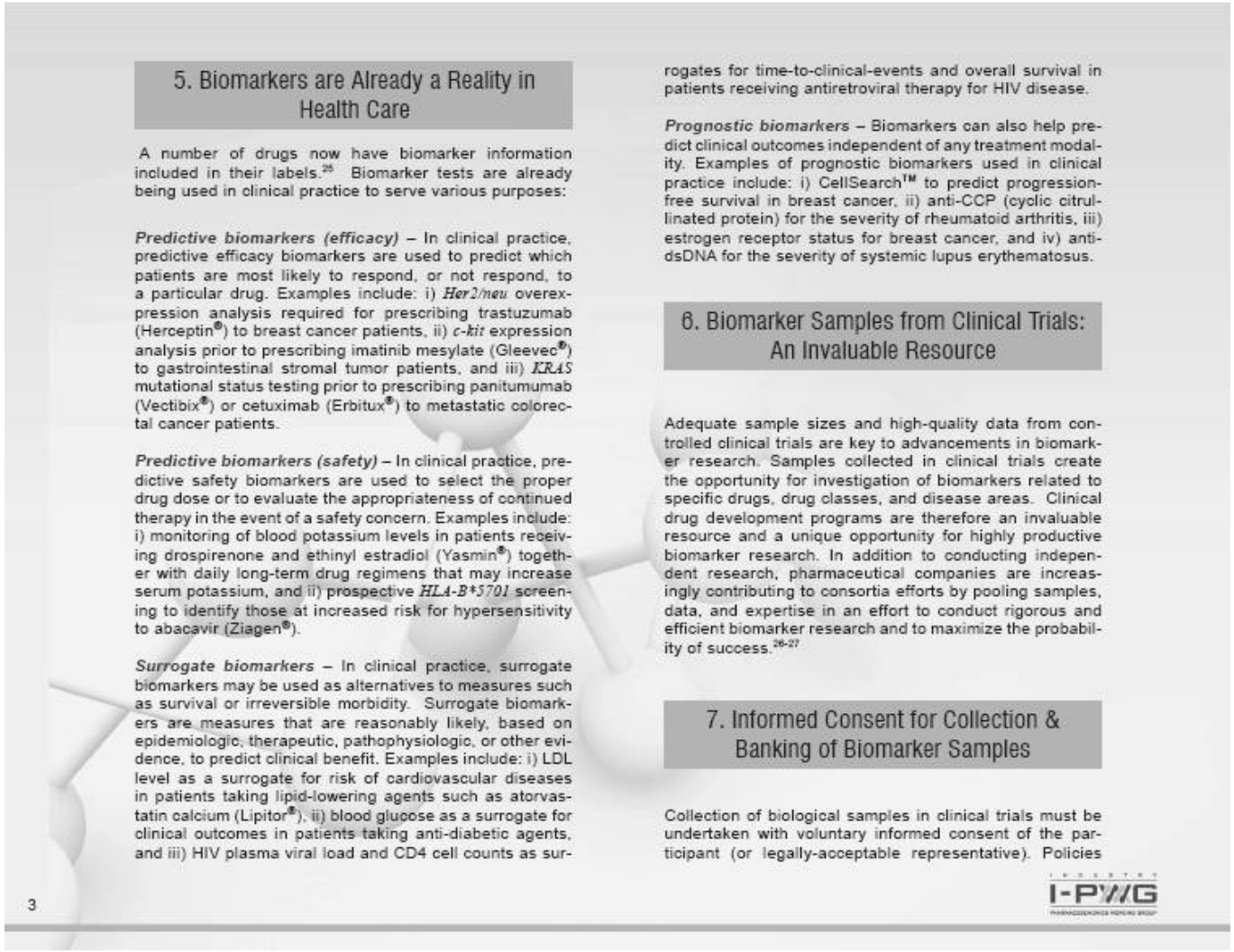

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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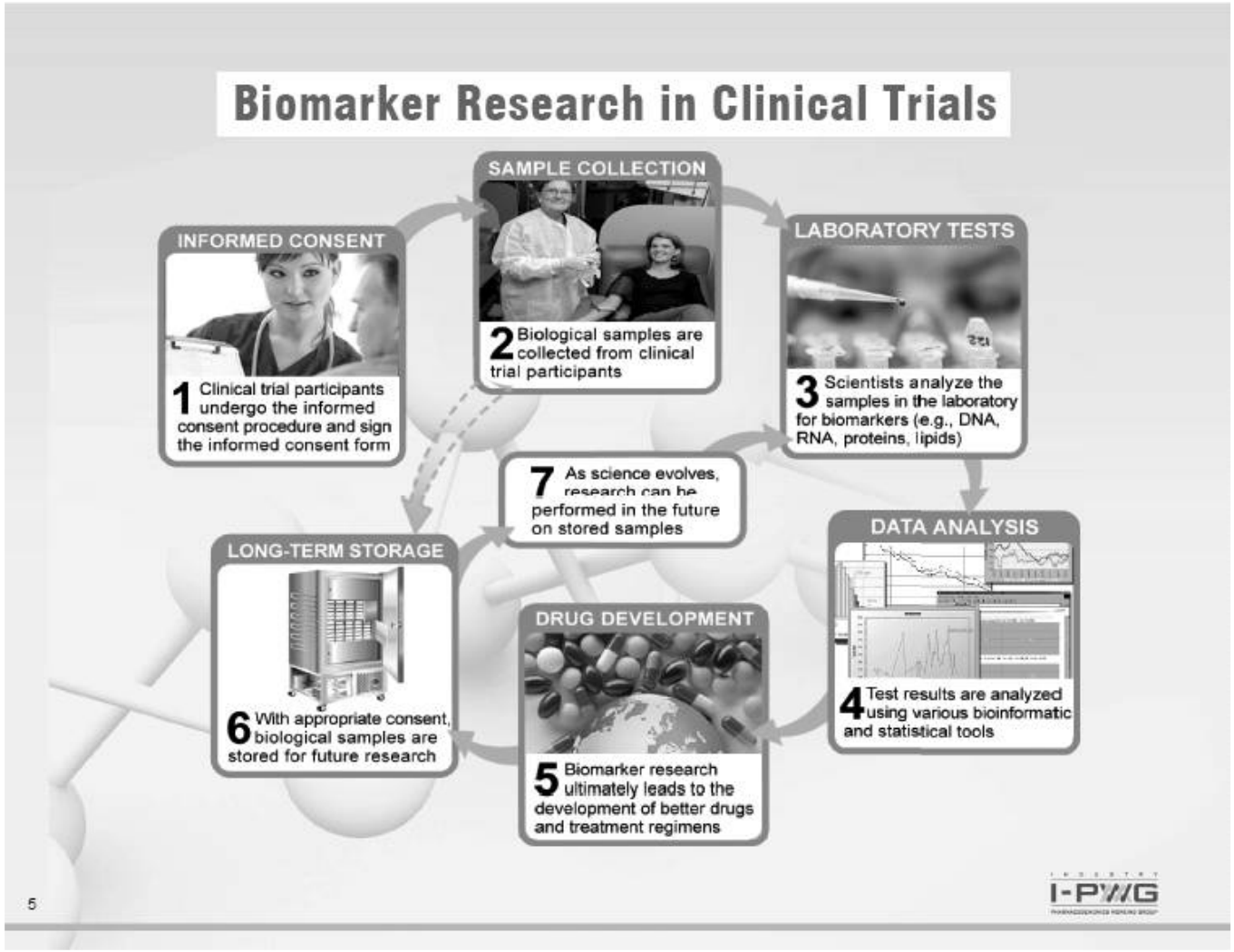
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the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

