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TITLE:

A Phase II Study of Pembrolizumab (MK-3475) in Subjects with Relapsed or Refractory Primary Mediastinal Large B-cell Lymphoma (rrPMBCL) or Relapsed or Refractory Richter Syndrome (rrRS)

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-3475-170-06	08-JUL-2020	To provide conditions for ending the study.
MK-3475-170-05	06-FEB-2018	The efficacy update for subjects with rrPMBCL was updated to be conducted at 9 months after the last subject initiated treatment and 12 months after the last subject initiated treatment. This change was implemented because PMBCL is an aggressive disease, and the expectation for response rate is low and the overall survival (OS) is less than 1 year, so the statistical analysis plan was revised to further characterize the efficacy at an earlier time point.
MK-3475-170-04	20-NOV-2017	<p>This amendment was to expand the Dose Modification and Toxicity Management Guidelines table to cover supportive care, monitoring, and follow up. Myocarditis row was also added. Clarification was also added to provide flexibility for collection of survival follow-up information.</p> <p>Additionally, the collection of samples for PK analyses was ended and associated language in the protocol was updated or omitted, enrollment of the Richter Syndrome cohort was ended, requirement for immediate notification of site personnel if a male subject impregnates a partner was removed, and clarification of the post-allogeneic stem cell follow-up was added. The statistical analysis plan was updated in response to the end of the RS cohort enrollment.</p>

Document	Date of Issue	Overall Rationale
MK-3475-170-03	23-AUG-2017	<p>This amendment implemented recommendations from the FDA to perform an interim analysis for the rrPMBCL group when at least 50% of these subjects are evaluable for a response. Also recommended by FDA was formal hypothesis testing of the primary objective, ORR, which was added, and additional long-term follow-up of subjects who underwent allogeneic stem cell transplant. In response to changes in the analysis of the primary objective, updates to the statistical analysis plan were also made to the sample size and power calculations and to add an O-Brien-Fleming Type I error spending function for the final analysis of the rrPMBCL hypothesis.</p>
MK-3475-170-02	18-JAN-2017	<p>This major amendment included updates to clarify the inclusion criteria with regard to consent/assent to the use of samples for future biomedical research and to require that subjects with Richter syndrome (RS) must have at least 1 lesion attributable to malignancy and with appropriate correlation to anatomic imaging, with uptake greater than that of normal liver tissue. Adequate organ function laboratory criteria were also updated to clarify requirements for the studied population, to include those with RS. Exclusion criteria were also updated/clarified to provide for the RS cohort.</p> <p>Tumor imaging and assessment for RS subjects was clarified and additional clarification was made to the timing of follow-up and confirmatory imaging.</p> <p>Additional updates were made in the dose modification guidelines, guidelines for discontinuation due to pregnancy, and other updates to pembrolizumab standard protocol template text. New sections were added to provide guidance on pregnancy testing, post-allogeneic stem-cell transplantation follow-up.</p> <p>Clarifications and corrections were made to increase accuracy and avoid confusion.</p>

Document	Date of Issue	Overall Rationale
MK-3475-170-01	13-JUN-2016	<p>This amendment added a cohort of subjects with Richter syndrome to the study to be treated with pembrolizumab in order to confirm the safety and efficacy of pembrolizumab in subjects with Richter syndrome based on preliminary data from another pembrolizumab trial. Modifications to the response criteria specific for Richter syndrome were also made.</p> <p>In addition, the futility analysis was removed from the protocol because data from other trials supported the continuation of enrollment.</p>
MK-3475-170-00	14-JUL-2015	Original Protocol

