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TITLE:

A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL)

IND NUMBER: 118604
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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 17	07-Dec-2022	To add language allowing eligible participants to enroll in an extension study, if available, following the end of MK-3475-087. To clarify that specific events will be collected as ECIs for 18 months from the date of the allogeneic transplant unless the trial closes earlier (Sweden-specific).
Amendment 16	05-Dec-2022	To add language allowing eligible participants to enroll in an extension study, if available, following the end of MK-3475-087. To clarify that specific events will be collected as ECIs for 18 months from the date of the allogeneic transplant unless the trial closes earlier.
Amendment 15	23-Aug-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address (Sweden-specific).
Amendment 14	23-Aug-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 13	17-May-2021	To update the dose modification and toxicity management guidelines for irAEs (Sweden-specific).
Amendment 12	19-Apr-2021	To update the dose modification and toxicity management guidelines for irAEs.
Amendment 11	24-Oct-2017	Added additional safety data collection (Sweden-specific).
Amendment 10	29-Sep-2017	Added clarification on allostem cell transplant data collection.
Amendment 9	01-Feb-2017	Added clarification on OS interim and posttreatment analyses (Sweden-specific).

Document	Date of Issue	Overall Rationale
Amendment 8	27-Jan 2017	Added clarification on efficacy interim and posttreatment analyses.
Amendment 7	15-Oct-2016	Clarified timing of efficacy analyses.
Amendment 6	13-Oct-2016	Clarified timing of efficacy analyses.
Amendment 5	25-Feb-2016	Revised statistical section and added safety updates (Sweden-specific).
Amendment 4	Not done	N/A
Amendment 3	21-Dec-2015	Revised statistical section and added safety updates.
Amendment 2	26-May-2015	Ensure language alignment with other protocols and CHMB recommendations.
Amendment 1	Not done	N/A
Original protocol	27-Feb-2015	N/A

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.10	Beginning and End of Trial Definition	Added language regarding extension study.	Revision to allow eligible participants to enroll in an extension study, if available, following the end of MK-3475-087.
7.1.5.4.1	Follow-up Post-allogenic Stem Cell Transplantation	Added parenthetical statement regarding the study closing early.	Revision to clarify that specific events will be collected as ECIs for 18 months from the date of the allogeneic transplant unless the trial closes earlier.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Minor administrative, formatting, grammatical, and typographical changes were made throughout the document to ensure clarity and accurate interpretation of the intent of the protocol.

1.0 TRIAL SUMMARY

Abbreviated Title	A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL)
Trial Phase	Phase II
Clinical Indication	**Cohort 1:** Subjects with relapsed/refractory classical Hodgkin lymphoma (cHL) who have **failed** to achieve a response or progressed after autologous stem cell transplant (auto-SCT) and have relapsed after treatment with or failed to respond to brentuximab vedotin post auto-SCT. **Cohort 2:** Subjects with relapsed/refractory classical Hodgkin lymphoma (cHL) **who were unable to achieve a CR or PR to salvage chemotherapy** and did not receive auto-SCT, but have relapsed after treatment with or failed to respond to brentuximab vedotin. **Cohort 3:** Subjects with relapsed/refractory classical Hodgkin lymphoma (cHL) who have failed to achieve a response to or progressed after auto-SCT and have not received brentuximab vedotin **post** auto-SCT. **These subjects may or may not have received brentuximab vedotin as part of primary treatment, or salvage treatment.**
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Cohorts 1, 2 and 3: pembrolizumab 200mg IV every three weeks
Number of trial subjects	Approximately 180 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 35 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, eligible subjects will receive treatment on Day 1 of each 3-week dosing cycle. Treatment with pembrolizumab will continue for up to 35 cycles (approximately 24 months) per subject or until documented confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. Subjects who attain a complete response (CR) may consider stopping trial treatment if they meet criteria for holding therapy. At the discretion of the investigator, these subjects will be eligible for retreatment if they experience disease progression, as long as they meet the criteria for retreatment and the trial is ongoing. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than disease progression 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. All subjects will be followed for overall survival until death, withdrawal of consent, or the end of the study.

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, single arm, multi-cohort, nonrandomized trial of pembrolizumab (MK-3475) in subjects with relapsed or refractory classical Hodgkin lymphoma: who have failed to achieve a response or progressed after auto-SCT and have relapsed after treatment with or failed to respond to brentuximab vedotin post auto-SCT (Cohort 1); who were unable to achieve a CR or PR to salvage chemotherapy and did not receive auto-SCT, but have relapsed after treatment with or failed to respond to brentuximab vedotin (Cohort 2); and subjects who have failed to respond to or progressed after auto-SCT and have not received brentuximab vedotin post auto-SCT. **These patients may or may not have received brentuximab vedotin as part of primary or salvage treatment** (Cohort 3).

Approximately 180 subjects will be enrolled in this trial to examine the safety and efficacy of pembrolizumab 200 mg fixed dose administered every 3 weeks (Q3W). Approximately 60 subjects will be enrolled in each of the cohorts. Adverse events will be monitored every three weeks throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment with pembrolizumab will continue up to 35 cycles (approximately 24 months) per subject or until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. Per the investigator's discretion subjects who attain an investigator-determined confirmed complete response (CR) may consider stopping trial treatment after receiving at least 24 weeks (8 cycles) of therapy. At least two doses must be received after CR is documented. These subjects will be eligible for retreatment after they have experienced disease progression at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial remains open (refer to Section 7.1.5.2.2 for further details).

After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events and events of clinical interest [ECIs] will be collected for 90 days after the end of treatment). Subjects who discontinue treatment for reasons other than disease progression 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. All subjects will be followed for overall survival until death, withdrawal of consent or the end of the study, whichever comes first.

The primary objectives of the trial are to determine safety, tolerability, and overall response rate (ORR) by independent central review (utilizing the IWG response assessment criteria per Cheson 2007) of pembrolizumab in subjects with relapsed and/or refractory classical Hodgkin Lymphoma. Secondary objectives include further analysis of various efficacy parameters (complete remission rate [CRR], progression free survival [PFS], overall survival [OS] and duration of response [DOR]). Response assessments, by independent central

review, utilizing the 5-point scale according to the Lugano Classification; analysis of PD-L1 expression and corresponding efficacy; changes in health related quality of life assessments, along with the relationship of candidate efficacy/resistance biomarkers and anti-tumor activity of pembrolizumab will be investigated as exploratory objectives.

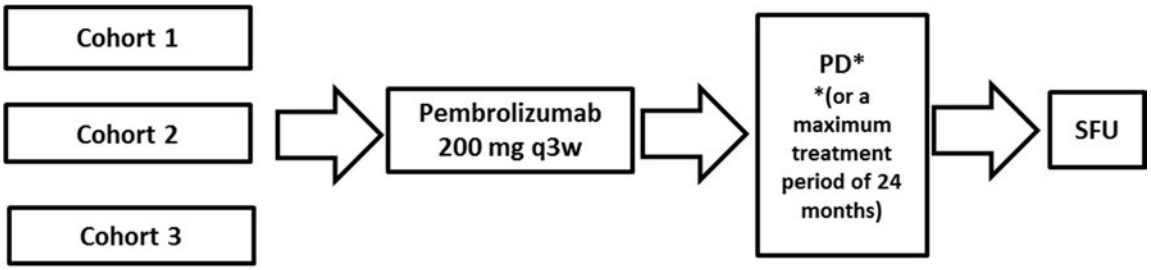
Unless specified otherwise, the statistical analyses will be conducted separately by cohort. In addition, a separate clinical study report may be issued for a single cohort if the actual enrollment rate among cohorts is markedly different.

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

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



N= 180; 3 Cohorts (60 subjects/cohort): read Entry Criteria in section 5.1

Cohort 1: who failed to achieve a response or progressed after auto-SCT and have relapsed after treatment with or failed to respond to brentuximab vedotin (BV)

Cohort 2: who were unable to achieve a CR or PR to salvage chemotherapy and did not receive auto-SCT and have relapsed after treatment with or failed to respond to BV

Cohort 3: who failed to respond to or progressed after auto-SCT and have not received BV post auto-SCT. These subjects may or may not have received BV as part of primary or salvage treatment.

*PD = progressive disease
SFU = survival follow-up

Figure 1 Trial Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Within each of, and pooled over, the 3 specified cohorts defined in Section 5.1.2. for subjects with relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL):

(1) **Objective:** To determine the safety and tolerability of pembrolizumab.

Within each of the 3 cohorts of subjects with R/R cHL:

(2) **Objective:** To evaluate the Overall Response Rate (ORR) of pembrolizumab by independent central review according to the International Working Group (IWG) response criteria (Cheson, 2007).

Hypothesis: Intravenous administration of single agent pembrolizumab will result in an ORR of greater than 20% in each of the three cohorts using IWG response criteria (Cheson, 2007) by independent central review.

3.2 Secondary Objective(s) & Hypothesis(es)

Within each of the 3 cohorts of subjects with R/R cHL:

(1) **Objective**: Evaluate ORR of pembrolizumab by investigator assessment according to the IWG response criteria; and additionally by independent central review using the 5-point scale according to the Lugano Classification.

(2) **Objective**: Evaluate Complete Remission Rate (CRR) of pembrolizumab by independent central review and by investigator assessment according to the IWG response criteria; and additionally by independent central review using the 5-point scale according to the Lugano Classification.

(3) **Objective**: Evaluate Progression Free Survival (PFS) and Duration of Response (DOR) of pembrolizumab by independent central review and by investigator assessment according to the IWG response criteria.

(4) **Objective**: Evaluate the Overall Survival (OS) of pembrolizumab.

3.3 Exploratory Objectives

Within each of, and potentially pooled over, the 3 cohorts of subjects with R/R cHL:

(1) **Objective:** To evaluate ORR, CRR, PFS and DOR for subjects who continue treatment with pembrolizumab beyond documented progression (see Section 8.6.1).

(2) **Objective:** To explore the PK profile of pembrolizumab (see Section 7.1.3.2.1)

(3) **Objective:** To evaluate changes in health-related quality-of-life assessments from baseline using the EORTC QLQ-C30 and EuroQol EQ-5D (see Section 4.2.3.2.1.2)

(4) **Objective:** To further evaluate pembrolizumab immunogenicity and exposure of the proposed dose and dosing regimen (see Section 4.2.3.3).

(5) **Objective**: To compare the extent of pre-pembrolizumab PD-L1 expression in tumor biopsies for pembrolizumab responders versus non-responders (see Section 4.2.3.2.1.1)

(6) **Objective:** To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of pembrolizumab utilizing pre- and post-treatment lymph node biopsies and blood sampling (see Section 4.2.3.4).

(7) **Objective:** To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome will be analyzed for association with clinical data collected in this study (See Section 4.2.3.4).

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

Pembrolizumab (previously known as MK-3475 and SCH 9000475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2 without ADCC or CDC activity.

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 pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and 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 (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling

molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [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, T regs 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 [13; 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 [13]. 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 (MEL) [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 and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [22; 23; 24; 25; 26; 27]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (refer to the IB).

In a phase 1/2 study of 135 patients with advanced melanoma treatment with pembrolizumab produced an ORR of 38% (95% CI, 25% to 44%). Many of the responses were durable, with a median duration that had not been reached after a median follow-up time of 11 months [49].

4.1.3 Ongoing Clinical Trials

Ongoing clinical trials are being conducted in advanced melanoma, non-small cell lung cancer, head and neck cancer, urothelial tract cancer, gastric cancer, and triple negative breast cancer and in a number of hematologic malignancies. For study details please refer to the IB.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

4.2.1.1 Hodgkin Lymphoma

Hodgkin lymphoma (HL) accounts for approximately 10 percent of all lymphomas and approximately 0.6 percent of all cancers diagnosed in the developed world annually [30]. In the United States, HL newly presents in over 8,400 individuals per year accounting for approximately 8.7% of all lymphomas in the US [31; 32]. Classical HL (CHL) is divided into four histologic subtypes: Nodular Sclerosis CHL, Mixed cellularity CHL, Lymphocyte rich CHL and Lymphocyte depleted CHL [33]. Although, HL is curable in 80% of patients diagnosed, new therapies are needed, especially for patients who present with advanced disease. The standard of care for patients with relapsed or refractory HL is salvage chemotherapy followed by autologous stem-cell transplantation (auto-SCT), which can induce long-term remissions in approximately 50% of patients [34; 35]. For patients who experience relapse or progressive HL within 1 year after auto-SCT, especially those who have received newer agents such as brentuximab vedotin (anti-CD-30), the prognosis is exceedingly poor with a median survival time of approximately 1.2 years [36]. Varied classes of novel agents have demonstrated activity in patients with relapsed/refractory HL who have failed auto-SCT. However, the median PFS is still remains less than 6 months [42;43;44;45]**.** Although brentuximab vedotin has demonstrated an ORR of 75%, median PFS is only 5.6 months requiring the development of additional therapies that will improve PFS in this patient population [35]. Patients with progressive disease after brentuximab vedotin have no available standard of care and represent an urgent unmet medical need.

4.2.1.2 Rationale for Evaluating anti-PD-1 Therapy in Hodgkin Lymphoma

Hematologic (Heme) malignancies are known to be responsive to a variety of immunotherapies. Allogeneic cellular therapy (bone marrow transplant and donor lymphocyte infusions) is effective in chronic myeloid leukemia (CML), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and many lymphomas. While data are currently limited, there is some indication that PD-L1/PD-1 biology may be an important mechanism of tumor immune escape in Heme malignancies.

High frequency of expression of PD-L1 by IHC and flow cytometry has been demonstrated in classic HL, and NHL tumor cells including primary mediastinal large B cell lymphoma (PMLBCL) [29]. A recent integrative analysis reveals selective 9p24.1 amplification, which includes the PD-L1 and PD-L2 loci, increased PD-L1 expression, and further induction via

JAK2 in nodular sclerosing HL and PMLBCL [38]. Furthermore, Epstein–Barr virus (EBV) infection of malignant Reed Sternberg cells, which is implicated in approximately 40% of cases of HL, contributes to overexpression of PD-L1 even in the absence of 9p24.1 amplification. The EBV latent membrane protein 1 exerts direct and indirect effects on PD-L1 promoter and enhancer elements leading to increased PD-L1 protein expression (Green et al, 2012, Clin Cancer Res).