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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

14. Contributing authors

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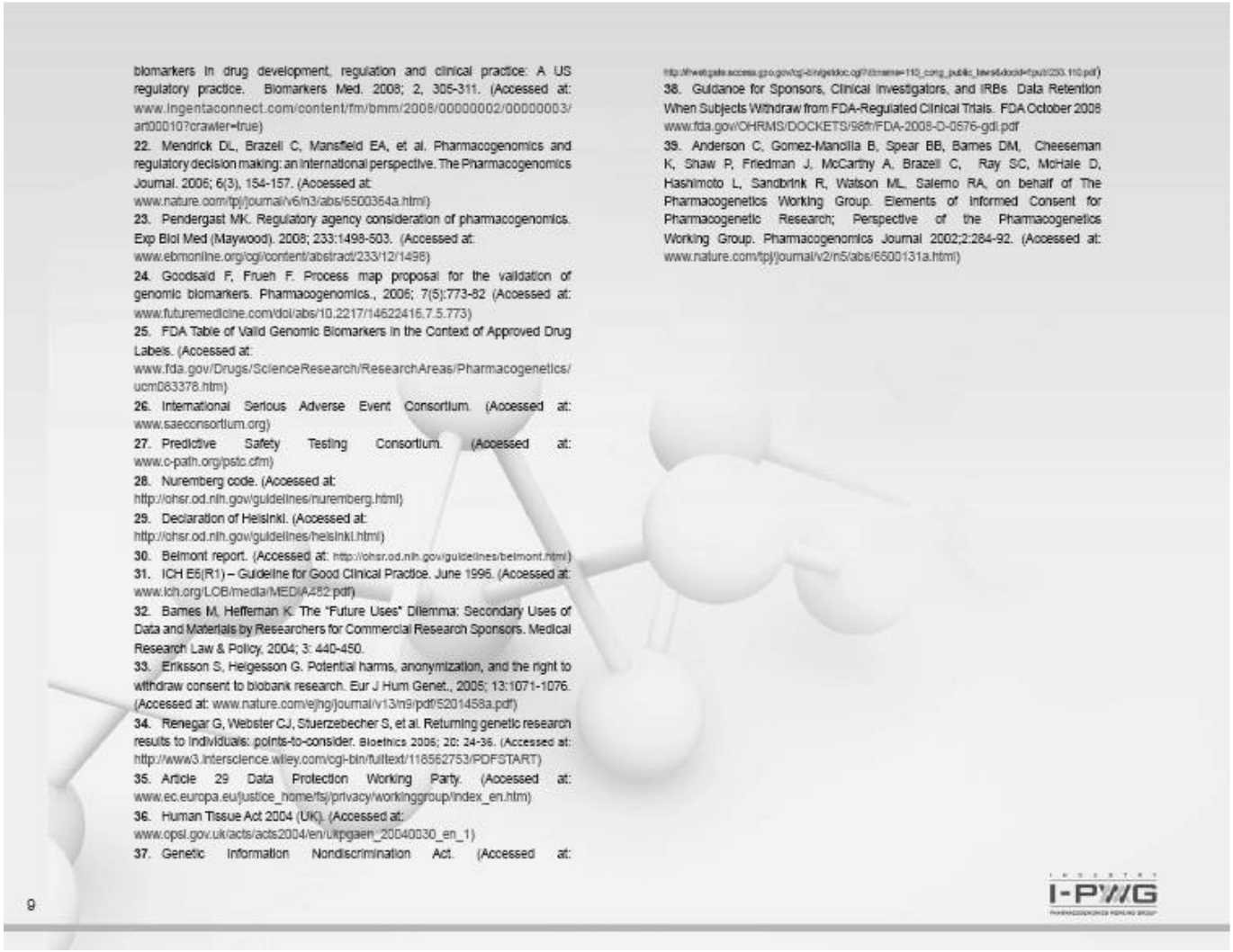

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12.4 Abbreviations

Abbreviation/Term	Definition
AE	adverse event
ADA	anti-drug antibodies
ADL	activities of daily living
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APaT	all patients as treated
aPTT	activated partial thromboplastin time
ASaT	all subjects as treated
AST	aspartate aminotransferase
BID	twice daily
BRAT	bananas, rice, apple sauce, and toast
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIV	central imaging vendor
CR	complete response
CRF	case report form
CrCl	calculated creatinine clearance
CSR	clinical study report
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
DILI	drug-induced liver injury
DKA	diabetic ketoacidosis
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DPD	dihydropyrimidine dehydrogenase
DRAE	drug-related adverse event
eCRF	electronic case report form
EBER	Epstein-Barr encoded small RNA
EBNA	Epstein-Barr nuclear antigen
EBV	Epstein-Barr virus
ECI	events of clinical interest
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eDMC	external Data Monitoring Committee
EOC	Executive Oversight Committee
ePRO	electronic patient-reported outcome
ERC	Ethics Review Committee
EuroQol	European Quality of Life
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
FSH	follicle-stimulating hormone