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.3	Extent of Trial Treatment	Added the condition “and the trial is still ongoing” to the option for restarting treatment if a subject who had a complete response subsequently progresses.	To allow for ending the trial.
5.10	Beginning and End of the Trial	Added that the trial may be ended by the Sponsor.	To allow for ending the trial.
5.11	Clinical Criteria for Early Trial Termination	Added that the trial may be ended by the Sponsor.	To allow for ending the trial.
7.1.5.4.1 7.2.3.2.1	Follow-Up Post-Allogeneic Stem Cell Transplantation Follow-Up Post-Allogeneic Stem Cell Transplantation	Added that follow-up for ECI post allogeneic stem cell transplant would continue for 18 months “unless the trial closes earlier.”	To allow for ending data collection on post-treatment allogeneic stem cell transplants when the trial is closed.
9.1	Investigational Product	Added the liquid formulation of pembrolizumab to Table 13.	To update and add pertinent details to the formulation information.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	A phase II study of pembrolizumab in subjects with relapsed or refractory primary mediastinal B-cell lymphoma (rrPMBCL) or relapsed or refractory Richter Syndrome (rrRS)
Trial Phase	Phase II
Clinical Indication	Treatment of subjects with relapsed or refractory PMBCL or RS.
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous (IV)
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab (MK-3475) 200 mg every 3 weeks (Q3W).
Number of trial subjects	Approximately 106 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 45 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form 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 a maximum of 35 administrations (approximately 2 years) per subject or until documented disease progression by investigator assessment, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. The total duration of participation is up to approximately 2 years. Subjects who attain a complete response (CR) as determined by independent central review 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 AE monitoring (serious adverse events (SAEs) and events of clinical interest (ECIs) 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 by telephone for OS 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 an open label, multicenter, single-arm trial of pembrolizumab (MK-3475) in subjects with relapsed or refractory Primary Mediastinal Large B-Cell Lymphoma (rrPMBCL) or relapsed or refractory Richter syndrome (rrRS).

Subjects with rrPMBCL must have failed to achieve a complete response (CR) or relapsed after autologous stem cell transplant (auto-SCT) or are ineligible for auto-SCT and have failed to respond or relapsed after ≥ 2 lines of prior treatment. Subjects with rrRS must have transformed from underlying chronic lymphocytic leukemia (CLL), and have been treated with at least 1 previous therapy for RS, and must be either refractory or have progressive disease (PD).

Subjects with PMBCL and rrRS are required to submit screening positron emission tomography (PET)/computed tomography (CT) scans for confirmation of measurable disease before enrolling in the study.

Pathologic diagnosis of rrPMBCL and rrRS via local institutional review is acceptable to enable study enrollment. Tissue is to be submitted for central review (Section 7.1.2.7.6).

Approximately 106 subjects will be enrolled in this trial to examine the safety and efficacy of pembrolizumab 200 mg fixed dose administered every 3 weeks (Q3W). This will give a sample size of approximately 50 subjects in the analysis population of PMBCL, and approximately 50 subjects with RS, for safety and efficacy, assuming that approximately 6% of the total of 106 enrolled subjects will not be treated. RS cohort is closed early after enrollment of 24 subjects. In the rrPMBCL cohort, a single interim analysis will be conducted (Section 8.7). Adverse events (AEs) will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment will continue up to a maximum of 35 administrations of pembrolizumab (approximately 2 years) per subject or until documented disease progression by investigator assessment, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, 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 a confirmed CR by independent central review may consider stopping trial treatment after receiving at least 8 administrations of pembrolizumab. At least two administrations of pembrolizumab must be received after CR is documented. These subjects will be eligible for retreatment for up to 17 administrations of pembrolizumab (approximately 1 year) 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 (see Section 7.1.5.2.1).

In subjects with rrRS, additional therapies to treat the underlying CLL (according to treatment guidelines) may be added (Section 5.5.1) at the physician's discretion if medically necessary and with Sponsor approval.

After the end of treatment, each subject will be followed for 30 days for AE monitoring (serious adverse events [SAEs] 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 by telephone contact for OS until death, withdrawal of consent or the end of the study, whichever comes first.

The primary objective of the trial is to determine the objective response rate (ORR) as assessed by independent central review (utilizing the International Working Group [IWG] response assessment criteria per Cheson 2007 [1]) of pembrolizumab in subjects with relapsed or refractory PMBCL. For subjects with rrRS, IWG criteria with special considerations for RS will be used (Section 12.7).