A phase 1 clinical trial conducted in advanced hematologic malignancies using CT-011, showed clinical responses in 6 of 17 patients including HL and NHL patients [39]. Preliminary results from our ongoing Phase 1b study evaluating MK-3475 10 mg/kg every 2 weeks in patients with hematologic malignancies including myelodysplastic syndromes, HL, PD-L1-positive non-Hodgkin lymphoma, and multiple myeloma indicate a response rate of 53.3%, including a complete response rate of 20.0 % in heavily pretreated HL patients who had progressed after all lines of prior therapy including stem cell transplant [46].

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for Fixed Dose pembrolizumab

An open-label Phase I trial (KEYNOTE 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab (MK-3475). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab (MK-3475) showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). The maximum tolerated dose (MTD) was not reached.

In KEYNOTE 001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab (MK-3475) at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluation of 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab (MK-3475) at 2 mg/kg versus 10 mg/kg Q3W. The ORR was 26% (21/81) in the 2mg/kg group and 26% (20/76) in the 10 mg/kg group (FAS). The proportion of subjects with drug-related AE, grade 3-5 drug-related AE, serious drug-related AE, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group. In Cohort B3, advanced melanoma subjects (irrespective of prior ipilimumab therapy) were randomized to receive pembrolizumab (MK-3475) at 10 mg/kg Q2W versus 10 mg/kg Q3W. The ORR was 30.9% (38/123) in the 10mg/kg Q2W group and 24.8% (30/121) in the 10 mg/kg Q3W group (APaT). The proportion of subjects with drug-related AE, grade 3-5 drug-related AE, serious drug-related AE, death or discontinuation due to an AE was comparable between groups.

PK data analysis of pembrolizumab (MK-3475) administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q3W dosing schedule. Because Q3W dosing is more convenient for patients, Q3W dosing will be further studied.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab (MK-3475) in relapsed/refractory classical Hodgkin lymphoma is based on data in melanoma patients: 1) similar efficacy and safety of pembrolizumab (MK-3475) when dosed at either 2 mg/kg or 10 mg/kg Q3W, 2) the flat exposure-response relationships of pembrolizumab (MK-3475) for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (MK-3475) (as assessed by the population PK model).

These observations in melanoma patients may be extended to HL because MK-3475 is expected to drive anti-tumor effect through immune system activation, and HL and melanoma patients show similar pembrolizumab (MK-3475) driven activation of immune system as measured by ex-vivo cytokine release assay. Additionally, exposures of pembrolizumab (MK-3475) in HL patients (at 10 mg/kg Q2W) are comparable to those in melanoma patients. Based on these data, the dynamics of pembrolizumab (MK-3475) target engagement is not expected to vary meaningfully between HL and melanoma patients.

The choice of 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab (MK-3475) showing that the fixed dose of 200 mg Q3W will provide exposures that: 1) are optimally consistent with those obtained with 2 mg/kg dose Q3W, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. While the existing data suggest 200 mg Q3W as the optimal dose, dose modification may be considered if efficacy or toxicity with 200 mg Q3W is found to be unfavorable.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

The primary safety objective of this study is to characterize the safety and tolerability of pembrolizumab in subjects with relapsed or refractory Hodgkin Lymphoma. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by

subjects who have received pembrolizumab, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse events 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.

4.2.3.2 Efficacy Endpoints

The primary efficacy objective of this study is to evaluate the anti-tumor activity of pembrolizumab in subjects with relapsed or refractory classical Hodgkin lymphoma. The primary efficacy endpoint for Hodgkin lymphoma will be overall response rate (ORR) as assessed by independent central review per Cheson 2007 International Working Group (IWG) response criteria for malignant lymphoma [40]. ORR will also be assessed using the 5-point scale per the Lugano Classification [41] by independent central review as a secondary endpoint.

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

4.2.3.2.1 Exploratory

4.2.3.2.1.1 PD-L1 Expression

PD-L1 expression in tumor tissue will be characterized by immunohistochemistry to explore the relationship between tumor PD-L1 expression and response to treatment with pembrolizumab (MK-3475).

4.2.3.2.1.2 Patient Reported Outcomes

EORTC QLQ-C30 and eEQ-5D are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

EORTC QLQ-C30

EORTC QLQ-C30 was developed to assess the quality of life of cancer subjects. It has been translated and validated into 81 languages and used in more than 3,000 studies worldwide. It contains 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, pain) and additional single symptom items. It is scored on a 4-point scale (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much). The EORTC QLQ-C30 instrument also contains 2 global scales that use 7-point scale scoring with anchors (1 = very poor and 7 = excellent).

eEuroQoL-5D

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 QALYs. The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [37]. 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 will always be completed by subjects first before completing the EORTC QLQ-C30.

4.2.3.3 Pharmacokinetic Endpoints

Blood samples will be obtained to measure pharmacokinetics of serum pembrolizumab monotherapy. The pembrolizumab serum maximum concentration (C_{max}) and minimum concentration (C_{trough}) at planned visits and times will be summarized.

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

4.2.3.4 Planned Exploratory Biomarker Research

Biomarker research to identify factors important for pembrolizumab therapy may be pursued. For example, pre- and post-dose bone marrow biopsies/aspirates, lymph node biopsies and blood samples from this study may undergo flow cytometric, proteomic, genomic, and transcriptional analyses at a central laboratory. Lymph node biopsies and blood samples will be evaluated using DNA sequencing. Utilizing both pre- and post-treatment tumor biopsies and/or blood samples (serum or plasma), change in baseline of candidate biomarkers will also be assessed using Nanostring/RNAseq for gene expression as well as Nanostring for miRNA profiling.

Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab therapy and other immunologic targets. In addition, biomarker assay characterization may be performed to evaluate factors important for the identification of biomarkers.

Assays may include but are not limited to:

Multiplex Flow Cytometric Analysis

Emerging data suggest that blockade of the PD-1/PDL-1 pathway results in enhanced T cell mediated immune response. To test the hypothesis that T cell activation mediated by pembrolizumab treatment correlates with clinical response, total T cell count and T cell subsets in peripheral blood, eg, Naïve, activated, memory and regulatory T cells, will be assessed pre- and post-dose and in both responders and non-responders. NK cells enumeration will also be performed pre- and post-dose in both responders and non-responders.

Transcriptional Analyses

mRNA expression profiling in archival material, lymph node samples, and blood samples will be completed to assess gene expression and to attempt to define a gene set critical for clinical response to pembrolizumab. The hypothesis to be tested is that pembrolizumab responders will exhibit a "stalled Cytotoxic T Lymphocyte (CTL)" response within the tumor reflected in the physical proximity between PD-1 and PD-L1 expression and the presence of an aborted (eg, weak but discernible) interferon-gamma transcriptional program will be detectable by profiling analyses. Global profiling will also be pursued.

Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (eg, IL-10).

Gene Sequencing

New data are emerging that suggest we can define certain tumor types as having high mutational burden. There is a potential that this hypermutated state may correlate with response to pembrolizumab therapy, and/or that the converse, 'hypomutated' state may correlate with non-response.

Genome-wide whole exome sequencing (WES) may be performed from archival material, lymph node samples, and blood samples to assess genomic events such as but not limited to mutational burden as well as to evaluate fusion and amplification events such as 9p24.1 amplification.

Planned Genetic Analysis

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

4.2.3.5 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of Future Biomedical Research are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. 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/vaccination 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. Based on results from the ongoing clinical studies, there is no contraindication to the continued clinical investigation of pembrolizumab.

In addition, beneficial effects of pembrolizumab have been seen in several trials to date. Publications of a significantly positive benefit/risk ratio have been reported for melanoma both in a single arm study encompassing nearly 1000 patients (KEYNOTE 001), which led to USFDA approval in September 2014, and in a randomized comparison to chemotherapy (KEYNOTE-002 – detailed in the IB). Additional potential benefits for Hodgkin Lymphoma are addressed in section 4.2.1.2 which details responses observed in KEYNOTE-013 trial; a multi-cohort Phase Ib study of which one cohort enrolled subjects with relapsed or refractory classical Hodgkin lymphoma (n = 31) that have failed, are ineligible for, or refused a stem cell transplant and have relapsed after treatment with or failed to respond to Brentuximab vedotin. Published results from this study indicate an overall response rate (ORR) of 65%, including a complete response rate (CRR) of 16%. In terms of safety, most adverse events

observed were Grade 1 and 2, which resolved with appropriate clinical management. No Grade 4-5 drug related adverse events (DRAEs) were reported, but two patients discontinued therapy due to a DRAE: Grade 2 pneumonitis, and Grade 3 nephrotic syndrome [47]. The present study, KEYNOTE-087 (ClinicalTrials.gov, NCT02453594), is a multicenter, single-arm, multicohort phase 2 study of pembrolizumab in 3 cohorts of patients. Among 210 treated patients in cohorts 1 (n = 69), 2 (n = 81), and 3 (n = 60), all patients had refractory disease or relapsed HL. Per blinded independent central review, the ORR was 69.0% (95% CI, 62.3% to 75.2%), and the CRR was 22.4% (95% CI, 16.9% to 28.6%). By cohort, ORRs were 73.9% for cohort 1, 64.2% for cohort 2, and 70.0% for cohort 3. Thirty-one patients had a response ≥ 6 months. With a median of 13 treatment cycles, the most common treatment-related AEs (TRAEs) were hypothyroidism (12.4%) and pyrexia (10.5%). The most common grade 3/4 TRAEs were neutropenia (2.4%), dyspnea (1%), and diarrhea (1%). Immune-mediated AEs (events with potentially drug-related immunologic causes regardless of treatment attribution) and infusion-related reactions were reported in 60 patients (28.6%), most commonly hypothyroidism (13.8%). Nine patients (4.3%) discontinued because of TRAEs (myocarditis, myelitis, myositis, pneumonitis, infusion-related reactions, cytokine release syndrome), and 26 patients (12.4%) experienced TRAEs resulting in treatment interruptions. Two patients died during follow-up as a result of septic shock and acute graft-versus-host disease, respectively; neither of these deaths were considered to be treatment related [48]. Taken together, the observed efficacy and safety data indicate that MK-3475 has the potential to alter the disease course in these RRHL patients and potentially prolong patient survival.

In conclusion, pembrolizumab demonstrates a very promising anti-cancer activity in relapsed or refractory Hodgkin Lymphoma patients with an acceptable safety profile compared to those of existing therapeutic options. On-going and planned studies will allow for a more comprehensive analysis of benefit/risk balance of pembrolizumab.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with relapsed or refractory de novo classical Hodgkin lymphoma of at least 18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

2. Be ≥18 years of age on day of signing informed consent.

3. Have relapsed* or refractory* de novo classical Hodgkin lymphoma *and* meet **one** of the following cohort inclusions:

   *Relapsed: disease progression after most recent therapy
   *Refractory: failure to achieve CR or PR to most recent therapy

   a. **Cohort 1:** Have failed to achieve a response or progressed after auto-SCT. Subjects must have relapsed after treatment with or failed to respond to brentuximab vedotin post auto-SCT.

   b. **Cohort 2:** Were unable to achieve a complete or a partial response to salvage chemotherapy and did not receive auto-SCT. Subjects must have relapsed after treatment with or failed to respond to brentuximab vedotin.

   c. **Cohort 3:** Have failed to achieve a response or progressed after auto-SCT and have not have received brentuximab vedotin **post** auto-SCT. Note: **These subjects may or may not have received brentuximab vedotin as part of primary treatment, or salvage treatment.**

4. Have measurable disease defined as at least one lesion that can be accurately measured in at least two dimensions with spiral CT scan. Minimum measurement must be > 15 mm in the longest diameter or > 10 mm in the short axis.

5. Be able to provide an evaluable core or excisional lymph node biopsy for biomarker analysis from an archival or newly obtained biopsy at Screening. In addition subjects **may** provide additional biopsy at Week 12 and at the time of discontinuation due to progression. 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 7.1.2.6.8 for an explanation.

6. Must have a performance status of 0 or 1 on the ECOG Performance Scale.

7. Must demonstrate adequate organ function as defined in Table 1; all screening labs should be performed within 7 days of treatment initiation.

Table 1 Lymphoma Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1000 / mcL
Platelets[b]	≥75,000 / mcL
Hemoglobin[b]	≥8 g/dL
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (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 ULN
AST (SGOT) and ALT (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 as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

[a] Creatinine clearance should be calculated per institutional standard.
[b] Hemoglobin and platelet requirements cannot be met by use of recent transfusion or growth factor support (G-CSF or erythropoietin) within **2** weeks prior to treatment initiation unless bone marrow infiltration by disease is documented, in which case red blood cell transfusion is allowed.

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

9. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of birth control as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

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

5.1.3 Subject Exclusion Criteria

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

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

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

3. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (ie, ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

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

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

   -Note: Subjects with ≤ Grade 2 neuropathy 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.

   -Note: Toxicity that has not recovered to ≤ Grade 1 is allowed if it meets the inclusion requirements for laboratory parameters defined in Table 1.

5. Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. (Subjects who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of GVHD.)

6. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

7. Has known clinically active CNS involvement.

8. Has active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement

therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment

9. Has a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis.

10. Has an active infection requiring intravenous systemic therapy.

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

12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

13. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

14. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

15. Has known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected).

16. Has received a live vaccine within 30 days prior to first dose.

5.2 Trial Treatment(s)

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

Table 2 Trial Treatment

Study Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
pembrolizumab	200mg	Q3W	IV Infusion	Day 1 of each treatment cycle	experimental

Trial treatment should begin on the day of randomization or as close as possible to the date on which the subject is allocated/assigned.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

All subjects will receive 200 mg via IV infusion Q3W. Details on the preparation and administration are provided in the Pharmacy Manual.