Abbreviation/Term	Definition
FT4	free thyroxine
GCP	Good Clinical Practice
GFR	glomerular filtration rate
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HLA	human leukocyte antigens
HPV	human papillomavirus
HR	hazard ratio
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHC	immunohistochemistry
INR	international normalized ratio
IO	immuno-oncology
irAEs	immune-related adverse events
IRB	Institutional Review Board
irRECIST	immune-related RECIST
ISH	in situ hybridization
ITSM	immunoreceptor tyrosine-based switch motif
IV	intravenous
IVRS	interactive voice response system
IWRS	integrated web response system
LDH	lactate dehydrogenase
LMP	latent membrane protein
mAb	monoclonal antibody
MRI	magnetic resonance imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
NCI	National Cancer Institute
NPC	nasopharyngeal cancer
NPV	negative predictive value
NSAID	non-steroidal anti-inflammatory drug
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PFS	progression-free survival
PGt	pharmacogenetic
PI	Principal Investigator
PIN	Personal Identification Number
PK	pharmacokinetic
PO	by mouth
PPV	positive predictive value
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QW	every week

Abbreviation/Term	Definition
Q2W	every 2 weeks
Q3W	every 3 weeks
RBC	red blood cell
R/M	recurrent or metastatic
RECIST	response evaluation criteria in solid tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedures
SQ	subcutaneous
sSAP	supplemental statistical analysis plan
T1DM	type 1 diabetes mellitus
T3	triiodothyronine
TIL	tumor-infiltrating lymphocyte
TSH	thyroid-stimulating hormone
TTP	time to progression
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

12.5 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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

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

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

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

RECIST version 1.1* will be used in this study for assessment of tumor response. Although RECIST 1.1 references to maximum of 5 target lesions in total and 2 per organ, Merck allows maximum of 10 target lesions in total and 5 per organ. After initial disease progression, tumor response assessment will be per irRECIST (see Section 7.1.5.1.6).

While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging modality in this study.

* As published in the European Journal of Cancer:

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

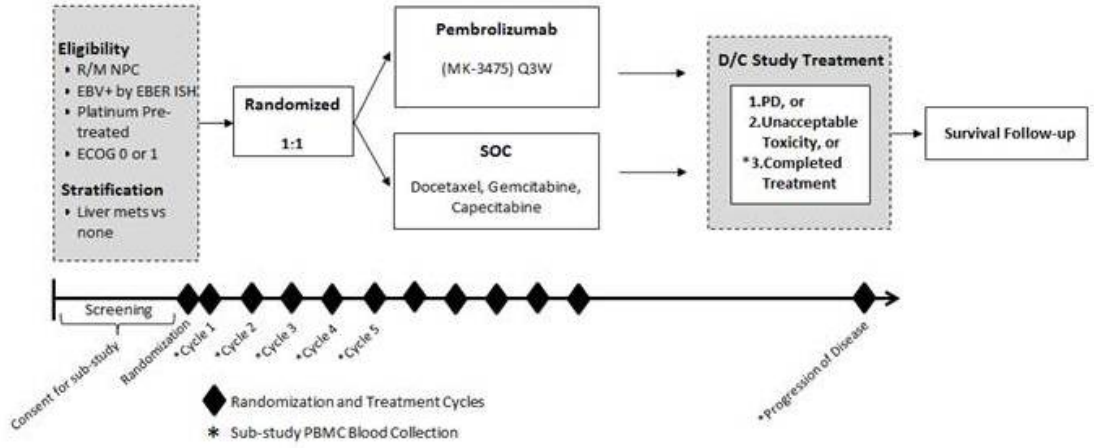
12.8 List of Strong CYP3A4 Inhibitors

For subjects receiving docetaxel, avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole).

Taxotere (docetaxel) Prescribing Information, 12/2013.

12.9 Optional Sub-Study Trial

12.9.1 Optional Sub-Study Trial Diagram



12.9.2 Optional Sub-Study Trial Flow Chart

Details regarding the procedures listed in this table are outlined in Section 7.0.

Trial Period:	Screening Phase	Treatment Cycles (3-Week Cycles)						End of Treatment	Post-Treatment Visits		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 6 cycles 5	6	Discon	Safety Follow-up	Efficacy Follow Up	Survival Follow-up[a]
Scheduling Window (Days)[b]:	-30 to -1	+3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose	Every 6 weeks post discon	Every 12 weeks
Administrative Procedures											
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Subject Identification Card	X										
Laboratory Procedures performed for translational sub-study											
Blood collection[c]		X	X	X	X	X[d]		X[d]			

a. After documented disease progression, or the start of new anti-cancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).
b. In general, the window for each visit is ± 3 days unless otherwise noted.
c. Details for collection can be found in Section 7.1.4, Laboratory Procedures/Assessments.
d. Blood collection for the sub-study will occur at Cycle 5 and at the time of disease progression. If disease progression occurs after Cycle 80 Day 1, a sample should not be collected at the time of disease progression.

12.10 Contraceptive Guidance

12.10.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

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

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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 FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or 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.

12.10.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
Progestogen-only subdermal contraceptive implant[b,c] IUS[c,d] Non-hormonal IUD Bilateral tubal occlusion
Azoospermic partner (vasectomized or secondary to medical cause) This 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. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence 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 intervention. 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.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] Male condoms must be used in addition to female participant hormonal contraception. [d] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

Supplemental Statistical Analysis Plan (sSAP)

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1. INTRODUCTION

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

MK-3475 KN -122 is titled A Phase III Trial of MK-3475 (Pembrolizumab) in Platinum Pre-treated, Recurrent/Metastatic Nasopharyngeal Cancer. The study started enrollment on 5th May, 2016 and completed enrollment on 28th May, 2018.

2. SUMMARY OF CHANGES

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
3.6.1.1	Statistical Methods for Efficacy Analyses	1. Added sensitivity analysis for OS based on ASaT population. 2. Added sensitivity analysis for OS which excludes subjects who initiate new PD-1/PD-L1 inhibitors. 3. Added sensitivity analysis for OS which censors subjects who initiate new PD-1/PD-L1 inhibitors at the start date of new PD-1/PD-L1 inhibitors.	To evaluate the impact on OS from non-treated subjects and also from subjects who started new PD-1/PD-L1 inhibitors.

3. ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 STATISTICAL ANALYSIS PLAN SUMMARY

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

Study Design Overview	A Phase III Study of Pembrolizumab (MK-3475) vs. Standard Chemotherapy in Subjects with Platinum Pre-treated, Recurrent or Metastatic Nasopharyngeal Cancer (KEYNOTE-122)

Treatment Assignment	This is an open-label study. Approximately 230 subjects will be randomized in a 1:1 ratio to receive pembrolizumab (MK-3475) or one of the three standard of care (SOC) treatments (Docetaxel, Gemcitabine or Capecitabine). The stratification factor used for this study is: Liver Metastasis (presence of any liver metastasis versus absence of all liver metastasis).
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Participants as Treated (ASaT) Patient Reported Outcome (PRO): PRO full analysis set (FAS)
Primary Endpoint	Overall Survival (OS)
Key Secondary Endpoints	1. Progression-free Survival (PFS) per RECIST 1.1 by BICR 2. Objective response rate (ORR) per RECIST 1.1 by BICR. 3. Duration of response (DOR) per RECIST 1.1 by BICR.
Statistical Methods for Key Efficacy	The primary hypothesis for OS will be evaluated by comparing pembrolizumab (MK-3475) to SOC using a stratified log-rank test. Estimation of the hazard ratio will be performed using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the non-parametric Kaplan-Meier method. The same approach will be applied to the secondary hypothesis for PFS per RECIST 1.1 by BICR. The secondary hypothesis for ORR per RECIST 1.1 by BICR will be evaluated by comparing pembrolizumab (MK-3475) to SOC using Stratified Miettinen and Nurminen method. The same stratification factors used for randomization (Liver Metastasis) will be applied to the stratified log-rank test, stratified Cox model and the stratified Miettinen and Nurminen method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. There are no events of interest that warrant elevation as Tier 1 event in this study. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons via the Miettinen and Nurminen method; only point estimates by treatment group are provided for Tier 3 safety parameters.

Interim Analyses	**Efficacy** One IA will be performed in this study. Results will be reviewed by an external data monitoring committee. The IA and final analysis (FA) are summarized below. Details are provided in Section 3.7. • IA: o Timing: 161 OS events and all subjects have been followed up for at least 18 months (estimated to be approximately 42.5 months after the first subject is randomized). If OS events accrue slower than expected and fewer than 161 events are observed ~44.5 months after the first participant is randomized, then the Sponsor may conduct the interim analysis at that time. o Testing: Inferential analyses for OS will be provided. If superiority of OS is declared, then inferential analysis for PFS will be conducted. Furthermore, if superiority of PFS is also declared then inferential analysis for ORR will be conducted. • FA: o Timing: 184 OS events and all subjects have been followed up for at least 30 months (estimated to be approximately 54.5 months after the first subject is randomized). If OS events accrue slower than expected and fewer than 184 events are observed ~56.5 months after the first participant is randomized, then the Sponsor may conduct the final analysis at that time. The efficacy boundaries will be adjusted accordingly in such a situation. o Testing: Inferential analysis for OS will be provided if superiority is not declared at the IA. Note: If superiority of OS is declared at the FA, and not at the IA, the test statistics computed for PFS at the IA will be used to conduct inferential analysis. Similarly, the test statistics computed for ORR at the IA will be used to conduct inferential analysis if superiority of both OS and PFS is declared at the FA and not at the IA. **Safety:** o Every 6 months since first subject is randomized. Results will be reviewed by an external data monitoring committee.
Multiplicity	The type I error rate for this study is strongly controlled at 2.5% (one-sided) with full alpha allocated to the OS hypothesis. A group sequential approach will be used to allocate alpha between the interim and final analyses of OS. The study will be declared a success if OS is shown to be successful. If the statistical criterion for success in OS hypothesis is met at an interim analysis or final analysis, the key secondary endpoint of PFS will be tested at the alpha level determined by the alpha shifting schema that follow the graphical approach of Maurer and Bretz (2013) [3] as described in Section 3.8. Similarly, if the PFS hypothesis is successful, alpha will be shifted to the key secondary endpoint of ORR using the same graphical approach of Maurer and Bretz.

Sample Size and Power	The planned sample size is approximately 230 subjects. For the primary endpoint OS, the trial provides approximately 92.9% power to demonstrate that pembrolizumab (MK-3475) is superior to SOC at a one-sided 2.5% alpha-level, if the true underlying hazard ratio of OS is 0.6 For the key secondary endpoint PFS, the trial provides approximately 98.9% power to demonstrate that pembrolizumab (MK-3475) is superior to SOC at a one-sided 2.5% alpha-level, if the true underlying hazard ratio of PFS is 0.55. For the secondary endpoint ORR, the trial provides approximately 94% power to demonstrate that pembrolizumab (MK-3475) is superior to SOC at a one-sided 2.5% alpha-level, assuming response rate in the SOC arm is 15% and 20% true treatment difference between two arms. Further details are provided in Section 3.9.

3.2 RESPONSIBILITY FOR ANALYSES/IN-HOUSE BLINDING

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

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IVRS. Although the trial is open label, analyses or summaries generated by randomized treatment assignment, or actual intervention received will be limited and documented. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment.

Planned IA is described in Section 3.7. The results of the IA will not be shared with the investigator prior to the completion of the study. Access to the allocation schedule for summaries or analyses for presentation to the eDMC will be restricted to an unblinded external statistician, and, as needed, an external scientific programmer performing the analysis, who will have no other responsibilities associated with the study.

Treatment-level results of the IA will be provided by the external unblinded statistician to the eDMC. The eDMC will serve as the primary reviewer of the treatment-level results and will make recommendations for discontinuation of the study or modification to an Executive Oversight Committee of the SPONSOR. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the eDMC Charter.

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

3.3 HYPOTHESES/ESTIMATION

Objectives and hypotheses of the study are stated in Section 3.0 of the protocol – Objectives and Hypotheses.

The study will be declared a success if the primary endpoint OS is shown to be successful.

3.4 ANALYSIS ENDPOINTS

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

3.4.1 Efficacy Endpoints

Primary

Overall Survival

Overall Survival is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of analysis will be censored at the date of last known contact.

Secondary

Progression-free survival (PFS) – RECIST 1.1 by BICR

Progression-free-survival is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first. See Section 3.6.1.1 for definition of censoring.

Objective Response Rate (ORR) – RECIST 1.1 by BICR

Objective response rate is defined as the proportion of the subjects in the analysis population who achieve a confirmed complete response (CR) or partial response (PR). Responses are based upon BICR per RECIST 1.1.

Duration of Response (DOR) – RECIST 1.1 by BICR

For subjects who demonstrated confirmed CR or PR, response duration is defined as the time from the date of first response (CR or PR) until the date of first documented disease progression or death. Duration of response for subjects who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment.

Exploratory

Exploratory endpoints of this study include PFS2; and PFS using immune-related RECIST (irRECIST) as assessed by BICR.

3.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.3.2 – Safety Endpoints, of the Protocol.