Secondary objectives for each cohort include other efficacy parameters as progression free survival (PFS), OS, disease control rate (DCR), duration of response (DOR) and safety and tolerability. Analysis of programmed cell death ligand 1 (PD-L1) expression and corresponding efficacy; along with the relationship of candidate efficacy/resistance biomarkers and anti-tumor activity of pembrolizumab, and ORR utilizing the 5-point scale Lugano Classification (Section 12.8) will be investigated as exploratory objectives for each cohort.

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](#).

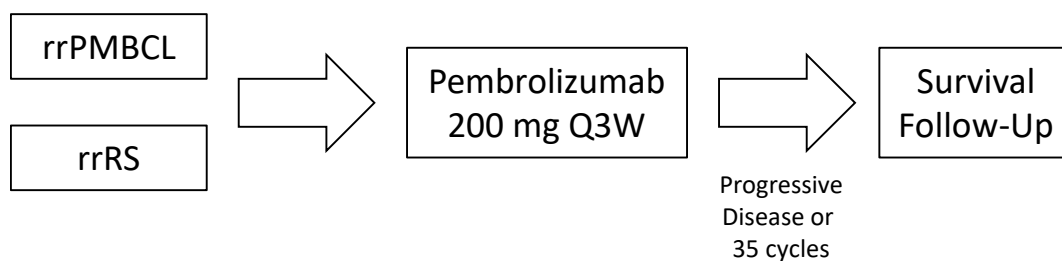


Figure 1 Trial Diagram

Abbreviations not defined above: mg – milligram(s), Q3W – every three weeks, rrPMBCL - relapsed or refractory primary mediastinal large B-cell lymphoma; rrRS: relapsed or refractory Richter syndrome.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In subjects with rrPMBCL or rrRS:

1. **Objective:** rrPMBCL: Estimate the ORR of pembrolizumab by independent central review according to the IWG response criteria (Cheson, 2007 [1]).

Hypothesis: Intravenous (IV) administration of single agent pembrolizumab will result in an ORR of greater than 15% using IWG response criteria by independent central review.

2. **Objective:** rrRS: Estimate the ORR of pembrolizumab by independent central review according to the IWG response criteria (Cheson, 2007 [1]) with special considerations for RS (Section 12.7).

3.2 Secondary Objective(s) & Hypothesis(es)

In subjects with rrPMBCL or rrRS:

1. **Objective:** To estimate the ORR of pembrolizumab by investigator assessment according to the IWG response criteria (Cheson, 2007 [1]) or IWG with special considerations for RS.
2. **Objective:** To evaluate PFS, DOR, and DCR of pembrolizumab by independent central review and investigator assessment according to the IWG response criteria (Cheson, 2007 [1]) or IWG with special considerations for RS.
3. **Objective:** To evaluate the OS of pembrolizumab.
4. **Objective:** To determine the safety and tolerability of pembrolizumab.

3.3 Exploratory Objectives

In subjects with rrPMBCL or rrRS:

1. **Objective:** To evaluate efficacy (ORR, PFS, DOR, and DCR) by independent central review according to the IWG response criteria (Cheson, 2007 [1]) or IWG with special consideration for RS, incorporating response assessments for subjects continuing pembrolizumab treatment after initial progression.
2. **Objective:** To evaluate the ORR of pembrolizumab by independent central review, using the 5-point scale according to the Lugano Classification (Cheson, 2014 [2]).
3. **Objective:** To compare the extent of pre-pembrolizumab PD-L1 expression in tumor biopsies for pembrolizumab responders versus non-responders (see Section 4.2.3.5).
4. **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 4.2.3.5).

5. **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 4.2.3.5).
6. **Objective:** To evaluate changes in health-related quality-of-life assessments from baseline using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-Core 30 items (C30) and European Quality of Life 5-Dimension (EuroQoL, EQ-5D [see Section 4.2.3.4]).