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

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

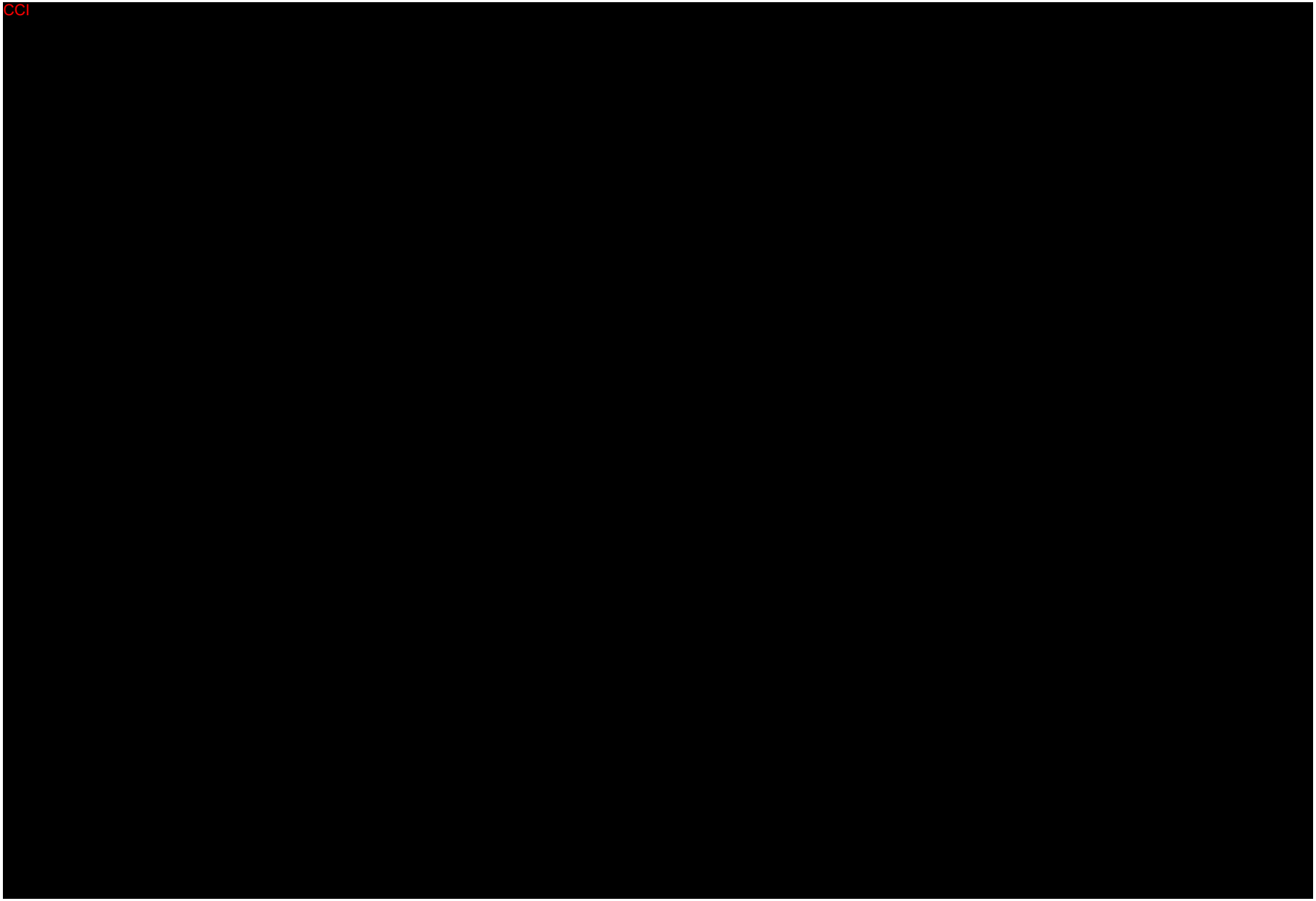
AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation 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.

Hematological Toxicity Management Guidelines for Pembrolizumab are provided in Table 3. Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 4.

CCI [redacted]

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Treatment Discontinuation (after consultation with Sponsor)
CCI [redacted]				N/A
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any life-threatening event*

CCI



CCI

[redacted]

CCI

[redacted]

5.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Interruptions from the treatment plan for greater than 3 days and up to 3 weeks may be allowed, but require consultation between the investigator and Sponsor, and written documentation of the collaborative decision on subject management.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 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 (ie, infusion time is 30 minutes: -5 min/+10 min).

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

5.2.3 Extent of Trial Treatment

- All subjects who experience a partial response or have stable disease may remain on treatment for up to 35 cycles (approximately two years) or until progression. Per the investigator's discretion subjects who achieve a CR are eligible to restart treatment upon documented progression as long as they meet eligibility criteria specified in the protocol (See Section 7.1.5.2.2).

- Subjects who achieve a CR and choose not to stop therapy may continue treatment for a total duration of 35 cycles (approximately two years).

5.2.4 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

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

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the 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. Subject may remain on anti-coagulation therapy as long as the PT or PTT is within therapeutic range of the intended use of anticoagulants

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

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Any need for radiotherapy should be considered progressive disease and result in discontinuation of study therapy.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and oral typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus

vaccines and are allowed; however intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

There are no prohibited therapies during the Post-Treatment Follow-up Phase. Subjects must be discontinued from the active follow-up phase if they begin a non-trial treatment for their underlying disease.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to refer to Section 5.2.1.2 for dose modification guidelines.

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

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

  - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.

  - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.

  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

  - For **T1DM** or **Grade 3-4** Hyperglycemia

    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):

    - In hyperthyroidism, non-selective beta-blockers (eg, propranolol) are suggested as initial therapy.

    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.

  - **Grade 3-4** hyperthyroidism

    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:

  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).

    - Treat with IV or oral corticosteroids

  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.

  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:

  - For **Grade 2** events, treat with corticosteroids.

  - For **Grade 3-4** events, treat with systemic corticosteroids.

  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 5 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 (eg, antihistamines, 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 one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, 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 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 4: Life-threatening; pressor or ventilatory support indicated	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. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug 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.

5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Therefore, non-pregnant, non-breastfeeding women may only be enrolled if they are willing to follow the Clinical Trial Facilitation Group (CTFG) Guidance (Final Version 2014-09-15, Sections 4.1 and 4.2) for highly effective birth control as outlined below, or are considered to be highly unlikely to conceive. Highly unlikely to conceive is defined as:

1. surgically sterilized, or

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

3. not heterosexually active for the duration of the study. Subjects should use birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods.

Such methods include:

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

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

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will be immediately discontinued from the trial treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the

Sponsor. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 7.2.2.

5.7.4 Use in Nursing Women

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

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 7.1.4 – Other Procedures.

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

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- Documented disease progression Note: Subjects may continue to receive trial treatment beyond progression if the subject meets the criteria outlined in Section 7.1.2.6.7.
- Unacceptable adverse experiences as described in Section 5.2.1.2, 5.6.1, and 7.2
- Intercurrent illness that prevents further administration of treatment
- Investigator’s decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

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

5.8.1 Discontinuation of Study Therapy after CR

Per investigator discretion subjects who attain a CR may consider stopping pembrolizumab after receiving a minimum of 8 cycles (approximately six months) of treatment with at least two doses since CR has been confirmed. Subjects who later experience disease progression will be eligible for retreatment with pembrolizumab at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.2.2.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

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

Upon study completion, subjects are to be discontinued and may be enrolled in an extension study using pembrolizumab monotherapy, if available.

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 Study Flow Chart: Cohorts 1, 2, and 3

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**									**End of Treatment**	**Post-treatment**		
						To be repeated beyond 9 cycles								
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	9	Discon	Post-Treatment Safety Follow-up[b]	Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days) [d]:	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Last Dose (±3 days)	Every 12 weeks (±7 days)	Every 12 weeks (±14 days)
Administrative Procedures														
Informed Consent	X[e]													
Informed Consent for Future Biomedical Research [f]	X													
Inclusion/Exclusion Criteria	X													
Subject Identification Card	X													
Demographics and Medical History	X													
Prior and Concomitant Medication Review[g]	X	X	X	X	X	X	X	X	X	X	X	X		
Obtain randomization number and study drug assignment using IVRS/IWRS[d]	X													
Pembrolizumab Administration[a]		X	X	X	X	X	X	X	X	X				
Post-study anticancer therapy status													X	X
Survival Status [c]		◄											►	X
Clinical Procedures/Assessments														
Review Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	X[i]	X	
Full Physical Examination[j]	X					X				X[j]	X[j]		X	
Directed Physical Examination[j]		X		X				X						
Vital Signs and Weight [k]	X	X	X	X	X	X	X	X	X	X	X		X	
12-Lead Electrocardiogram	X													
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X		X	
Pulmonary Function Test [l]	X													

Trial Period:	Screening Phase	Treatment Cycles [a]									End of Treatment	Post-treatment		
						To be repeated beyond 9 cycles								
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	9	Discon	Post-Treatment Safety Follow-up[b]	Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days) [d]:	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Last Dose (±3 days)	Every 12 weeks (±7 days)	Every 12 weeks (±14 days)
Neck, Chest, Abdominal, Pelvic PET, CT [m]	X					X[m,n]				X[m]	X[o]		X[b]	
Disease Response Assessment by Cheson Criteria 2007[m]						X				X[m]	X		X	
Assessment of Lymphoma B Symptoms [m]	X					X				X[m]	X		X	
Laboratory Procedures/Assessments: analysis performed by local laboratory														
Pregnancy Test – Urine or Serum β-HCG [p]	X													
PT/INR and aPTT [q]	X [r]													
CBC with Differential [s]	X [r]	X	X	X	X	X	X	X	X[u]		X	X [t]	X	
Comprehensive Chemistry Panel [s]	X [r]	X	X	X	X	X	X	X	X[u]		X	X [t]	X	
LDH[s]	X [r]					X				X[v]	X	X [t]		
Urinalysis [s]	X [r]		X		X		X		X[w]			X [t]		
T3 (or FT3 per local standard), FT4 and TSH[s]	X [r]		X		X		X		X[w]			X [t]		
Bone Marrow Biopsy & Aspirate [x,y]	X													
Bone marrow morphology, Cytogenetics [z]	X													
Laboratory Procedures/Assessments: analysis performed by central laboratory														
Archival Lymph Node Biopsy [y]	X													
Lymph Node Biopsy[y, aa]	X					X					X[aa]			
Whole Blood for Correlative Studies (RNA/DNA)[bb]	X		X			X					X [bb]			

Trial Period:	Screening Phase	Treatment Cycles [a]									End of Treatment	Post-treatment		
						To be repeated beyond 9 cycles								
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	9	Discon	Post-Treatment Safety Follow-up[b]	Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days) [d]:	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Last Dose (±3 days)	Every 12 weeks (±7 days)	Every 12 weeks (±14 days)
Whole Blood for Correlative Studies (Immunophenotyping)[cc]		X	X	X		X								
Blood for Biomarker Studies (plasma and serum)[dd]	X													
Plasma for Correlative Studies (Nanostring)[ee]	X					X								
Anti-pembrolizumab Antibodies [ff]		X[ff]	X[ff]		X[ff]		X[ff]		X[ff]			X[ff]	X[ff]	
Pharmacokinetics pembrolizumab[ff]		X[ff, gg]	X[ff]		X[ff]		X[ff]		X[ff,gg]			X[ff]	X[ff]	
Blood for Genetics[hh]		X												
Patient Reported Outcomes														
EuroQol EQ-5D[ii]		X	X	X	X	X				X[ii]	X	X		
EORTC QLQ-C30[ii]		X	X	X	X	X				X[ii]	X	X		

a. IV pembrolizumab at 200mg flat dose over 30 minutes will be administered once every 3 weeks. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified.

b. Post-Treatment Safety Follow up: Visit should occur at 30 days after the last infusion. The Discontinuation visit should occur as close as possible to the last infusion. If the Discontinuation visit occurred at or beyond 30 days after the last infusion, the Post-Treatment Safety Follow up visit and the Discontinuation visit may be combined into one visit, as long as assessments from both visits are performed

Follow-up visits: In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. The imaging schedule should proceed every 12 weeks from the day of the last imaging performed before subject enters the follow up period.

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

d. In general, the window for each visit is ± 3 days unless otherwise noted. Study personnel will access IVRS/IWRS to obtain the screening number. Once the subject meets enrollment criteria, the study personnel will access IVRS/IWRS to obtain the randomization number and study drug assignment. Cycle 1 treatment must be given within 3 days of randomization number assignment in IVRS/IWRS.

e. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
f. Signing the informed consent for future biomedical research (FBR) samples is optional. Detailed instructions for the management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
g. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
h. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
i. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment), and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment, or that occur within 18 months after allogeneic transplant.
j. Full physical exam to be performed at screening Cycle 5 Day1, Cycle 9 Day1, every 12 weeks after the Week 24 assessment (eg, Cycle 13, Cycle 17, Cycle 21, etc.), and at the time of discontinuation. Directed physical exam to be performed at Cycle1 Day 1, Cycle 3 Day1, and Cycle 7 Day 1only.
k. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at Visit 1 only.
l. Pulmonary function tests should include an assessment of forced vital capacity, forced expiratory flow between 25 and 75 percent of FVC (FEF25-75), forced expiratory volume in one second and peak expiratory flow (PEF) and diffusion capacity. Additionally, oxygen saturation as assessed by pulse oximetry is required. These tests should be performed at baseline and subsequently at the discretion of the investigator. Hemoglobin must be obtained within 3 days of pulmonary function testing.
m. Treatment response assessment is based upon the IWG response criteria (Cheson 2007). "Diagnostic quality" CT and PET scans should be performed at Screening (within 28 days prior to first dose of trial treatment). If PET or CT scan at Screening is positive for disease of the neck, subsequent CT scans must include the neck. If CT and PET scans at Screening are negative for disease in the neck, subsequent CT scans may omit the neck. Following screening, CT scans should be repeated every 12 weeks for subsequent assessments. PET should be repeated at Week 12, Week 24, to confirm CR, and as clinically indicated. PET may provide additional information when progression is suspected, and can be obtained at the investigator's discretion. Response assessments should occur at Wk. 12, and every 12 weeks (+/- 7 days) following the Wk. 12 assessment. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. The first assessment may be performed earlier than 12 weeks if in the opinion of the investigator the patient is clinically progressing. During the follow up period, the imaging schedule should proceed every 12 weeks from the day of the last imaging performed before subject enters the follow up period. Assessment of lymphoma B symptoms should occur with each disease response assessment. Bone marrow assessment is required to document CR, if the bone marrow was involved at screening.
n. If subjects have stable disease, partial response, or complete response a repeat CT scan is not required for confirmation, they should continue on the every 12 week assessment schedule. In the setting where a subject assessment shows PD at the Week 12 disease response assessment study drug may be continued, at the discretion of the PI, until the next disease response assessment provided that the subjects' clinical condition is stable. However, imaging should occur at any time where there is clinical suspicion of progression
o. In subjects with PD at Wk. 12, who continued study therapy beyond week 12 a radiological assessment should be performed at the time of treatment discontinuation. If previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation isn't mandatory.
p. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
q. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects.
r. Laboratory tests for screening are to be performed within 7 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
s. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
t. Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.