3.4.3 Patient Reported Outcome (PRO) Endpoints

Exploratory

Exploratory PRO endpoints as described in Section 4.2.3.3 of the Protocol will be evaluated.

PRO endpoints include mean score changes from baseline to the latest time point at which Completion rate of treated participants (CR-T) is approximately 60% and Compliance rate of eligible participants (CR-E) is approximately 80% based on blinded data review prior to the database lock as measured by:

- EQ-5D Health State Score using visual analogue scale (VAS)

3.5 ANALYSIS POPULATIONS

3.5.1 Efficacy Analysis Populations

The Intention-to-Treat (ITT) population will serve as the population for primary efficacy analysis. All randomized subjects will be included in this population. Subjects will be included in the treatment group to which they are randomized. The ITT population consists of all randomized subjects whether or not treatment was administered. Any subject who receives a treatment randomization number will be considered to have been randomized. Details on the approach to handling missing data are provided in Section 3.6 Statistical Methods.

3.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any subject who receives the incorrect study medication for one cycle but receives the correct treatment for all other cycles will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the subject is incorrectly dosed.

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

3.5.3 PRO Analysis Population

The PRO analyses are based on the PRO Full Analysis Set (FAS) population, defined as all randomized participants who have at least one PRO assessment available and have received at least one dose of the study intervention. Participants will be analyzed in the treatment group to which they are randomized.

3.6 STATISTICAL METHODS

This section describes the statistical methods that address the primary, secondary and exploratory objectives as stated in the protocol.

Statistical methods for efficacy analyses are described in Section 3.6.1. Statistical testing and inference for safety analyses are described in Section 3.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 3.8, Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses.

3.6.1 Statistical Methods for Efficacy Analyses

3.6.1.1 Overall Survival (OS)

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The same stratification factors used for randomization will be used as the stratification factors in both the stratified log-rank test and the stratified Cox model for the analyses in all subjects. In order to evaluate the robustness of the OS endpoint, comparison of OS based on ASaT population may be performed as a sensitivity analysis. ASaT population only includes subjects who are treated with study medication and subjects are analyzed according to actual treatment received.

Since subjects in the standard of care arm are expected to discontinue treatment earlier compared to subjects in the pembrolizumab arm, and they may switch to another anti PD-1 treatment following confirmation of progressive disease, adjustment for the effect of crossover on OS may be performed based on recognized methods, e.g. the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1989) [6], based on an examination of the appropriateness of the data to the assumptions required by the methods.

The RPSFT model provides a randomization-based estimate of the treatment effect corrected for bias introduced by crossover from the control arm to a new experimental treatment. The model is referred as rank preserving as it assumes that, for two subjects *i* and *j*, if subject *i* failed before subject *j* when both were on one treatment, then subjects *i* would also fail before subject *j* if both subjects took the same alternative treatment. This assumption may not be plausible as certain subjects are likely to benefit more or less than others from different treatments due to biological factors. However, testing for any violations of this assumption in real data may not be possible. The method also assumes an equal treatment effect for subjects switching to a treatment as for those initially allocated to receive it. For the RPSFT method, time post treatment-switch is adjusted using an accelerated failure time model, and then the resulting adjusted time to events is analyzed using the same methods as the primary analyses. The 95% confidence intervals of the hazard ratio for OS after adjustment of the new treatment effect will be provided at the final analysis.

In order to further evaluate the effect of crossover, 2 additional sensitivity analyses may be performed. In the first sensitivity analysis, any subjects who initiate new PD-1/PD-L1 inhibitors will be excluded from the ITT population for comparison of OS. In the second sensitivity analysis, any subjects who initiate new PD-1/PD-L1 inhibitors will be censored at the date of the initiation of the earliest PD-1/PD-L1 inhibitor.

It is very important to assess trial data, crossover mechanism, and treatment effect to determine which method is likely to be most appropriate to evaluate the crossover effect.

The Kaplan-Meier estimates of the OS rate at 12 months, 24 months and other time points of interest will also be estimated.

The proportional hazards assumption of the Cox model may be examined using both graphical and analytical methods for the primary OS analysis. The log[-log] of the survival function vs. time for OS will be plotted for the comparison between the experimental arm and the standard of care arm.

A comparison of two survival functions in the experimental arm and the standard of care arm will be provided based on weighted differences of Kaplan-Meier curves using the restricted mean survival time (RMST) method proposed by Uno, Tian, et al [7]. The RMST is simply the population average of the amount of event-free survival time experienced during a fixed study follow-up time. This quantity can be estimated by the area under the Kaplan-Meier curve up to the follow-up time. The clinical relevance and feasibility of conducting the study should be taken into account in the choice of follow-up time to define RMST (near the last observed event time assuming that the period of clinical interest in the survival experience is the whole observed follow-up time for the trial, but avoiding the very end of the tail where variability may be high) ; a description of the RMST as a function of the cutoff time may be of interest. The difference of two RMSTs for two treatment groups will be estimated and 95% confidence interval will be provided.

One assumption for stratified Cox proportional hazard model is that, the treatment hazard ratio (HR) is constant across the strata. In case of a strong deviation from the assumption, which can result in a notably biased and/or less powerful analysis, a sensitivity analysis may be performed based on a two-step weighted Cox model approach by Mehrotra (2012) [4]. The first step is to estimate the treatment effect (log-hazard ratio) for each stratum and then the stratum specific estimates are combined to make overall inference using strata sample size weights.

3.6.1.2 Progression-Free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The same stratification factors used for randomization will be used as the stratification factors in both the stratified log-rank test and the stratified Cox model for the analyses in all subjects.

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

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 2 sensitivity analyses with a different set of censoring rules will be performed. The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second sensitivity analysis considers initiation of new anticancer treatment, or discontinuation of treatment due to reasons other than complete response, whichever occurs later, to be a PD event for participants without documented PD or death. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 1.

The Kaplan-Meier estimates of the PFS rate at 6 months, 12 months and other time points of interest will also be estimated.

In case there is an imbalance between the treatment groups on disease assessment schedules or censoring patterns, we may also perform one additional PFS supportive analysis using Finkelstein (1986)’s likelihood-based score test [1] for interval-censored data, which modifies the Cox proportional hazard model for interval censored data. The interval will be constructed so that the left endpoint is the date of the last disease assessment without documented PD and the right endpoint is the date of documented PD or death, whichever occurs earlier.

Table 1 Censoring rules for Primary and Sensitivity Analyses of PFS

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

In case the proportional hazards assumption doesn't hold, the same approaches as for OS may be applied to PFS as appropriate. For example, RMST method for testing the weighted difference of Kaplan-Meier curves and the two-step weighted Cox model to assess the treatment effect on progression free survival.