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

Pembrolizumab (previously known as MK-3475 and SCH 9000475) is a potent and highly selective humanized monoclonal antibody of the immunoglobulin (Ig)G4/kappa isotype designed to directly block the interaction between the programmed cell death-1 receptor (PD-1) and its ligands, PD-L1 and programmed cell death ligand 2 (PD-L2) without antibody-dependent cell-mediated cytotoxicity or complement dependent cytotoxicity activity. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the IB.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [3]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies [4, 5]. 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 cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [6, 7]. The structure of murine PD-1 has been resolved [8]. 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 and an immunoreceptor tyrosine based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 ζ , PKC θ and ZAP70 which are involved in the CD3 T-cell signaling cascade [7, 9, 10, 11]. 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 [12, 13]. 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 [14, 15]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [16]. 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 [3, 13, 17, 18, 19]. 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 [20]. 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 monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of interferon gamma, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [21, 22, 23, 24, 25, 26]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (refer to the IB).

In a Phase 1/2 study of 135 subjects with advanced melanoma treatment with pembrolizumab produced an ORR of 38% (95% confidence interval [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 [27].

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, 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 Primary Mediastinal Large B-Cell Lymphoma

Non Hodgkin lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originated in B-lymphocytes, T-lymphocytes or natural killer cells. In the United States, (US) B-cell lymphomas comprise 80 to 85% of NHL subjects. It is estimated that in 2015 around 71,850 new NHL cases will be diagnosed in United States, with approximately 19,790 deaths due to the disease [28]. Diffuse Large B-Cell lymphoma (DLBCL) is the most common type of adult NHL in both North America and Europe, making up 30% to 40% of NHL. PMBCL is a distinct subtype of NHL that histologically can be indistinguishable from DLBCL and account only for 2% to 3% of all cases. This subtype tends to occur in young adults with a median age of 35 years with a slight female predominance [29, 30, 31]. Interestingly, gene expression profiling has revealed that the pattern of gene expression in PMBCL is more similar to classical Hodgkin lymphoma (CHL) than DLBCL [32, 33].

The optimal therapeutic approach to PMBCL is controversial due to the limited availability of prospective studies resulted from the rarity of the disease. For the most part, therapeutic approaches for PMBCL have been the same as the ones used for other subtypes of DLBCL, with regimens like R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) widely used in front line. However, the recently reported high efficacy of increased dose intensity regimens as MACOP-B (methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) followed by mediastinal radiation therapy in this disease suggests it may require a unique therapeutic approach [34, 35, 36]. Two retrospective studies have reported data regarding comparison between CHOP-like regimens and MACOP-B-like regimens as induction chemotherapy for subjects with PMBCL [36, 37]. In these studies CR rates were between 49% and 53% with projected 10-year overall survival rates between 44% and 77% and projected 10-year progression free survival rates between 35% and 78%, respectively.

Overall, in the absence of randomized PMBCL clinical trials recommendations for optimal front line treatment for PMBCL subjects is more controversial than for other subtypes of DLBCL, with the consensus in US that R-CHOP followed by +/- radiotherapy or dose adjusted R-EPOCH (rituximab, etoposide phosphate, prednisone, vincristine sulfate [Oncovin], cyclophosphamide, doxorubicin hydrochloride [Hydroxydaunorubicin]) followed by +/- radiotherapy for persistent local disease are the preferred options for front line treatment.

There is currently very limited data available regarding the optimal treatment for relapsed or refractory PMBCL. The current approach is to extrapolate from modalities commonly used in the relapsed and refractory setting for other DLBCL subtypes like auto-SCT following front line or salvage chemotherapy regimens for auto-SCT ineligible subjects.