u. CBC with Differential, Comprehensive Chemistry Panel should be performed every 2 cycles after Cycle 8 (eg, Cycle 10, Cycle 12, Cycle 14, etc.).
v. LDH to be performed every 4th cycle after the Wk. 12 assessment (eg, Cycle 9, Cycle 13, Cycle 17, etc.).
w. Thyroid function tests (T3, FT4, and TSH) and urinalysis should be repeated every 2 cycles after Cycle 8 until treatment discontinuation (eg, Cycle 10, Cycle 12, etc.).
x. All subjects will have bone marrow biopsy/aspirate performed at baseline. Bone marrow aspirate will be performed if considered part of local standard of care. If this test is not done as part of local standard of care, then this test does not need to be performed. Subsequent bone marrow assessments will only be performed in subjects who have bone marrow involvement. A bone marrow assessment should be performed to confirm CR (if subject had bone marrow involvement) and as clinically indicated.
y. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
z. Bone marrow morphology and cytogenetics should be performed at baseline. Cytogenetics will be performed only if considered standard of care in your country. If this test is not done as part of local standard of care, then this test does not need to be performed.
aa. Tumor biopsies are required for subjects at Screening. At Screening an archival biopsy may be used, if an archival biopsy is not available a new biopsy must be obtained. Tumor biopsies **may** be obtained at Wk. 12 (± 7 days). A biopsy is also **highly recommended** at time of discontinuation due to progression, but is not required. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous and the tissue sample should have proper size to enable multiple planned biomarker analyses, but not artificially decrease the longest diameter of the lesion. If a tumor biopsy was of a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.
bb. Whole blood for Correlative Study samples (RNA/DNA) should be collected at Screening, pre-dose on Cycle 2 Day 1, at the time of the Wk. 12 disease response assessment, and upon progression. See Procedures Manual. Any leftover samples from the correlative blood studies will be stored for future biomedical research if the subject signs the FBR Consent.
cc. Whole Blood for Correlative Study samples (Immunophenotyping) should be collected pre-dose on Cycle 1, Cycle 2, Cycle 3 and pre-dose at the time of the Wk. 12 disease response assessment. Cycle 5. See Procedures Manual. Any leftover samples from the correlative blood studies will be stored for future biomedical research if the subject signs the FBR Consent.
dd. Plasma and Serum biomarker samples should only be collected at Screening.
ee. Plasma for Correlative Studies (Nanostring) should be collected at Screening and post-dose on Wk. 12. See Procedures Manual. Any leftover samples from the correlative blood studies will be stored for future biomedical research if the subject signs the FBR Consent.
ff. For Both PK and anti-pembrolizumab antibody; Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter (eg, Cycle 12, Cycle 16, Cycle 20, etc.), 30 days after discontinuation of study drug and 3 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab (-24 to 0 hrs. window at Cycle 1; -48 to 0 hrs. window at subsequent visits is allowed).
gg. For PK sample collection only; Additional post-dose peak PK samples will be drawn within 30 minutes (0 – 45 minutes) after end of pembrolizumab infusion at Cycles 1 and 8. An additional single PK sample should be drawn at 24 hours (20 – 28 hours) (Day 2), between 72 and 168 hours (48 – 192 hours) (Day 4-8), and 336 hours (288 – 384 hours) (Day 15) after Cycle 1 dosing.
hh. This sample should be drawn for planned genetic analysis of DNA and drug response unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection of the sample for these purposes. If the sample is collected, any leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent.
ii. Patient reported outcomes (PROs) are assessed every cycle for the first five cycles and every 12 weeks thereafter until PD while the subject is receiving study treatment. PROs will also be obtained at the Treatment Discontinuation Visit and 30-day Safety Follow-up Visit. If the Treatment Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, PROs do not need to be repeated. PROs are to be administered by trained site personnel and completed electronically by subjects. It is strongly recommended that all electronic PROs (ePROs) are administered prior to drug administration, adverse event evaluation and disease status notification. The PROs should be administered in the following order: EQ-5D followed by EORTC QLQ-C30.

6.2 Study Flow Chart: Cohorts 1, 2, and 3: Second Course Phase (Retreatment for Post-Complete Response Relapse Only)

Trial Period:	**Treatment Cycles [a]**									**End of Treatment**	**Post-treatment**		
					To be repeated beyond 9 cycles								
Treatment Cycle/Title:	1	2	3	4	5	6	7	8	9	Discon	Post-Treatment Safety Follow-up	Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days)[d]	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Last Infusion (±3 days)	Every 12 weeks (±7 days)	Every 12 weeks (±14 days)
Administrative Procedures													
Eligibility Criteria[e]	X												
Prior and Concomitant Medication Review[f]	X	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab Administration[a]	X	X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X	X
Survival Status [c]	◄											►	X
Clinical Procedures/Assessments													
Review Adverse Events [g]	X	X	X	X	X	X	X	X	X	X	X[h]	X	
Full Physical Examination[i]	X				X				X[i]	X[i]			
Directed Physical Examination[i]			X				X						
Vital Signs and Weight[j]	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Neck, Chest, Abdominal, Pelvic PET/CT [k]					X[l,k]				X[k]	X[m]		X[b]	
Disease Response Assessment by Cheson Criteria 2007 [k]	X				X				X[k]	X		X	
Assessment of Lymphoma B Symptoms [k]					X				X[k]	X		X	
Laboratory Procedures/Assessments: analysis performed by local laboratory													
Pregnancy Test – Urine or Serum β-HCG[n]	X												
CBC with Differential [o]	X	X	X	X	X	X	X	X[q]		X	X[p]		
Comprehensive Chemistry Panel [o]	X	X	X	X	X	X	X	X[q]		X	X[p]		
LDH [o]					X				X[r]	X	X[p]		
Urinalysis [o]	X	X		X		X		X[s]			X[p]		
T3 (or FT3 per local standard), FT4 and TSH[o]	X	X		X		X		X[s]		X	X[p]		

Trial Period:	Treatment Cycles [a]									End of Treatment	Post-treatment		
					To be repeated beyond 9 cycles								
Treatment Cycle/Title:	1	2	3	4	5	6	7	8	9	Discon	Post-Treatment Safety Follow-up	Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days)[d]	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Last Infusion (±3 days)	Every 12 weeks (±7 days)	Every 12 weeks (±14 days)
Bone Marrow Biopsy & Aspirate[t, u]	X												
Lymphoma adequate organ function laboratory tests [v]	X												

a. IV pembrolizumab at 200mg flat dose over 30 minutes will be administered once every 3 weeks. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified.

b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. The imaging schedule should proceed every 12 weeks from the day of the last imaging performed before subject enters the follow up period.

c. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted approximately every 12 weeks to assess for survival status. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).

d. In general, the window for each visit is ± 3 days unless otherwise noted.

e. Any procedures to confirm eligibility should be conducted prior to dosing. Subjects who in the first course of treatment attained a CR and discontinued or finished treatment, may restart trial treatment if they meet the criteria specified in Section 7.1.5.2.2 and if eligibility has been confirmed by completing all Cycle 1 assessments prior to dosing.

f. Prior medications – Record all medications taken within 28 days of Cycle 1 visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.

g. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.

h. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment or that occur within 18 months after allogeneic transplant.

i. Full physical exam to be performed at Cycle 1, Cycle 5 Day 1, Cycle 9 Day 1, repeated every 4 cycles after the Week 24 assessment (eg, Cycle 13, Cycle 17, Cycle 21, etc.), and at the time of discontinuation. Directed physical exam to be performed on Cycle 1 Day 1, Cycle 3 Day 1 and Cycle 7 Day 1 only.

j. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.

k. Treatment response assessment is based upon the IWG response criteria (Cheson 2007). "Diagnostic quality" CT and PET scans should be performed prior to Cycle 1 dosing (within approximately 6 weeks prior to first dose of trial treatment) and subject must meet criteria described in Section 7.1.5.2.2. If PET or CT scan at Cycle 1 is positive for disease of the neck, subsequent CT scans must include the neck. If CT and PET scans at Cycle 1 are negative for disease in the neck, subsequent CT scans may omit the neck. Following Cycle 1, CT scans should be repeated every 12 weeks for subsequent assessments. PET should be repeated at Week 12, Week 24, to confirm CR, and as clinically indicated. PET may provide additional information when progression is suspected, and can be obtained at the investigator's discretion. Response assessments should occur at Wk. 12, and every 12 weeks (± 7 days) following the Wk. 12 assessment. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. The first assessment may be performed earlier than 12 weeks if in the opinion of the investigator the patient is clinically progressing. During the follow up period, the imaging schedule should proceed every 12 weeks from the day of the last imaging performed before subject enters the follow up period.

Assessment of lymphoma B symptoms should occur with each disease response assessment. Bone marrow assessment is required to document CR if the bone marrow was involved at screening

l. If subjects have stable disease, partial response, or complete response a CT scan confirmation assessment is not required, they should continue on the every 12 week assessment schedule. Therefore in the setting where a subject assessment shows PD at the Week 12 disease response assessment, study drug may be continued until next disease response assessment provided that the subjects' clinical condition is stable. However, imaging should occur at any time where there is clinical suspicion of progression.
m. Subjects with PD at week 12, who continued study therapy beyond week 12 a radiological assessment should be performed at the time of treatment discontinuation. If previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation isn't mandatory.
n. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
o. At Cycle 1, lab tests should be within 7 days prior to dosing. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
p. Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
q. CBC with Differential, Comprehensive Chemistry Panel may be performed every 2 cycles after Cycle 8 (eg, Cycle 10, Cycle 12, Cycle 14, etc.).
r. LDH may be performed every 4th cycle after the week 12 assessment (eg, Cycle 9, Cycle 13, Cycle 17, etc.).
s. Thyroid function tests (T3, FT4 and TSH) and urinalysis should be repeated every 2 cycles after Cycle 8 until treatment discontinuation (eg, Cycle 10, Cycle 12, etc.).
t. Bone marrow assessments will only be performed in subjects who have bone marrow involvement. A bone marrow assessment should be performed to confirm CR (if subject had bone marrow involvement) and as clinically indicated.
u. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
v. Conduct tests to evaluate organ function as per Table 1.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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. Prior history of acute and chronic GVHD, maximum grade, and dates will be collected.

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 within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in the study will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial through the Safety Follow-up visit. In addition, new medications started within 28 days prior to and during the Second Course Phase 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.

7.1.1.6 Disease Details and Treatments

7.1.1.6.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.6.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, prior transplantation, radiation, and surgeries and record in the trial database.

7.1.1.6.3 Subsequent Antineoplastic Therapy Status

The investigator or qualified designee will collect transplant parameters (ie. date and type of transplant, conditioning regimen), and will review all new antineoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new antineoplastic therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new antineoplastic therapy has been initiated the subject will move into survival follow-up.

7.1.1.7 Assignment of Screening Number

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

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

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

7.1.1.8 Assignment of Randomization Number

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

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

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

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

Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences 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.

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 5.6.1 regarding the identification, evaluation, and management of AEs of a potential immunological etiology.

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening and repeated as per the frequency defined in the Study Flow Chart. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to

trial treatment administration. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.4 Electrocardiogram

A standard 12-lead ECG will be performed using local standard procedures at screening. Clinically significant abnormal findings should be recorded as medical history.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG status (see Section 12.5) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Assessment of Disease and Tumor Imaging

7.1.2.6.1 Criteria for Assessment of Disease

1. Anti-tumor activity of pembrolizumab will be evaluated using the following criteria

   - Revised Response Criteria for Malignant Lymphoma. (Cheson et al, *J Clin Oncol, 2007)* [40] See Section 12.7

   The International Working Group criteria will be applied by the site as the primary measure for assessment of disease response and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study therapy).

2. Anti-tumor activity of pembrolizumab will also be evaluated by independent central review as part of the exploratory analyses using the following criteria:

5-Point-Scale per the Lugano Classification (Cheson et al, *J Clin Oncol, 2014*) [41] See Section 12.7.1

7.1.2.6.2 Lymphoma Disease Response Assessment

Lymphoma response assessment by CT/PET is based on the International Working Group response criteria for malignant lymphoma (Cheson et al, J Clin Oncol, 2007) [41]. Local reading (investigator assessment with site radiology reading) will be used to determine subject eligibility and for subject management. The Sponsor will also receive radiologic images for a retrospective analysis of subject eligibility and treatment response to be

performed by a central vendor. Assessment of lymphoma B symptoms should occur with each lymphoma disease response assessment.

7.1.2.6.3 Disease Assessment of Immunotherapeutic Agents

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard response assessment criteria may not provide a complete response assessment of immunotherapeutic agents such as pembrolizumab. Therefore in the setting where a subject assessment shows PD, study drug may be continued, at the discretion of the PI, until the next disease response assessment provided that the subjects' clinical condition is stable. However, imaging should occur at any time where there is clinical suspicion of progression.

NOTE: With next response assessment if the disease is clinically stable or clinically improved, an exception may be considered to continue treatment upon consultation with the Sponsor.

7.1.2.6.4 Timing of Disease Assessments

Uniform disease response assessments will occur every 12 weeks following the first assessment at Week 12 (see Table 6 below).

Table 6 Disease Response Assessments

Indication	Assessment Frequency
HL (Cohorts 1, 2, and 3)	Every 12 weeks following first assessment at Week 12

7.1.2.6.5 Initial Disease Assessment

Initial disease assessment or tumor imaging must be performed within 28 days prior to the first dose of trial treatment. The site study team must review pre-trial images to confirm the subject has measurable disease as defined in the inclusion criteria.

Disease assessments or scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. CT and PET should be used throughout the study at time-points designated in Section 6.0-Flowchart. For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in follow-up assessments.

7.1.2.6.6 Disease Assessments During the Trial

Disease assessments should be performed per the frequency defined above. There is a ± 7 day window for assessments performed after Day 1. If PET and CT scan at Screening are negative for disease involvement in the neck, subsequent CT scans may not include neck. If PET and CT scans at Screening are positive for disease involvement of the neck, subsequent CT scans must include neck. Following screening, CT scans should be repeated every 12 weeks for subsequent assessments. PET should be repeated at Week 12, Week 24, to confirm CR or PD and as clinically indicated. Disease assessments and imaging should not be delayed for delays in cycle starts.