3.6.1.3 Objective Response Rate (ORR)

Stratified Miettinen and Nurminen's [5] method will be used for comparison of the objective response rates between the treatment groups. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be provided. The same stratification factors used for randomization will be used as the stratification factors in the analysis of all subjects. Sensitivity analyses will be performed for comparison of ORR based on investigator's assessment.

3.6.1.4 Duration of Response (DOR)

For subjects who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. Censoring rules for DOR are summarized in Table 2. DOR will be assessed using RECIST 1.1 separately by BICR and by investigator's assessment.

For each DOR analysis, a corresponding summary of the reasons responding subjects are censored will also be provided. Subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~5 months of the data cutoff date are considered ongoing responders at the time of analysis. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 2 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anti-cancer therapy, if any	Censor (non-event)
Death or progression after ≤1 missed disease assessments and before new anti-cancer therapy, if any	PD or death	End of response (event)
Note: A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

3.6.1.5 Analysis Strategy for Key Efficacy Endpoints

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 3.

Table 3 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint:			
OS	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT • All subjects	Censored at last known alive date
Key Secondary Endpoints:			
PFS (RECIST 1.1) by BICR	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT • All subjects	Censored according to rules in Table 1
ORR (RECIST 1.1) by BICR	Stratified Miettinen and Nurminen method	ITT • All subjects	Subjects with missing data are considered non-responders
DOR (RECIST 1.1) by BICR	Summary statistics using Kaplan-Meier method	All responders in ITT	Non-responders are excluded in analysis
Abbreviations: BICR = blinded independent central review; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors.			

The strategy to address multiplicity issues with regard to multiple treatment comparisons, multiple endpoints, multiple populations, and interim analyses is described in Section 3.6.5, Interim Analyses, and in Section 3.8, Multiplicity.

3.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 4). The tiers differ with respect to the analyses that will be performed. Adverse experiences (specific terms as well as system organ class terms) that are not pre-specified as Tier 1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed.

Safety parameters or adverse events of interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance. For this protocol, there are no Tier 1 events as acceptable and manageable safety/tolerability profile of pembrolizumab monotherapy has been established.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory and vital signs parameters that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for

between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

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

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, any DRAE, any Grade 3 through 5 AE, any serious AE, any AE which is both drug-related and Grade 3 through 5, any AE that is both serious and drug-related, due to AE, discontinued due to an AE, and death that are not pre-specified as Tier 1 endpoints will be considered Tier 3 endpoints. Laboratory test toxicity grade shift from baseline is considered a Tier 3 event. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Safety Analyses by Time Period or Exposure-Adjusted

Frequency of AE by time period from first dose (e.g., 0-3, 3-6, 6-12 and beyond 12 mos) may also be provided. In each time interval, the denominator is the number of patients at risk for the event during the particular time period, defined as participants who are event-free at the start of the interval.

To properly account for the potential difference in follow-up time between the study arms, which is expected to be longer in the pembrolizumab arm, AE incidence density adjusted for treatment exposure analyses may be performed as appropriate. Based on emerging external data, the supportive analysis strategy for safety parameters may be modified to improve the integrity and efficiency of the design. Should this happen, the change will be documented in supplemental SAP, if not in a protocol amendment, at the earliest time before any analysis of the data.

Time to Grade 3-5 AE

Time to Grade 3-5 AE will be summarized by treatment.

Table 4 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Specific Grade 3-5 AEs (incidence ≥5% of subjects in one of the treatment groups)	X	X
	Specific serious AEs (incidence ≥5% of subjects in one of the treatment groups)	X	X
	Specific AEs (incidence ≥10% of subjects in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Any SAE		X
	Any Grade 3-5 AE		X
	Any DRAE		X
	Any Serious and DRAE		X
	Any Grade 3-5 and DRAE		X
	Discontinuation due to AE		X
	Death		X
	Specific AEs, SOCs (incidence >0% of subjects in all of the treatment groups)		X
	Change from Baseline Results (lab toxicity grade)		X

Abbreviations: AE = adverse event; CI = confidence interval; DRAE = drug-related adverse event; SAE = serious adverse event; SOC = System Organ Class; X = results will be provided

† Adverse Experience references refer to both Clinical and Laboratory AEs.

Based on emerging external data, the supportive analysis strategy for safety parameters may be modified to improve the integrity and efficiency of the design.

3.6.3 Statistical Methods for the Exploratory Analyses of Progression-free Survival 2 (PFS2)

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

The analysis of PFS2 will be conducted using the same statistical methods as the primary analysis of PFS and OS, for example, the stratified log-rank test and Cox model.

3.6.4 Summaries of Baseline Characteristics and Demographics

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

3.6.5 Patient Reported Outcomes (PRO) Analysis

This section describes the planned analyses for the key PRO endpoints. As there is no formal hypothesis testing for PRO endpoints, nominal p-values will be provided for treatment comparisons of pembrolizumab vs. standard of care. No multiplicity adjustment will be performed.

3.6.5.1 PRO compliance summary

Completion and compliance of EQ-5D by visit and by treatment will be described. Numbers and percentages of complete and missing data at each visit will be summarized. An instrument is considered complete if at least one valid score is available according to the missing item rules outlined in the scoring manual for the instrument.

Completion rate of treated participants (CR-T) is defined as the number of treated participants who complete at least one item over the number of treated participants at each time point.

$$\text{CR-T} = \frac{Number\ of\ participants\ who\ complete\ at\ least\ one\ item}{Number\ of\ randomized(allocated)\ participants\ in\ the\ PRO\ analysis\ population}$$

The completion rate is expected to shrink in the later visit during study period due to the participants who discontinued early. Therefore, another measurement, Compliance rate of eligible participants (CR-E) will also be employed as the support for completion rate. CR-E is defined as the number of treated participants who complete at least one item over number of eligible participants who are expected to complete the PRO assessment, not including the participants missing by design such as death, discontinuation, translation not available.

$$\text{CR-E} = \frac{Number\ of\ participants\ who\ complete\ at\ least\ one\ item}{Number\ of\ eligible\ participants\ who\ are\ expected\ to\ complete}$$

The reasons of non-completion and non-compliance will be provided in supplementary table:

- Completed as scheduled
- Not completed as scheduled
- Off-study: not scheduled to be completed.