In the case of auto-SCT results from the Grupo Espanol de Linfomas y Transplante Autologo de Medula Osea (GEL-TAMO) group suggested that auto-SCT should be considered for subjects who do not achieve CR to front line treatment but who are still judged to be sensitive to chemotherapy, although in the absence of randomized clinical trials these results

continue to be controversial [38]. The GEL-TAMO group registry included 71 subjects with PMBCL who received induction chemotherapy, followed by auto-SCT as frontline therapy. At transplant, 49% of subjects were in CR, 32% in partial response/remission (PR) and 18% failed induction therapy; 53% received radiotherapy. After the transplant, 75% of subjects achieved CR. With a median follow-up of 52.5 months, the OS, PFS and disease-free survival at 4 years from diagnosis were, respectively, 84%, 81% and 81% for the first CR subjects and 49%, 42% and 82% for the induction failure (PR and refractory) subjects. Disease progression was the main cause of death (79%). Based on these results, the GEL-TAMO group concluded that subjects with PMBCL presenting at diagnosis with high-risk features or PR response to induction therapy had an encouraging survival with frontline auto-SCT. However, subjects who received the transplant after failing the induction regimen have a very poor prognosis and should be tested with other innovative approaches.

In US, the recommendation from the National Comprehensive Cancer Network for subjects who are not eligible for auto-SCT is to be treated in the context of clinical trials or alternatively with individualized salvage chemotherapy regimens with or without rituximab depending on whether the patient was deemed to be refractory to previous rituximab regimens. In a pilot study of 46 subjects with relapsed or refractory B-cell lymphoma, the majority of whom had DLBCL (72%), rituximab, gemcitabine, and oxaliplatin resulted in an ORR of 83% and half of the subjects achieved a CR [39]. The 2-year event-free survival and OS rates in this study were 43% and 66% respectively. The lack of clinical trials focusing on rrPMBCL make difficult the ability to select a specific chemotherapy regimen for this patient population, with no defined standard of care in the relapsed and refractory setting.

Preliminary results from our ongoing Phase 1b study evaluating pembrolizumab 10 mg/kg every 2 weeks (Q2W) in subjects with hematologic malignancies including myelodysplastic syndromes, Hodgkin lymphoma (HL), PD-L1-positive NHL, rrPMBCL and multiple myeloma indicate a response rate of 53.3%, including a CR rate of 20.0% in heavily pretreated HL subjects who had progressed after all lines of prior therapy including stem cell transplant [40]. Preliminary results for the rrPMBCL cohort in this study indicate a response rate of 33.3%, including a CR rate of 11.1% for this patient population.

Overall, treatments for recurrence and progression of disease for PMBCL subjects are of limited efficacy and their prognosis is exceedingly poor [34, 36]. Subjects with PD after salvage treatment are unlikely to derive clinical benefit from current treatment modalities. Therefore, in the absence of standard of care, relapsed or refractory PMBCL represents an urgent unmet medical need.

4.2.1.2 Richter Syndrome

The 2008 World Health Classification of hematopoietic tumors defines RS as the transformation of CLL into a more aggressive lymphoma [41]. Approximately 2% to 10% of CLL patients will experience transformation to a more aggressive lymphoma during the course of their disease, with a transformation rate of 0.5% to 1% per year [42]. The vast majority of these transformations are DLBCL; transformation to HL is reported rarely.

Diagnosis of RS follows an investigation of apparently rapidly progressing underlying disease per signs and symptoms, and assessed by PET/CT. A standardized uptake value > 5

is suggestive of RS, which may be confirmed by lymph node biopsy demonstrating DLBCL (or HL).

The treatment for patients with RS is challenging due to the lack of randomized clinical trials to establish strategies. Standard treatment approaches for RS have been suboptimal, as evident by the overall survival duration. Induction therapy with R-CHOP can be used, but if the patient has previously received anthracyclines for their underlying disease, platinum-based inductions regimens may be considered. (Induction with ABVD [doxorubicin {Adriamycin}, bleomycin, vinblastine, dacarbazine] should be considered for RS to HL.) If eligible for SCT, allogeneic transplant is preferred (to also target the underlying disease) if there is a donor; otherwise auto-SCT may be considered for treatment of the DLBCL (not the underlying disease). For patients who do not respond to induction with anthracycline or platinum therapy, clinical trials of novel agents and/or supportive care should be considered [42].