Disease assessments and imaging should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

7.1.2.6.7 Disease Progression Assessments

After the first documentation of progression it is at the discretion of the investigator to keep a clinically stable subject on trial treatment or to stop trial treatment until repeat imaging performed 4-6 weeks later confirms progression. Clinical Stability may be defined as:

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

2) No decline in ECOG performance status.

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

Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If progression is confirmed, then the subject will be discontinued from trial treatment. If progression is not confirmed, then the subject should resume/continue trial treatment provided:

- The sponsor is consulted and provides approval to continue treatment

- No other anti-tumor therapy (eg, chemotherapy, radiation, etc.) has been administered

Patients should have their next scan according to the every 12-week schedule from first dose of study treatment, which would be approximately 12 weeks from the date of the scan that first showed progression. When feasible, subjects should not be discontinued until progression is confirmed.

7.1.2.6.8 Biopsy Collection and Correlative Studies Blood Collection

All subjects enrolled into this study must be able to provide an archived FFPE biopsy sample or newly obtained core or excisional biopsy (FNA not adequate) to be submitted for

characterization at a central lab. 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 sectioning date otherwise a new specimen will be requested.

Biopsy sites should be selected so that subsequent biopsies can be performed at the same location. Tumors that are inaccessible or contraindicated due to subject safety concerns are exempt from this requirement.

Bone marrow and lymph node biopsies will be collected as per Table 7 below.

Table 7 Bone Marrow and Lymph Node Biopsy Assessments

Indication	Timing of Biopsy
Cohorts 1, 2 and 3: Lymph Node Biopsy (Lymph node biopsy)	Screening biopsy (archival or new) is required. Biopsy at Wk. 12 (± 7 days) and at the time of discontinuation due to progression is optional but highly recommended.
Cohorts 1, 2 and 3: Bone marrow biopsy/aspirate (All subjects will have bone marrow biopsy/aspirate performed at Screening. Subsequent bone marrow assessments will only be performed in subjects who have bone marrow involvement.)	Screening, to confirm CR (if subject has bone marrow involvement), and as clinically indicated.

Blood for correlative biomarker studies should be collected as per Table 8 below.

Table 8 Blood for Correlative Studies

Cohorts	Timing of Correlative Blood Collection
Cohorts 1, 2, and 3	Whole Blood for RNA/DNA: Screening, pre-dose on Cycle 2 Day 1, Wk. 12 assessment, and upon progression.
Cohorts 1, 2, and 3	Whole Blood for Immunophenotyping: pre-dose on Cycles 1, 2, 3 and pre-dose on Wk. 12 assessment.
Cohorts 1, 2, and 3	Plasma for Nanostring: Screening and Wk. 12 assessment

7.1.2.7 Patient Reported Outcomes (PROs)

The EuroQol EQ-5D and EORTC QLQ-C30 questionnaires will be administered by trained site personnel and completed electronically by the subjects themselves. It is strongly recommended that all electronic PROs (ePROs) are administered prior to drug administration, adverse event evaluation and disease status notification. The ePROs are completed in the following order: EuroQol EQ-5D first, then EORTC QLQ-C30 at the time points specified in the Trial Flow Charts.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

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

Laboratory tests for hematology, chemistry, and urinalysis are specified in Table 9.

Table 9 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
CBC with differential	Alanine aminotransferase (ALT)	Protein	aPTT
Platelet count	Aspartate aminotransferase (AST)	Specific gravity	Total Triiodothyronine (T3) (or FT3)
WBC (total and differential)	Lactate dehydrogenase (LDH)	Microscopic exam, if abnormal results are noted	Free thyroxine (T4)
Red Blood Cell Count	Carbon Dioxide (CO_2 or bicarbonate) [a]	Urine pregnancy test	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	Creatinine		Anti-pembrolizumab Antibodies
Absolute Lymphocyte Count	Uric Acid		PK
	Calcium		Blood for FBR
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct and Indirect Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen [b]		

[a] If considered standard of care in your region. If these tests are not done as part of standard of care in your region then these tests do not need to be performed

[b] Blood Urea Nitrogen is preferred; if not available Urea may be tested.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 7 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.2.1 Pharmacokinetic Evaluations

To further evaluate pembrolizumab immunogenicity and pembrolizumab exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of anti-drug antibodies (ADA) and PK are currently planned as shown in the Trial Flowchart (Sections 6.1. and 6.2). Blood samples will be obtained to measure pharmacokinetics of serum pembrolizumab monotherapy. The pembrolizumab serum maximum concentration (C_{max}) and minimum concentration (C_{trough}) at planned visits and times will be summarized. If ongoing ADA and/or PK results continue to be consistent with existing ADA and/or PK data from other pembrolizumab clinical trials, it may be decided to discontinue or reduce further sample collection in this study.

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

Blood Collection for Serum MK-3475 Sample collection, storage and shipment instructions for serum samples will be provided in the procedure manual. PK samples should be drawn according to the PK collection schedule for subjects who receive pembrolizumab (MK-3475). Every effort should be taken to collect samples at 30 days (+/- 3 days) and 3 months (+/- 3 days) after end of pembrolizumab treatment.

7.1.3.2.2 Blood Collection for Anti-pembrolizumab Antibodies MK-3475

Sample collection, storage and shipment instructions for serum samples will be provided in the procedure manual. Anti- pembrolizumab antibody samples should be drawn according to the ADA collection schedule for subjects who receive pembrolizumab (MK-3475). Every effort should be taken to collect samples at 30 days and 3 months after end of pembrolizumab treatment for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis.

7.1.3.3 Future Biomedical Research

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

- Leftover DNA for future use
- Leftover Bone Marrow Biopsy/Aspirate samples
- Leftover Lymph node biopsies
- Leftover Correlative blood samples

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who attain a CR may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.2. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

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

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be

suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Laboratory equipment- as required for inclusion labs and trial assessments
- Imaging equipment- as required for trial objectives
- Infusion equipment- as required for administering drug product

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

7.1.5 Visit Requirements

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

7.1.5.1 Screening

Approximately 28 days prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor. Visit Requirements are outlined in Section 6.0.

Written consent for the main study must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests are to be performed within 7 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- When an archival biopsy is being used for PD-L1 characterization, it is not required to be obtained within 28 days prior to the first dose of trial treatment.

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

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

7.1.5.2 Treatment 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. Subjects who have not progressed may receive up to 35 cycles (approximately 2 years) of pembrolizumab during treatment period.

7.1.5.2.1 Subjects Who Continue Treatment Beyond Disease Progression

Subjects that continue treatment with pembrolizumab after documented disease progression (Section 7.1.5.2.2), must follow the same visit requirements as outlined in Section 6.2 Study Flow Chart.

7.1.5.2.2 Second Course Phase (Retreatment Period for Post-complete Remission Relapse ONLY)

Subjects may be eligible to receive up to an additional 17 cycles (approximately 1 year) of pembrolizumab in the Retreatment Period of this study if the study remains open and the subject meets all of the following conditions:

- Stopped (or completed) initial treatment with pembrolizumab after attaining an confirmed CR by investigator assessment according to respective response criteria
- Was treated for at least 24 weeks (8 cycles) with pembrolizumab before discontinuing therapy
- Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared
- Experienced an investigator-determined confirmed disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Have a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrate adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section

5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

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

- Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

- 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 achieved CR and received up to 35 doses (approximately 2 years) of treatment with pembrolizumab may be eligible for up to 17 doses (approximately 1 year) of retreatment. Subjects who restart treatment will be retreated at the same dose frequency as when they last received pembrolizumab.

Confirm subjects are eligible for retreatment as described above. The Second Course Eligibility Visit may be conducted on the day of the first dose, but eligibility must be confirmed prior to dosing. See Section 6.2 – Second Course Trial Flow Chart.

7.1.5.3 Post-treatment Visits

7.1.5.3.1 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 antineoplastic treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new antineoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded.

Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.2.2) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (± 7 days) to monitor disease status. Subjects should receive a full physical examination and ECOG status, vital

signs and labs should be repeated with each assessment. Every effort should be made to collect information regarding disease status until the start of new antineoplastic therapy, disease progression, death, end of the study, or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.2.2. Information regarding post-study antineoplastic treatment will be collected if new treatment is initiated.

For subjects who achieve CR determined by the investigator and are in the Follow-Up Phase, when they experience disease progression determined by investigator assessment are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.2.2 will move from the follow-up phase to the Second Course Phase. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment.

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7.1.5.4.2 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new antineoplastic therapy, the subject moves into the survival follow-up phase and should be contacted approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

CCI

7.1.5.4.3 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 participants who do not/will not have a scheduled study visit or study contact during the sponsor defined time period will be contacted for their survival status (excluding participants that have previously recorded a death event in the collection tool).

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

All adverse events that occur after the consent form is signed but before randomization/treatment allocation 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 randomization/treatment allocation through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

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

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

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

(Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

- Is a cancer;
- Is associated with an overdose.

Refer to Table 10 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until randomization/treatment allocation, 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 randomization/treatment allocation 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 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 randomization/treatment allocation, 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 randomization/treatment allocation 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 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:

- 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.

- 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).

- Post-transplant complications (see Sec 7.1.5.4.1) that occurred within 18 months from the date of the allogeneic transplant, for subjects who were previously exposed to pembrolizumab.

- Additional Adverse Events:

  Events of Clinical Interest identified from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier need to be reported to the Sponsor within 24 hours of the event consistent with standard SAE reporting guidelines and either by electronic media or paper. Sponsor Contact information can be found in the administrative binder.

  Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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

7.2.4 Evaluating Adverse Events

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

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

Table 10 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 an MSD 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 cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with 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	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
to Sponsor's Product (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.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If changes are made to the primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses post study initiation and prior to final database lock, the protocol will be amended (consistent with ICH Guideline E-9). After the protocol has been finalized and prior to the final database lock any changes to exploratory or other non-confirmatory analyses, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will also be identified in the CSR.

Unless specified otherwise, the statistical analyses will be conducted separately by cohort. In addition, a separate CSR may be issued for a single cohort if the actual enrollment rate among cohorts is markedly different.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized in Table 11 below; the comprehensive plan is provided in Sections 8.2-8.12.

Table 11 Statistical Analysis Plan Summary

Study Design Overview	This study, "A Phase II clinical trial of MK-3475 (pembrolizumab) in subjects with relapsed or refractory (R/R) classical Hodgkin Lymphoma (cHL)" is a multicenter, single arm, multi-cohort, nonrandomized trial of pembrolizumab (MK-3475) in subjects with relapsed or refractory classical Hodgkin lymphoma.
Treatment Assignment	Subjects meeting inclusion/exclusion criteria will be allocated to one of three cohorts, depending on their prior disease history and therapy: • Cohort 1: failed to achieve a response or progressed after auto-SCT and have relapsed after treatment with or failed to respond to brentuximab vedotin post auto-SCT. • Cohort 2: unable to achieve a CR or PR to salvage chemotherapy for an auto-SCT and did not receive auto-SCT, but have relapsed after treatment with or failed to respond to brentuximab vedotin. • Cohort 3: failed to respond to or progressed after auto-SCT and have not received brentuximab vedotin post auto-SCT. **These subjects may or may not have received brentuximab vedotin as part of primary treatment or salvage therapy.**
Analysis Populations	Efficacy: All Subjects as Treated (ASaT) Safety: All Subjects as Treated (ASaT)

Primary Endpoint(s)	The primary efficacy endpoint is the Overall Response Rate (ORR), defined as the proportion of subjects in the analysis population who have complete remission (CR) or partial remission (PR) using IWG criteria, Cheson 2007 at any time during the study. Response for the primary analysis will be determined by central review.
Key Secondary Endpoints	1. Complete Remission Rate 2. Progression-free Survival 3. Duration of Response 4. Overall Survival
Statistical Methods for Key Efficacy/ Immunogenicity/ Pharmacokinetic Analyses	The primary hypothesis will be evaluated, for each Cohort separately, by comparing ORR for MK-3475 to a fixed control rate using a binomial exact test. The point estimate of the ORR will be calculated for each Cohort as well as a 95% 2-sided exact confidence interval.
Statistical Methods for Key Safety Analyses	Within each Cohort, summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate. A pooled analysis over Cohorts may be performed as well to obtain a larger safety database.
Interim Analyses	An interim analysis will be performed by the sponsor in this study for futility alone and the results will be reviewed internally. The interim analysis would be conducted when 50% of the subjects within a cohort have been evaluated for response. Details are provided in Section 8.7.
Multiplicity	No multiplicity adjustment is planned as there is a single comparison of MK-3475 using 1 endpoint in the primary hypothesis within each Cohort. Other efficacy analyses will be considered supportive and/or explanatory.
Sample Size and Power	The planned sample size is 60 subjects for each Cohort for the primary analysis. For the three cohorts, there is at least 93% power (one-sided 2.5% alpha level) within each Cohort to demonstrate that MK-3475 is superior to a fixed control rate of 20% assuming the underlying MK-3475 ORR is at least 40%.

8.2 Responsibility for Analyses/In-House Blinding

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

This trial is being conducted as a non-randomized open-label study, ie, subjects, investigators, and sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

Unless stated otherwise, objectives will be evaluated within each Cohort. There is one hypothesis, within each Cohort, to be formally tested in this study, ie, whether the ORR is greater than a fixed control rate using the IWG criteria based on independent central review; details on how this will be tested appear below in Section 8.6.1.1. Secondary objectives,

again within each Cohort, will not involve hypothesis testing, and will assess the efficacy of pembrolizumab on secondary efficacy endpoints (CRR, PFS, DOR, and OS) and will include, where appropriate, assessments based on investigator and Lugano classification; details appear below in the corresponding sections of Section 8.6.1.

8.4 Analysis Endpoints

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

8.4.1 Efficacy Endpoints

Efficacy endpoints that will be evaluated are listed below, followed by the descriptions of the derivations of selected endpoints.

The primary efficacy endpoint is the Overall Response Rate (ORR), defined as the proportion of subjects in the analysis population who have complete remission (CR) or partial remission (PR) using IWG criteria (Cheson 2007) at any time during the study. Response for the primary analysis will be determined by central review.