In addition, reasons for non-completion as scheduled of these measures will be collected using "miss_mode" forms filled by site personnel and will be summarized in table format. The schedule (study visits and estimated study times) and mapping of study visit to analysis visit for PRO data collection is provided in the Table 5.

Table 5 PRO Data Collection Schedule and Mapping of Study visit to Analysis Visit

Treatment Week	Week 0 (Baseline)	Week 3	Week 6	Week 12 to Week 42 (Every 6 weeks)	Week 48
Day	1	22	43	Week number *7+1	337
Range (relative day to study)	[-7, 7]	[8, 32]	[33, 63]	[Week number*7-20, week number*7+21]	[316, 357]

3.6.5.2 Mean Change from Baseline

Based on blinded data review, weeks 12 and 18 were determined to be the latest time point at which CR-T is approximately 60% and CR-E is approximately 80% and will be used for the mean change from baseline analysis.

To assess the treatment effects on the PRO score change from baseline in the EQ-5D VAS outcome, a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [2] will be used. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline and the values observed at each post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will include the PRO score as the response variable, and treatment by study visit interaction, and stratification factors used for randomization as covariates. The cLDA model is specified as follows:

$$E(Y_{ijt}) = \gamma_0 + \gamma_{jtI} I(t > 0) + \beta X_i, j = 1,2,,3,..,n;\ t = 0,1,2,3,..k$$

where Y_{ijt} is the PRO score for subject i, with treatment assignment j, at visit t, γ_0 is the baseline mean for all treatment groups, γ_{jt} is the mean change from baseline for treatment group j at time t, X_i is the stratification factor (binary) vector for this participant, and β is the coefficient vector for stratification factors. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The cLDA model implicitly treats missing data as missing at random (MAR).

The treatment difference in terms of least square (LS) mean score change from baseline to the time point as specified at the beginning of this section will be estimated from this model, together with 95% CI and nominal p-value. In addition, model-based LS mean score with 95% CI will be provided by treatment group and study visit.

In addition, plots for the empirical mean score change from baseline across time till Week 48 will be provided.

3.7 INTERIM ANALYSES

3.7.1 Safety Interim Analyses

Safety interim analyses will be conducted every 6 months after the first subject is randomized. eDMC will review the unblinded safety summaries from these analyses and make appropriate recommendations.

Table 6 below provides a summary of the safety interim analyses.

Table 6 Summary of Interim Analysis Strategy for Safety

Key Endpoints	Timing	Estimated Months after First Participant Randomized	Primary Purpose of Analysis
percentage of participants with AEs	Every 6 months since first subject is randomized	~ 6, 12, 18, 24, 30, 36, 42, 48, 54 months	Safety evaluation
Abbreviations: AE = adverse event.			

3.7.2 Efficacy Interim Analyses

One interim analysis is planned in addition to the final analysis for this study. For the interim and final analyses, all randomized participants will be included. Results of the interim analyses will be reviewed by the DMC. Details of the boundaries for establishing statistical significance with regard to efficacy are discussed further in Section 3.8

The analyses planned, endpoints evaluated, and drivers of timing are summarized in Table 7.

Table 7 Summary of Interim and Final Analyses Strategy for Efficacy

Analyses	Key Endpoints	Timing	Estimated Months after First Participant Randomized	Primary Purpose of Analysis
Efficacy IA	• OS • PFS • ORR	161 OS events and all subjects have been followed up for at least 18 months. If OS events accrue slower than expected and fewer than 161 events are observed ~44.5 months after the first participant is randomized, then the Sponsor may conduct the interim analysis at that time.	~ 42.5 months	Demonstrate OS superiority. If successful, then test PFS superiority. If PFS is also successful, then test ORR superiority.
Efficacy FA	• OS	184 OS events and all subjects have been followed up for at least 30 months. If OS events accrue slower than expected and fewer than 184 events are observed ~56.5 months after the first participant is randomized, then the Sponsor may conduct the final analysis at that time.	~ 54.5 months	Demonstrate OS superiority if not declared at IA.
Abbreviations: FA = final analysis; IA = interim analysis; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.				

3.8 MULTIPLICITY

The overall type I error rate is strongly controlled at 2.5% (one-sided) with full alpha allocated to the OS hypothesis. A Lan-DeMets O'Brien-Fleming alpha-spending function is constructed to allocate alpha between the interim and final analyses of OS.

If the statistical criterion for success in OS hypothesis is met at an interim analysis or final analysis, the key secondary endpoint of PFS will be tested at the alpha level determined by the alpha shifting schema that follow the graphical approach of Maurer and Bretz (2013) [3]. Similarly, if PFS hypothesis is also successful then ORR hypothesis will be tested at the alpha level determined by the graphical approach of Maurer and Bretz (2013) [3] displayed below.

Figure 1 displays the multiplicity strategy diagram for the study.