In a report of patients with CLL treated with ibrutinib, approximately half of the patients with disease progression on ibrutinib had RS transformation. In these n=18 RS patients the median survival was 3.5 months (10 days to 6 months) following transformation despite treatment with commonly used regimen for DLBCL including R-EPOCH, R-CHOP, R-ICE (rituximab, ifosfamide, carboplatin, etoposide), or others [43]. In another report, in n=46 newly transformed RS patients treated with R-EPOCH the median PFS was 3.5 months and median OS was 5.9 months [44].

Patients with RS have a generally poor prognosis after transformation, and represent an unmet medical need.

4.2.1.3 Rationale for Evaluating anti-PD-1 Therapy in Primary Mediastinal Large B-Cell Lymphoma and Richter syndrome

Lymphoid malignancies are known to be responsive to a variety of immunotherapies, including allogeneic stem cell transplantation. 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 hematologic malignancies.

High frequency of expression of PD-L1 by immunohistochemistry and flow cytometry has been demonstrated in classic HL and NHL tumor cells including PMBCL [45]. A recent integrative genetic analysis revealed frequent selective 9p24.1 amplification in PMBCL, which includes the PD-L1 and PD-L2 loci, resulting in increased PD-L1 expression and further induction via JAK2 [45]. Amplification on chromosome 9p24 is observed in approximately 70% of PMBCL cases [46]. The 9p24 amplicon contains several key targets, such as *CD274* (encoding PD-L1), *PDCD1LG2* (encoding PD-L2) and *JAK2* [45, 47]. The frequent over-expression of PD-L1 and PD-L2 on PMBCL tumor cells suggests that this is an important mechanism for tumor evasion [48, 49]. Recurrent unbalanced rearrangements involving the major histocompatibility complex class II transactivator (*CIITA*), with multiple fusion partners, were reported in 38% of cases of PMBCL and these *CIITA* gene fusions were found to result in overexpression of PD-1 ligands [50]. These results further implicate the PD-1 pathway as a potential target in PMBCL.

A Phase I clinical trial conducted in advanced hematologic malignancies using CT-011, a humanized antibody anti PD-1, showed clinical responses in 6 of 17 subjects including HL and NHL subjects [51]. Preliminary results from our ongoing Phase Ib study [Keynote-013] evaluating pembrolizumab 10 mg/kg every 2 weeks in subjects with hematologic malignancies including myelodysplastic syndromes, HL, PD-L1-positive NHL, and multiple myeloma indicate a response rate of 53.3%, including a CR rate of 20.0% in heavily pretreated HL subjects who had progressed after all lines of prior therapy including stem cell transplant [40]. This is particularly important since PMBCL and HL share many common biological features, including the frequent 9p24 amplification mentioned above. Indeed, preliminary results for the rrPMBCL cohort in this study indicate a response rate of 33.3%, including a CR rate of 11.1% for this patient population.

From the preliminary results of a phase 2 trial [52] of pembrolizumab monotherapy for the treatment of rrCLL including RS, among 7 RS patients enrolled, there was 1 CR, 2 PR (possible CR for RS without nodal biopsy confirmation but residual underlying CLL, resulting in overall PR), 3 stable disease (SD), and 1 PD. Among these, 5 RS patients experienced previous PD on ibrutinib; all 5 had either CR/PR or SD with nodal or skin lymphoma responses [Data on file; Merck].

Two subjects with newly transformed RS without any prior treatment for RS have been treated with pembrolizumab monotherapy, and achieved PR [Data on file; Merck].