Secondary efficacy endpoints include: (1) ORR according to investigator (site) assessment using IWG criteria; (2) ORR according to central review using Lugano 5-point classification; (3) complete remission rate (CRR), defined as the proportion of subjects in the analysis population who have complete remission (CR) by IWG criteria; (4) progression-free survival (PFS), defined as the time from first dose to the first documented disease progression according to IWG criteria or death due to any cause, whichever occurs first; (5) duration of response (DOR), defined as time from first IWG response to disease progression in subjects who achieve a PR or better, and (6) overall survival (OS), defined as time from first dose to date of death.

Exploratory efficacy endpoints include: (1) eligibility for SCT post-study therapy (yes/no); (2) receiving SCT following post-study therapy (yes/no); (3) ORR, (4) DOR, (5) CRR, and (6) PFS, incorporating response assessments for subjects continuing pembrolizumab treatment after initial progression.

8.4.2 Safety Endpoints

Safety measurements are described in Section 7.

8.5 Analysis Population

8.5.1 Efficacy Analysis Population

The analysis of primary efficacy endpoints are based on the All Subjects as Treated (ASaT) population, ie, subjects will be included if they receive at least one dose of study medication.

Supportive analyses will be conducted in the Full Analysis Set (FAS) population, which consists of all subjects who 1) receive at least one dose of study medication; 2) have a

baseline disease assessment, and 3) have a post baseline disease assessment OR discontinue the trial due to progressive disease/drug related AE.

8.5.2 Safety Analysis Population

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

8.6 Statistical Methods

Unless specified otherwise, analyses will be conducted separately by Cohort.

Safety analyses are described in Section 8.6.2; efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 8.9, 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.

8.6.1 Statistical Methods for Efficacy Analyses

A summary of the primary analysis strategy for the primary and secondary efficacy endpoints is provided in Table 13 below.

8.6.1.1 Overall Response Rate (ORR)

The primary efficacy endpoint for this study is the Overall Response Rate (ORR), defined as the proportion of subjects who have response (CR or PR) according to the IWG criteria, and will be analyzed separately by cohort. The primary analysis will be conducted for that cohort when the last subject in that cohort has reached the Week 12 response assessment or has discontinued study therapy.

The analysis will consist of the point estimate and 95% 2-sided exact confidence interval (CI) using the Clopper-Pearson method which will have at least 95% coverage of the true rate. An exact binomial test will be conducted for each cohort versus a fixed control rate for each cohort.

Secondary analyses for ORR will be performed based on investigator's (ie, study site) assessment and by central review based on the Lugano Classification (JCO, 2014).

Since an investigator may still continue to treat subjects with MK-3475 who have progressed according to central review or by site assessment, exploratory analyses (point estimate and 95% 2-sided exact confidence interval) will be conducted for ORR to consider these subjects who later achieve PR or CR post-progression as responders.

8.6.1.2 Complete Remission Rate (CRR)

The complete remission rate (CRR), defined as the proportion of subjects who have a CR response according to the IWG criteria using central review. The analysis will consist of the point estimate and 95% 2-sided exact CI, separately by Cohort. Additional analyses will be based on site assessment and by central review using the Lugano (2014) criteria.

8.6.1.3 Progression-Free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve.

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 IWG criteria, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event.

A secondary analysis will be performed for PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint, we will perform two sensitivity analyses with a different set of censoring rules. The first sensitivity analysis is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis is the same as the primary analysis except that it considers initiation of new anticancer treatment to be a PD event for subjects without documented PD or death and lost to follow-up to be a PD event for subjects without documented PD or death and lost to follow-up after ≥ 2 missed disease assessments. The censoring rules for primary and sensitivity analyses are summarized in Table 12.

Table 12 Censoring rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment
No PD and no death; subject receives SCT following response to pembrolizumab	Censored at last disease assessment before SCT	Censored at last disease assessment before SCT	Censored at date of SCT
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
PD or death documented after ≤ 1 missed disease assessment	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 after ≥ 2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessments	Progressed at date of documented PD or death
No PD and no death and lost to follow-up after ≥2 missed disease assessments	Censored at last disease assessment prior to the ≥ 2 missed disease assessments	Censored at last disease assessment prior to the ≥ 2 missed disease assessments	Progressed at date of lost to follow-up.

Similar to the exploratory analysis for ORR above where subjects are treated with MK-3475 by the site following progression, an exploratory analysis will be performed on PFS incorporating additional response assessments; details on this analysis will appear in the sSAP.

8.6.1.4 Duration of Response (DOR)

Duration of response is defined, only for the subgroup of subjects who achieve CR or PR, as the time from start of the first documentation of objective tumor response (CR or PR) to the first documentation of tumor progression or to death due to any cause, whichever comes first. The analysis will consist of Kaplan-Meier estimates. Duration of response data will be censored on the date of the last disease assessment documenting absence of progressive disease for subjects who do not have tumor progression and are still on study at the time of an analysis, are given antitumor treatment (including stem cell transplant) other than the study treatment, or are removed from study prior to documentation of tumor progression.

Duration of Response will be based upon central review according to the IWG criteria; a secondary analysis of DOR will be conducted using investigator assessment. In addition, since stem cell transplant post-initiation of MK-3475 is considered to be an indicator of positive efficacy rather than failure of the current treatment, an exploratory analysis of DOR may be conducted where date of SCT is not considered censored for those subjects; details will appear in the sSAP.

8.6.1.5 Overall Survival (OS)

The median overall survival, if reached, will be estimated in the given analysis population, separately by cohort. In addition, the Kaplan-Meier method will be used to estimate the survival curve, separately by Cohort.

Table 13 Efficacy Analysis Methods for Primary and Secondary Efficacy Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Overall Response Rate • IWG criteria (2007) o Central review	Exact test of binomial parameter; 2-sided 95% exact CI	ASaT/FAS	Subjects with missing data are considered non-responders
Secondary:			
Overall Response Rate • IWG criteria (2007) o Study site • Lugano criteria (2014) o Central review	Point estimate; 2-sided 95% exact CI	ASaT/FAS	Subjects with missing data are considered non-responders
Complete Remission Rate • IWG criteria (2007) o Central review o Study site • Lugano criteria (2014) o Central review	Point estimate; 2-sided 95% exact CI	ASaT/FAS	Subjects with missing data are considered non-responders
Progression-free survival • IWG criteria (2007) o Central review o Study site	Summary statistics using Kaplan-Meier method	ASaT/FAS	Censored at last assessment (see Table 12 for sensitivity analyses based on alternative censoring)
Duration of Response • IWG criteria (2007) o Central review o Study site	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
Overall survival	Summary statistics using Kaplan-Meier method	ASaT/FAS	Censored at last assessment

As indicated in Section 8.6.1.1, the primary analysis of ORR will be conducted when the last treated subject has reached the Week 12 response assessment or has discontinued study therapy. At that time point, analyses of other efficacy endpoints in the table above (eg, DOR, CRR, PFS and OS) will also be conducted. An efficacy update for all endpoints in the table above will be conducted when the last treated subject has reached at least the Week 24 response assessment or has discontinued study therapy. An efficacy update will be conducted at one year after the last subject initiated treatment and then at 2 years after the last subject initiated treatment, which corresponds to the end of the protocol-specified treatment period. Subsequent yearly analyses will be conducted (ie, 3 years after the last subject initiated treatment, etc.) until the trial is complete, including follow-up information on subjects who enter the re-treatment period.

8.6.2 Statistical Methods for Safety Analyses

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

Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.3.1 Baseline Characteristics and Demographics

Baseline characteristics will be assessed by the use of tables and/or graphs for each Cohort. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, allocated, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by cohort either by descriptive statistics or categorical tables.

8.6.3.2 Patient-reported Outcomes (PRO)

EORTC QLQ-C30 and EuroQoL EQ-5D data will be summarized as part of the pre-specified exploratory analysis. Patient-reported treatment effects will be evaluated for each cohort separately at pre-specified time points while on treatment and 30 days following treatment discontinuation as measured by change from baseline in the QLQ-C30 QoL domain and all sub-scales/single items. In addition to the estimated mean effects, cumulative distribution and the number and proportion of patients who “improved,” “worsened,” or “remained stable” from baseline to a pre-defined visit will also be estimated. For EQ-5D, pre-specified exploratory analyses will be performed to describe the distribution of responses. Additional details will be included in the sSAP.

8.6.3.3 Population PK Analyses

Based on pharmacokinetic data obtained within this study, a separate population Pharmacokinetics (PK) analysis will be performed. The prospective details of this analysis will be specified in a separate population PK analysis plan.

8.6.3.4 Other Analyses

Subjects that respond to study therapy (CR/PR) in this study may now be considered for SCT (autologous for prior ineligible subjects, allogenic for previous transplant failure subjects). The number of subjects that become eligible for SCT post study therapy and the number of subjects that actually receive SCT post study therapy will be estimated using descriptive statistics, separately by cohort.

Descriptive statistics, including cross-tabulations, will be performed for those patients with evaluable samples, to assess PD-L1 expression using immunohistochemistry will be analyzed in the context of response determined by central review (CR, PR, SD, PD).

Additional exploratory analyses will be described in the sSAP.

8.7 Interim Analysis

An interim analysis will be performed within each cohort for the purpose of futility alone. The analysis will be performed and reviewed by the study team. In each cohort separately, the analysis will be performed based on response assessed by the investigators for 30 subjects. The analysis will be conducted when the 30th subject who starts study treatment for that cohort has reached the Week 12 response assessment or has discontinued study therapy prior to Week 12, ie, all 30 subjects will have been evaluated for response with at least the Week 12 response assessment or have discontinued prior to Week 12.

Enrollment into each cohort will not be paused pending the results of the analysis.

For Cohorts 1 2 and 3, if 6 or fewer responses (CR or PR at any assessment) out of 30 subjects are observed (20%), the cohort may be stopped for further enrollment. The operating characteristics of the futility stopping rule are given in Table 14 below, ie, the probability of potentially stopping a cohort under the rule for a range of true ORR for MK-3475.

Table 14 Operating Characteristics of Interim Analysis Rule

True ORR	Probability of Stopping Enrollment
	Cohorts 1, 2 and 3 (if observe ≤6/30 [20%])
5%	>0.99
10%	0.97
15%	0.85
20%	0.61
25%	0.35
30%	0.16
35%	0.06
40%	0.02
45%	<0.01

8.8 Sample Size and Power Calculation

Efficacy for each cohort will be analyzed separately.

The proposed sample size for each of the three cohorts is 60 subjects in the primary analysis population (ASaT), i.e. 180 subjects in all. To obtain 180 total subjects in the ASaT population, 190 will need to be enrolled in the study assuming that approximately 5% of enrolled subjects are not treated.

With 60 subjects per cohort in the primary analysis population, there is at least 93% statistical power (1-sided nominal 2.5% alpha) to detect a 40% or higher overall response rate (ORR) for the MK-3475 arm compared to a fixed control rate of 20% using the exact binomial test (nQuery version 2.0 software). Success for this hypothesis requires at least 16/60 responses. If an interim analysis is performed within a cohort (see Section 8.7), the power will be approximately 92%.

The selection of 20% as a fixed control rate is based partly on historical data in previously conducted studies in R/R HL prior to the approval of brentuximab vedotin, where response rates ranged between 18%-53% (Johnston et al, 2010, Feninger et al, 2011, Younes et al, 2012, and Moscowitz et al, 2012). However, since this study is being conducted in brentuximab vedotin failures and to date, there is no published data on the ORR in this particular patient population. Thus, a 20% ORR may be taken as a conservative control rate considering that all subjects to be enrolled in this study have failed an additional line of therapy (brentuximab vedotin) than seen previously.

8.9 Multiplicity

The false positive rate for testing the primary efficacy endpoint is controlled at 0.025 (1-sided) within each cohort. No additional multiplicity adjustment is required because each

cohort will be evaluated independently and only once, i.e. at the time of the primary analysis when all subjects in the cohort have reached the week 12 assessment or have discontinued study therapy.

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether ORR is consistent across various subgroups, the point estimate of the ORR (with an exact 95% CI) will be provided and plotted within each category of the following classification variables within each Cohort:

- Age category (≤65 vs. >65 years)
- Sex (female vs. male)
- Race (white vs. non-white)
- Region (US, ex-US)
- Number of prior therapies (<4 vs ≥4)

For Cohorts 1 and 3 only:

- Time elapsed since transplant failure (<12 months vs. ≥12)

If the observed numbers for a particular subgroup are too small to make a meaningful clinical interpretation, then that subgroup analysis will not be conducted.

8.11 Compliance (Medication Adherence)

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

8.12 Extent of Exposure

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

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 15.

Table 15 Product Descriptions

Product Name & Potency	Dosage Form
pembrolizumab (MK-3475) 100 mg/ 4 mL	Solution for Infusion

9.2 Packaging and Labeling Information

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

Subjects will receive open label pembrolizumab (MK-3475) vials.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

Trial site personnel will have access to a central electronic 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 MSD, is provided in Section 12.1 - 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, MSD, 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. MSD, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. MSD 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. MSD 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 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, 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 participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD 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 that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

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 MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. 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 such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). 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. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD 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

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

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

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

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

V. Investigator Commitment

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

to any specimens, test results, or medical information once the specimens have been rendered de-identified

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

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

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

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

5. Biorepository Specimen Usage

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

Analyses utilizing the Future Biomedical Research specimens may be performed by MSD, or an additional third party (e.g., a university investigator) designated by MSD. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the MSD Entrusted Keyholder. 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 the

specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to MSD.

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

Specimens from the trial site will be shipped to a central laboratory and then shipped to the MSD 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 MSD policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

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

maintains control over access to all specimen data. These data are collected for future biomedical research purposes only and will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Gender, Ethnicity and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. [insert: Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial. **OR** Buccal swab specimens will be collected inside the cheek with no associated venipuncture to obtain the specimen. Therefore, there will not be an additional risk for the subject.]