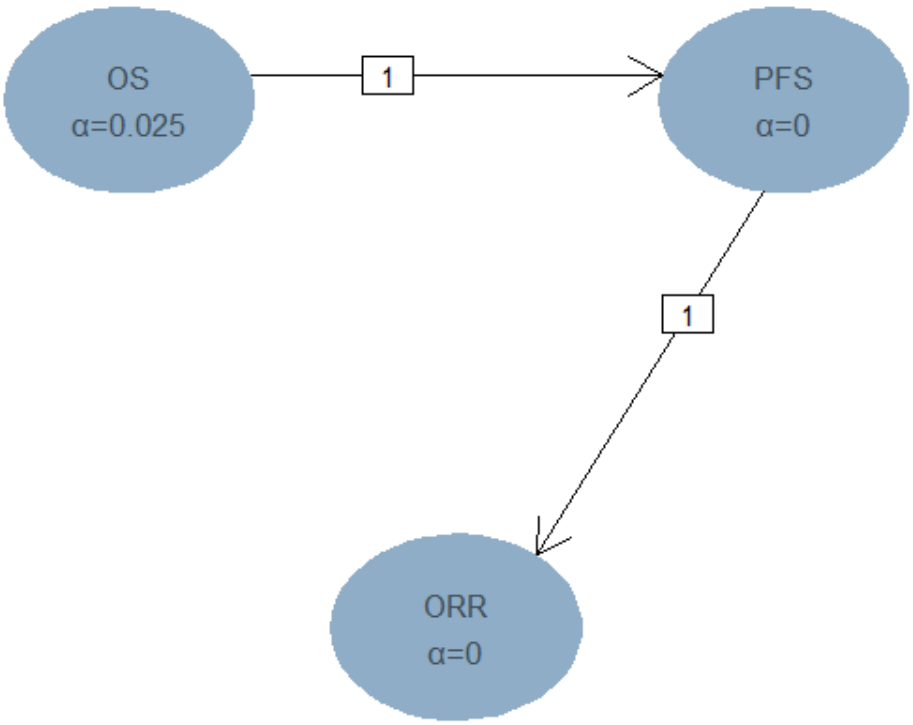

Figure 1 Multiplicity Strategy

3.8.1 Overall Survival Analyses

The OS hypothesis will be tested at the interim and the final analyses. The OS hypothesis will be tested at α=0.025. Table 8 below, demonstrates the bounds and boundary properties for OS hypothesis testing which were derived using a Lan-DeMets O'Brien-Fleming α spending function. The nominal α for testing is shown in the rows labeled "p (1-sided)". The approximate hazard ratio required to reach an efficacy bound is in the row labeled "HR at bound". The probability of crossing a bound is shown under the null hypothesis "P(Cross if HR=1)" and alternative hypothesis "P(Cross if HR=0.6)". Note that at the final analysis, these are the probabilities of crossing either

at the interim or final analysis; e.g., the final row indicates that the total power to reject the null hypothesis for OS is 92.9% if the α -level for testing is 0.025. If the actual number of events at the OS analyses differ from those specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming spending function accordingly. If the OS hypothesis is rejected at any analysis, the corresponding α=0.025 level (1-sided) will be rolled over to the PFS test.

Table 8 Efficacy Boundaries and Properties for OS Analyses.

Analysis	Value	α=0.025
IA: 87.5%	Z	2.13
N: 230	p (1-sided)	0.017
Events: 161	HR at bound	0.715
Month: 42.5	P(Cross) if HR=1	0.017
	P(Cross) if HR=0.6	0.867
Final	Z	2.046
N: 230	p (1-sided)	0.02
Events: 184	HR at bound	0.74
Month: 54.5	P(Cross) if HR=1	0.025
	P(Cross) if HR=0.6	0.929
Abbreviations: HR=hazard ratio; IA=interim analysis.		

3.8.2 Progression-Free Survival Analysis

The PFS hypothesis will be tested only once at the interim analysis. Note that if superiority of OS is declared at the final analysis and not at the interim analysis, the test statistics computed for PFS at the interim analysis will be used to conduct inferential analysis.

The PFS hypothesis will be tested at α=0.025 (if the OS null hypothesis is rejected). Table 9 below, analogous to the OS table explained above, shows the bound and boundary properties for the analysis of PFS. If the actual number of events at the PFS analysis differs from that specified in the table, the bound will be adjusted accordingly. If the PFS hypothesis is rejected, the α=0.025 level (1-sided) will be rolled over to the ORR hypothesis testing.

Table 9 Efficacy Boundaries and Properties for PFS Analysis.

Analysis	Value	α=0.025
IA	Z	1.96
N: 230	p (1-sided)	0.025
Events: 203	~HR at bound	0.759
Month: 42.5	P(Cross) if HR=1	0.025
	P(Cross) if HR=0.55	0.989

3.8.3 Objective Response Rate

ORR will be tested only once at the interim analysis. Note that, if superiority of OS is declared at the final analysis and not at the interim analysis, and furthermore superiority of PFS is also declared, the test statistics computed for ORR at the interim analysis will be used to conduct inferential analysis.

The ORR null hypothesis will be tested at α=0.025 (if both the PFS and OS null hypotheses are rejected). Power, as well as the approximate treatment difference required to reach the bound (ΔORR), are shown in Table 10, assuming underlying 15% and 35% response rates in the SOC and pembrolizumab arms, respectively.

Table 10 Possible Alpha-levels and Approximate ORR Difference Required to Demonstrate Efficacy for ORR

α	~ ΔORR	Power
0.025	10.4%	94.3%
Abbreviations: ORR = Objective response rate		

3.9 SAMPLE SIZE AND POWER CALCULATIONS

The study is event-driven and plans to randomize approximately 230 subjects with 1:1 ratio into the treatment groups of pembrolizumab and standard of care treatments, stratified by liver metastasis (present vs. absent).

One interim efficacy analysis is planned in this study. A Lan-DeMets O'Brien-Fleming α spending function is constructed to implement group sequential efficacy boundaries for the OS hypothesis.

OS

Two OS analyses are planned; at interim analysis and the final analysis. At the time of the final analysis, it is expected that approximately 184 deaths will have been observed between both the treatment arms. The study has a 92.9% power to detect a hazard ratio of 0.6 in pembrolizumab vs. standard treatment at alpha = 2.5% (one-sided).

The OS sample size calculation is based on the following assumptions: 1) overall survival follows an exponential distribution with a median of 12 months in the standard treatment arm; 2) underlying hazard ratio is 0.6 for all subjects; 3) an enrollment period of 24.5 months; 4) at least 30 months follow-up; and 5) a yearly dropout rate of 6%.

PFS:

PFS hypothesis will be tested only once at the interim analysis. At the time of the PFS analysis it is expected that approximately 203 PFS events will have been observed between both the treatment arms. The study has a 98.9% power to detect a hazard ratio of 0.55 in pembrolizumab vs. standard of care treatments at alpha = 2.5% (one-sided).

The PFS sample size calculation is based on the following assumptions: 1) progression-free survival follows an exponential distribution with a median of 5 months in the standard of care treatments arm; 2) underlying hazard ratio is 0.55 for all subjects; 3) an enrollment period of 24.5 months; 4) at least 18 months follow-up at interim analysis; and 5) a yearly dropout rate of 10%.

ORR:

ORR hypothesis will be tested only once at the interim analysis. The sample size of 230 for ORR testing at the α=0.025 level yields 94.3% power to detect a difference from an underlying 15% response rate in the SOC arm to 35% in the pembrolizumab arm.

The sample size and power calculations were performed in the software EAST 6 and R (package "gsDesign").

3.10 SUBGROUP ANALYSES AND EFFECT OF BASELINE FACTORS

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

- Age category (<65 versus ≥65 years)
- PD-L1 expression levels (CPS<10 vs. CPS ≥ 10)
- Liver metastasis(es): Present versus Absent
- Pembrolizumab (MK-3475) versus comparator therapies. Subjects will be analyzed according to the comparator identified by the site prior to randomization.

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above. In addition, a Forest plot will be produced, which provides the estimated point estimates and CIs for the treatment effect across the categories of subgroups listed above.

3.11 COMPLIANCE (MEDICATION ADHERENCE)

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

3.12 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.

4. REFERENCES

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