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for Fixed Dose Pembrolizumab

The planned dose of pembrolizumab for this trial is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications and regardless of tumor type. As outlined below, this dose is justified by:

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

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small cell lung cancer, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W vs. 10 mg/kg Q3W (Keynote-001 B2, Keynote-001 D, Keynote-002, Keynote-010, and Keynote-021), and 3 studies compared 10 mg/kg Q3W vs. 10 mg/kg Q2W (Keynote-001 B3, Keynote-001 F2, and Keynote-006). All of these studies demonstrated flat dose- and

exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and CHL, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in Keynote-001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

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

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy objective of this study is to evaluate the anti-tumor activity of pembrolizumab in subjects with rrPMBCL or rrRS. The primary efficacy endpoint will be ORR as assessed by independent central review, according to the IWG response criteria (Cheson, 2007 [1]) for PMBCL, and for RS, the IWG criteria with special considerations for RS (Section 12.7).

Other secondary efficacy endpoints will include PFS, DOR, DCR, OS and as exploratory endpoints, efficacy (ORR, PFS, DOR, and DCR) incorporating response assessments for subjects continuing pembrolizumab treatment after initial progression and ORR using the 5-point scale per the Lugano Classification.

4.2.3.2 Safety Endpoints

The safety and tolerability of pembrolizumab in subjects with rrPMBCL or rrRS will be characterized in this study. The 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 SAEs and ECIs.

Safety will be assessed by reported AEs using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, the occurrence of a Grade 2 or higher immune-related adverse events (irAEs) will be collected and designated as irAEs.

4.2.3.3 Patient Reported Outcomes

EORTC QLQ-C30, EQ-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 electronic (e) EQ-5D is a standardized instrument for use as a measure of health outcome. The eEQ-5D will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life years. The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a three 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.

4.2.3.4 Planned Exploratory Biomarker Research

Planned Genetic Analysis

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

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 deoxyribonucleic acid (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.

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 be limited to:

Multiplex Flow Cytometric Analysis

Emerging data suggest that blockade of the PD-1/PD-L1 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, e.g., Naïve, activated, memory and regulatory T cells, will be assessed pre- and post-dose and in both responders and non-responders. Natural killer cells enumeration will also be performed pre- and post-dose in both responders and non-responders.

Transcriptional Analyses

Messenger ribonucleic acid (RNA) 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” response within the tumor reflected in the physical proximity between PD-1 and PD-L1 expression and the presence of an aborted (e.g., 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 (e.g., interleukin-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 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.

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.

4.3 Benefit/Risk

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

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with rrPMBCL or rrRS, 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 (FBR). However, the subject may participate in the main trial without participating in FBR.
2. Be \geq 18 years of age on day of signing informed consent.

PMBCL:

3. Diagnosis of PMBCL, according to the World Health Organization (WHO) classification of neoplasms of the hematopoietic and lymphoid tissues (WHO Criteria, 2008 [48]). Subject must be able to provide an evaluable core or excisional lymph node biopsy for evaluation of PMBCL diagnosis from an archival or newly obtained lymph node biopsy at Screening. (Central review is not required before enrollment. Enrollment can be done on local pathologic review for diagnosis.)
4. Have relapsed^{*a} or refractory^{*b} PMBCL and:
 - Have relapsed after auto-SCT or have failed to achieve a CR or PR within 60 days of auto-SCT. Subjects may have received intervening therapy after auto-SCT for relapsed or refractory disease, in which case they must have relapsed after or be refractory to their last treatment.

OR

- For subjects who are ineligible for auto-SCT, have received at least ≥ 2 lines of prior therapy and have failed to respond to or relapsed after their last line of treatment. For subjects who received consolidative local radiotherapy after systemic therapy, local radiotherapy will not be considered as a separate line of treatment.

*^a **Relapsed Disease:** progression of disease after achieving a remission to the most recent therapy

*^b **Refractory Disease:** failure to achieve CR or PR to the most recent therapy

5. Must have been previously exposed to rituximab as part of prior lines of treatment.

Richter syndrome:

6. Pathologic diagnosis per local institutional review of Richter syndrome that transformed from CLL.
7. Have relapsed or refractory RS and has received at least 1 previous treatment for RS.