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

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure MSD database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

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

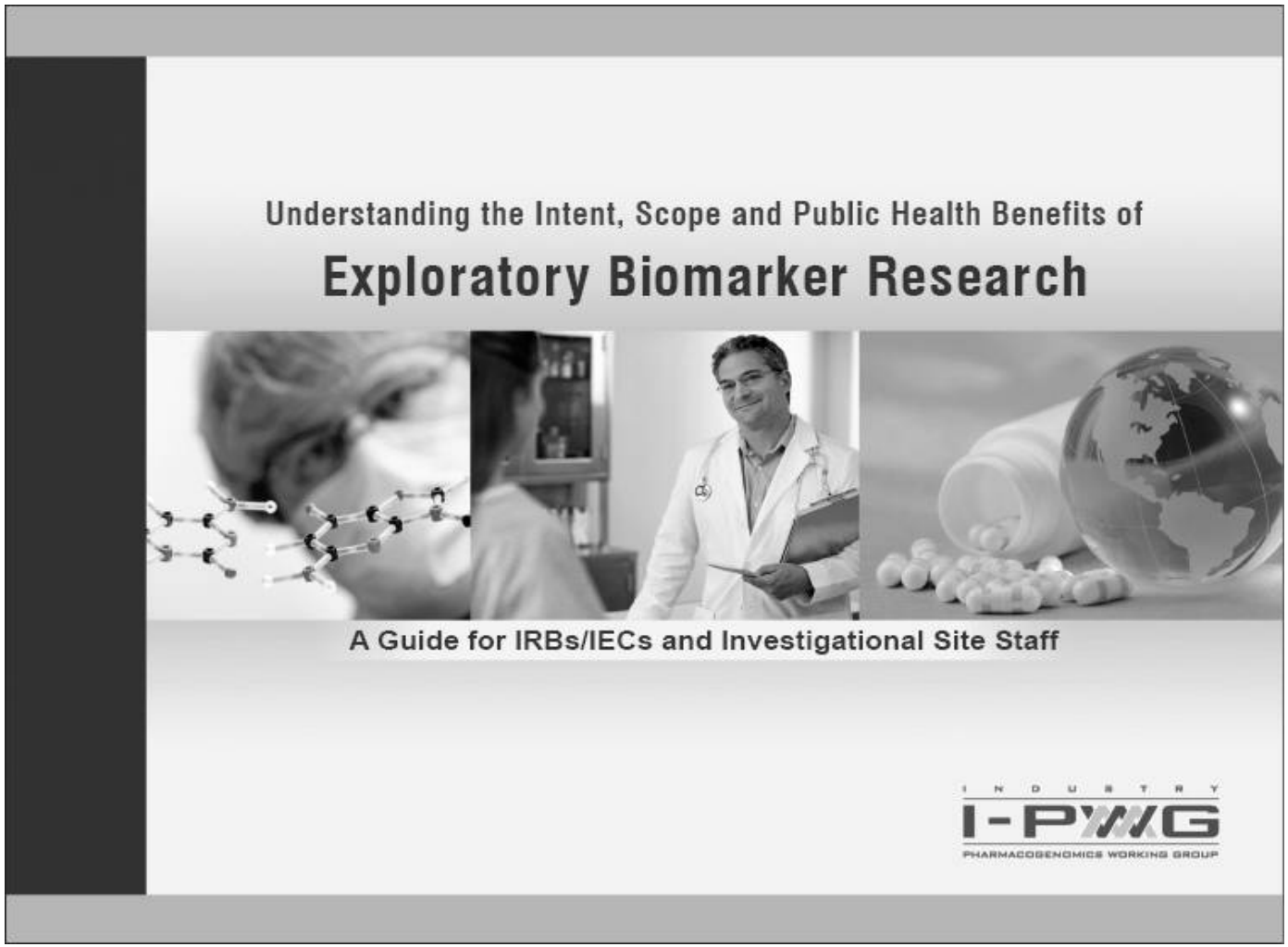
13. Questions

Any questions related to the future biomedical research should be e-mailed directly to CCI [redacted]

14. References

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

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



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

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

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

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

Importance to Drug Development

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

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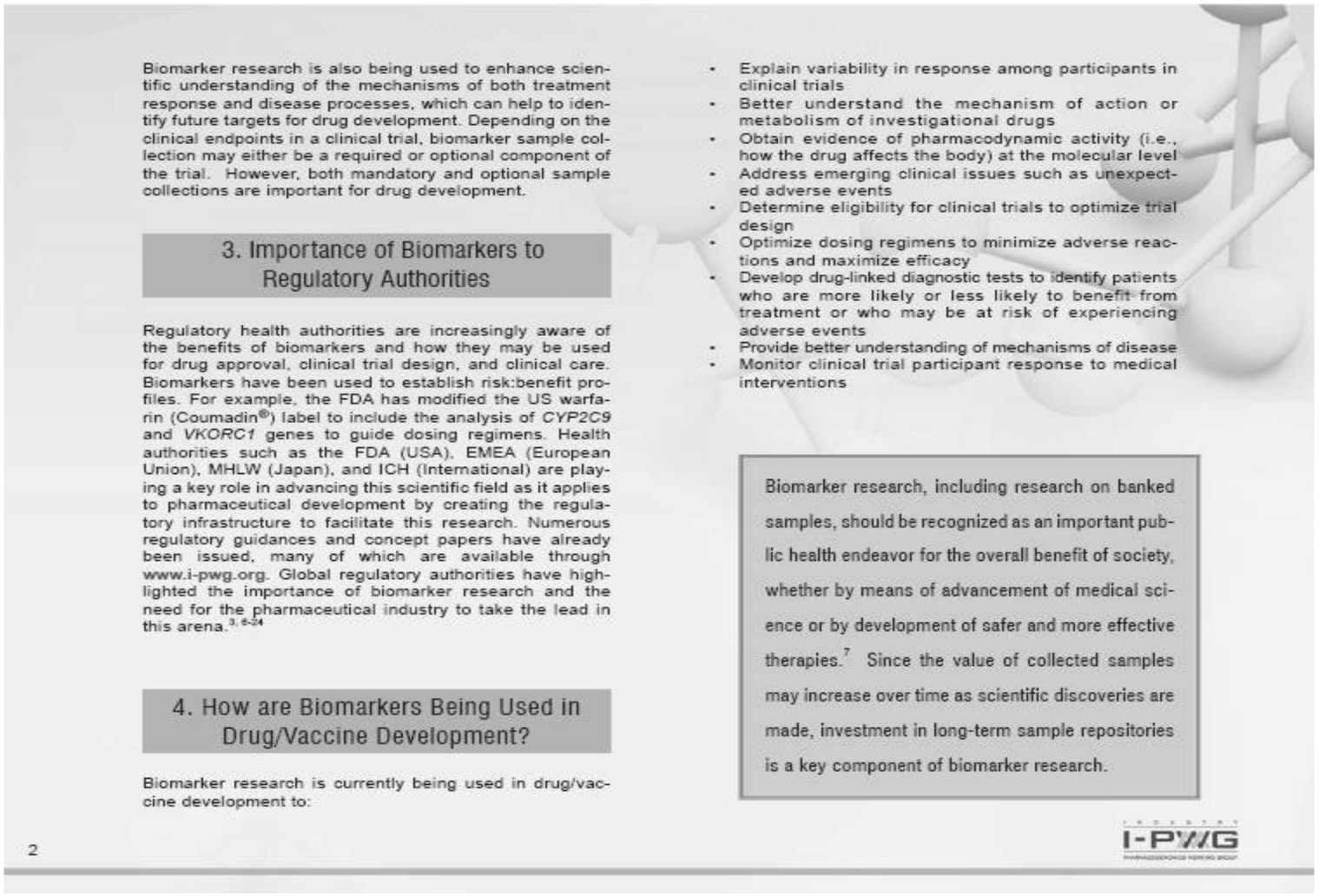
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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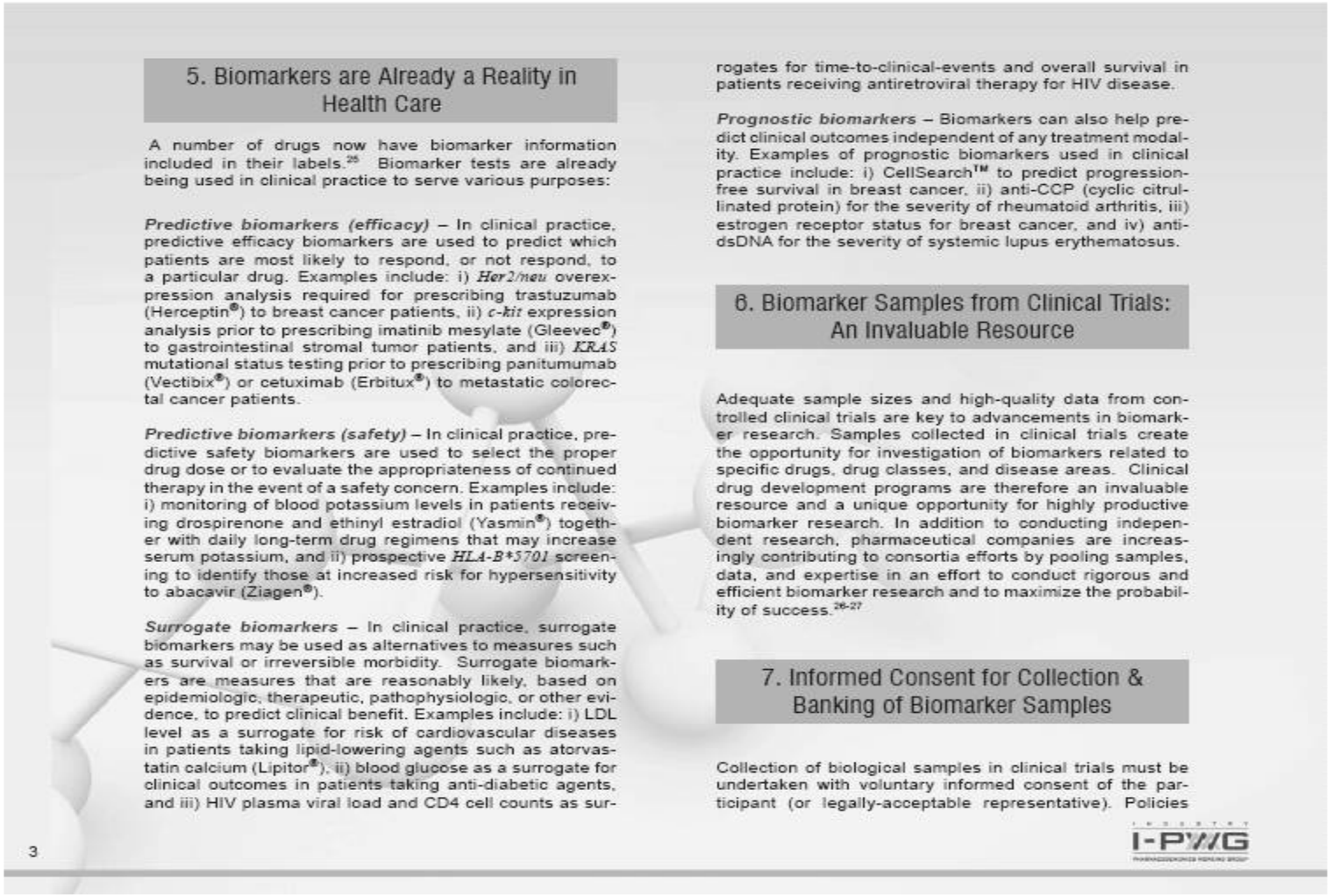

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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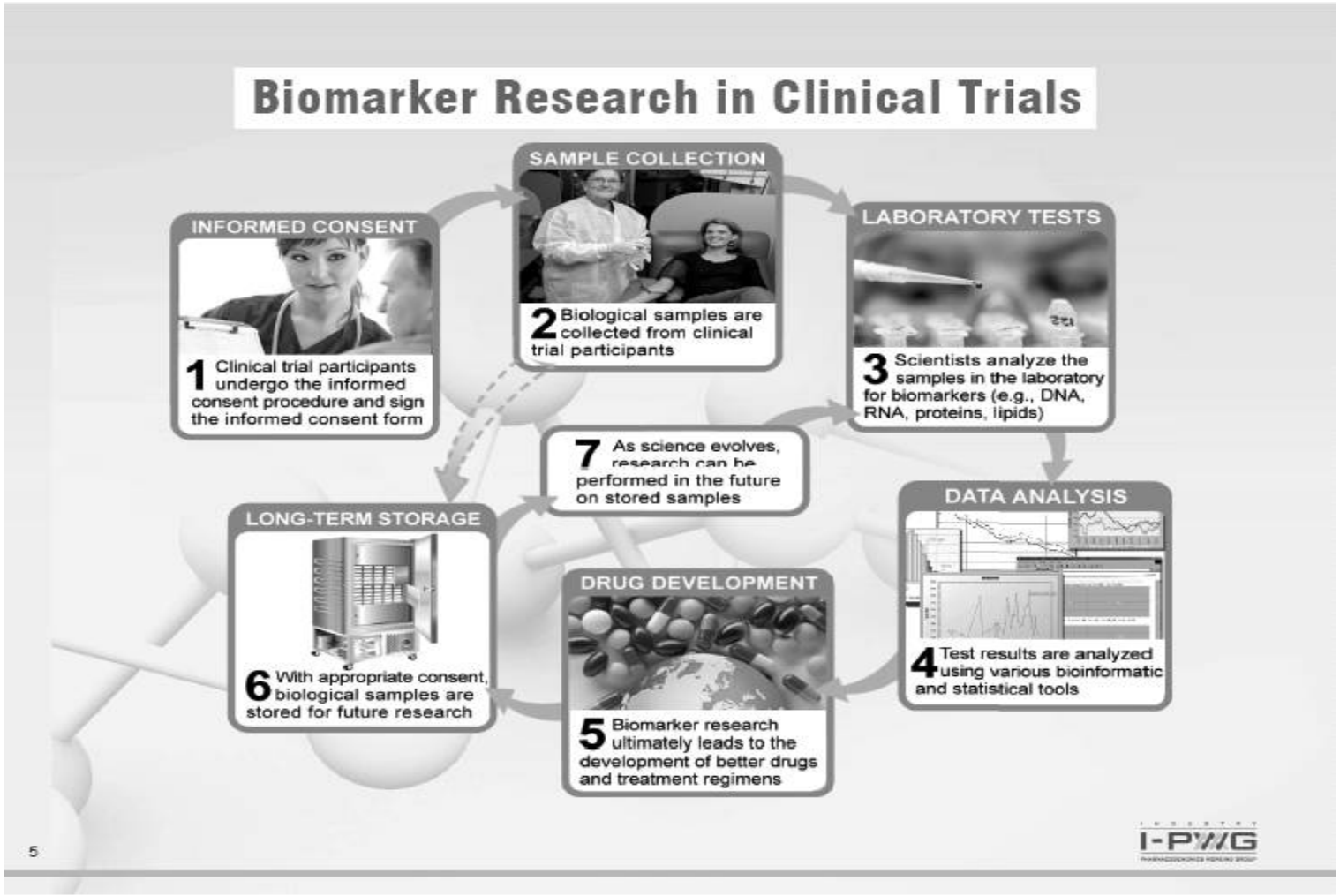
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the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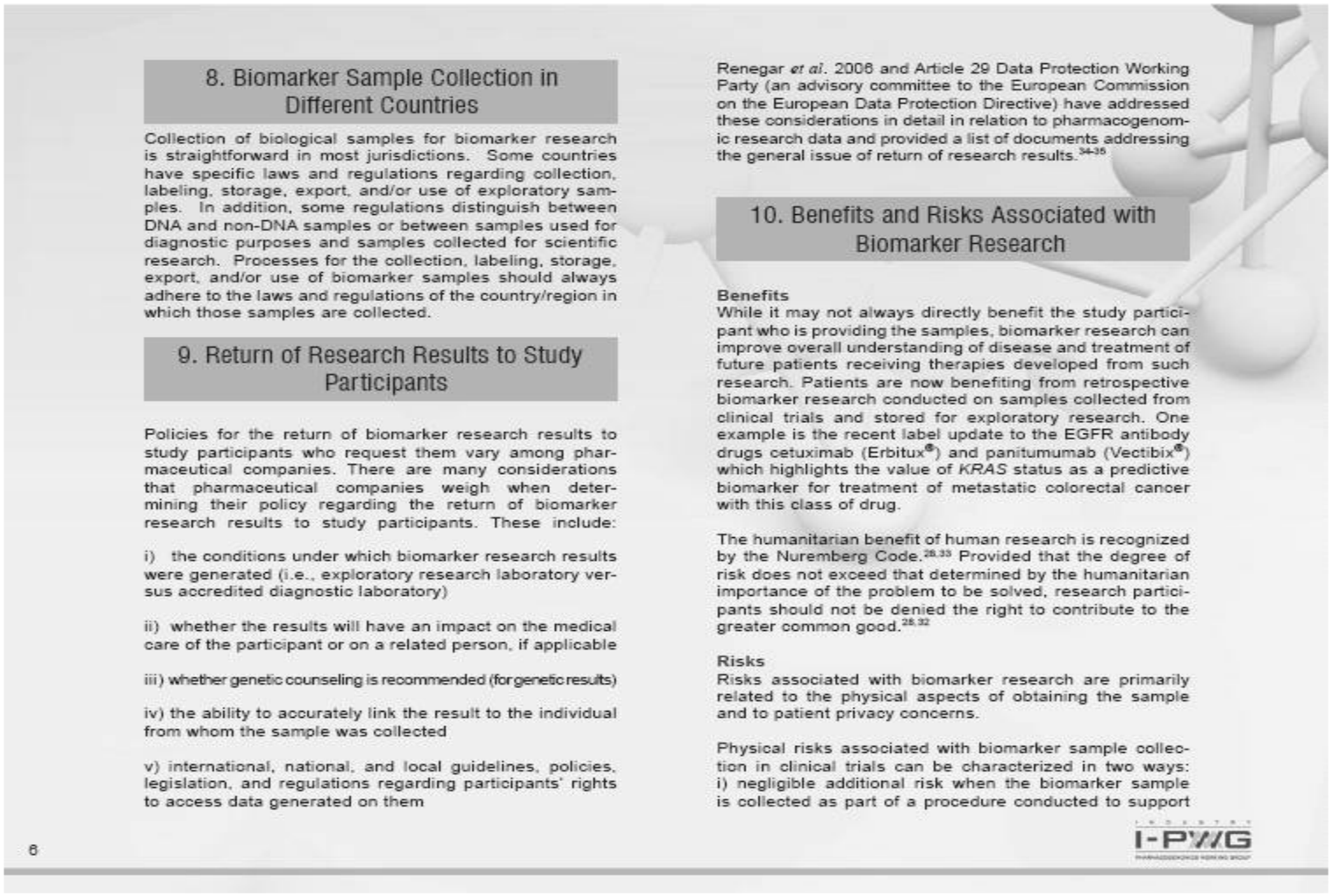

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

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

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

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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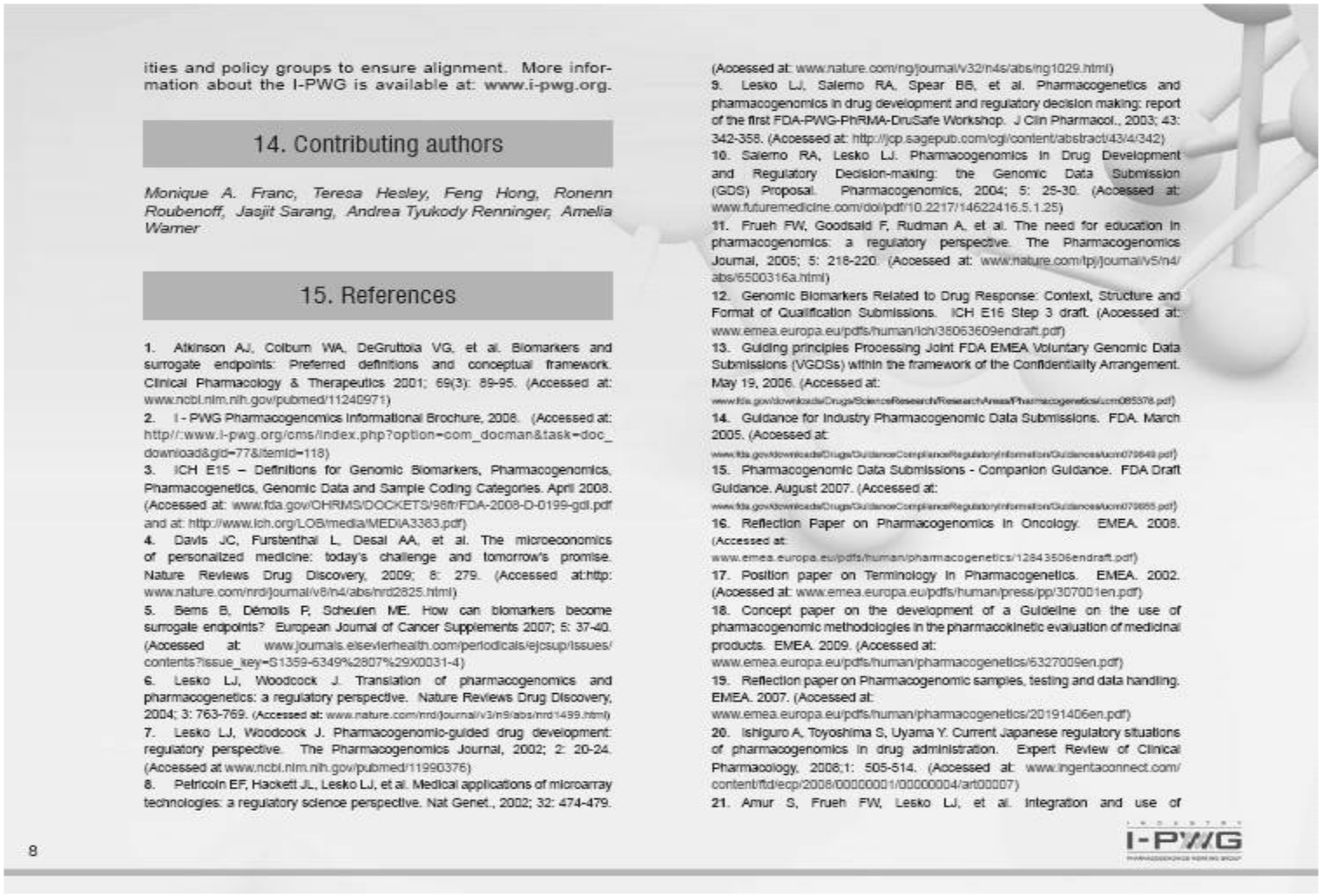

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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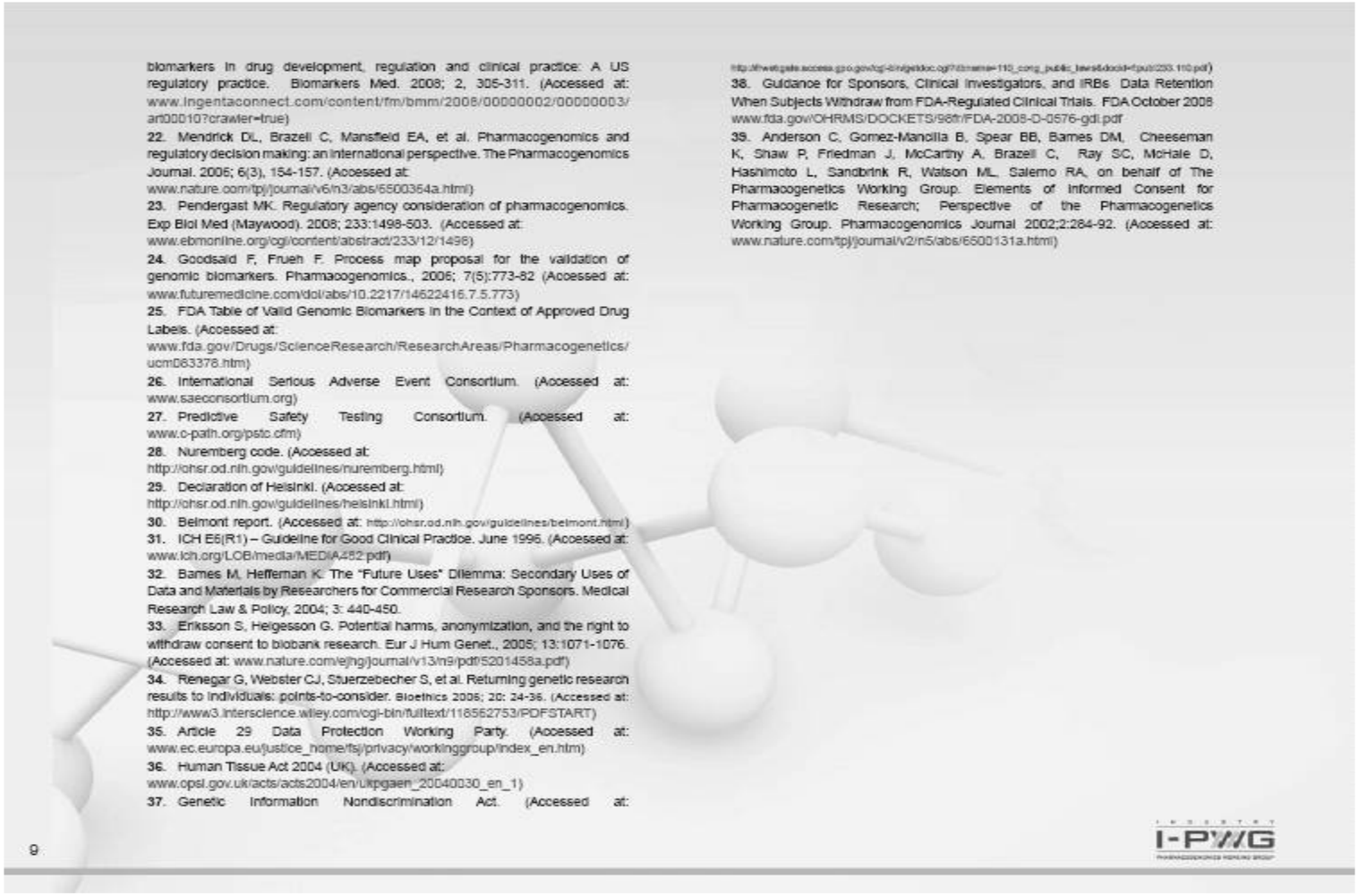

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www.i-pwg.org

12.4 Abbreviations

Abbreviation/Term	Definition
1L	First Line
AE	Adverse Event
ADA	Anti-Drug Antibodies
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
APaT	All Patients as Treated
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ß-HCG	Beta Human Chorionic Gonadotropin
CBC	Complete Blood Count
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
DAP	Data Analysis Plan
DNA	Deoxyribonucleic acid
DR	Drug Related
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
ePRO	Electronic Patient Reported Outcomes
ERC	Ethics Review Committee
FAS	Full Analysis Set
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
GC	Gemcitabine/Carboplatin
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HEA	Health Economic Assessment
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry

Abbreviation/Term	Definition
INR	International Normalized Ratio
irAEs	Immune-related Adverse Events
IRB	Institutional Review Board
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITT	Intention To Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWG	International Working Group
IWRS	Integrated Web Response System
Kg	Kilogram
KM	Kaplan-Meier
mAb	Monoclonal Antibody
mcL	Microliters
MEL	Melanoma
Mg	Milligram
Mg/kg	Milligram per Kilogram
mL	Milliliter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NA or N/A	Not Applicable
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PET	Positron emission tomography
PFS	Progression Free Survival
PGt	Pharmacogenetic
PIN	Personal Identification Number
PK	Pharmacokinetic
PK-PD	Pharmacokinetic-Pharmacodynamic
PO	Oral Administration
PR	Partial Response
PT	Prothrombin Time
PS	Performance Status
QoL	Quality of Life
R/M	Recurrent or Metastatic
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RR	Response Rate
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SFU	Survival Follow-Up
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase

Abbreviation/Term	Definition
SOC	Standard of Care
SOP	Standard Operating Procedures
T3	Total triiodothyronine
T4	Free thyroxine
TIL	Tumor Infiltrating Lymphocytes
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
V-type	Ig Variable-type
WBC	White Blood Cell

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 (eg, 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/reporting/ctc.html)

12.7 Lymphoma Disease Response Criteria

Cheson et al. Revised Response Criteria for Malignant Lymphoma. J Clin Oncol. 2007; 25:579-586.

Criteria for lymphoma disease assessment:

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	> 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	> 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by > 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, > 50% increase in SPD of more than one node, or > 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

12.7.1 Lugano Classification

Cheson et al. Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: Lugano Classification. J Clin Oncol. 2014; 32:3064-3065.

Revised Response Assessment

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	