All Subjects:

8. Have radiographically measureable disease by independent central review, defined as at least one lesion that can be accurately measured in at least two dimensions with appropriate anatomic imaging (CT scan or magnetic resonance imaging [MRI]). Minimum measurement must be > 15 mm in the longest diameter.
 - a. RS subjects must also be (PET positive at screening, defined as having at least one lesion, attributable to malignancy and with appropriate correlation to anatomic imaging, with uptake greater than that of normal liver tissue.
9. Must have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.
10. Life expectancy > 3 months
11. Must demonstrate adequate organ function as defined in [Table 1](#); all screening labs should be performed within 7 days of treatment initiation. (Subjects may be enrolled based on local laboratory results pending central laboratory results.)

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	PMBCL):>1,000.0/mcL/ RS:>500/mcL (unless marrow involvement) Granulocyte colony stimulating factor allowed during screening for RS only
Platelets	PMBCL \geq 75,000.0/mcL (RS: \geq 25,000/mcL) (unless marrow involvement)
Hemoglobin	\geq 8.0 g/dL (unless marrow involvement)
Renal	
Creatinine OR Measured or calculated ^a creatinine clearance (Glomerular filtration rate can also be used in place of creatinine or creatinine clearance)	\leq 1.5 X upper limit of normal (ULN) OR \geq 60.0 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Total bilirubin	\leq 1.5 X ULN OR Direct bilirubin \leq ULN for subjects with total bilirubin levels > 1.5 ULN
Aspartate aminotransferase (SGOT)and alanine aminotransferase (SGPT)	\leq 2.5 X ULN OR \leq 5 X ULN for subjects with liver metastasis
Albumin	\geq 3.0 g/100 mL
Coagulation	
International Normalized Ratio or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	\leq 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 \leq 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
Abbreviations: PMBCL – primary mediastinal B-cell lymphoma; RS – Richter Syndrome; SGOT – serum glutamate oxaloacetic transaminase; SGPT – serum glutamate pyruvic transaminase. ^a Creatinine clearance should be calculated per institutional standard.	

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

13. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception, as outlined in Section 5.7.2 – Contraception, for the course of the study 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.

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

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 investigational device within 4 weeks of the first dose of treatment.
2. Is receiving systemic steroid therapy < 3 days before the first dose of trial treatment or receiving any other form of immunosuppressive medication.

Note:

- a. Corticosteroid use on study after Cycle 1 for management of AEs, SAEs, and ECIs, as a premedication for IV contrast allergies/reactions, or if considered necessary for a subject's welfare is allowed.
 - b. Subjects who receive daily steroid replacement therapy are an exception. Daily prednisone at doses of 5 to 7.5 mg is an example of replacement therapy.
 - c. Equivalent hydrocortisone doses are also permitted if administered as replacement therapy.
3. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 (2 weeks for RS subjects) or who has not recovered (i.e., \leq Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier (2 weeks for RS subjects).
 4. Has had prior chemotherapy or targeted small molecule therapy within 2 weeks prior to study Day 1 or has had prior radiation therapy within 4 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from AEs due to a previously administered agent.

Exception: Subjects with RS with CLL may receive ibrutinib (or similar for CLL) up to 24 hours before first dose.

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 \leq 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 Graft versus Host Disease (GVHD)).
6. Has a known additional malignancy (except underlying CLL for RS) 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 active central nervous system (CNS) involvement. Subjects with prior CNS involvement are eligible if their CNS disease is in radiographic, cytological (for cerebrospinal fluid disease) and clinical remission.
8. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., 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-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 and 2 antibodies).
15. Has known active Hepatitis B (e.g., Hepatitis B surface antigen reactive) or Hepatitis C (e.g., Hepatitis C virus 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	200 mg	Q3W	IV infusion	Day 1 of each treatment cycle up to 35 administrations (approximately 2 years)	Experimental

Abbreviations: IV – intravenous; Q3W – every 3 weeks

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

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)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

All subjects will receive 200 mg pembrolizumab by IV infusion within a 30 minute period, Q3W. Details on the preparation and administration of study drug are provided in the Pharmacy Manual.

5.2.1.2 Dose Modification

Adverse events (both nonserious and serious) associated with pembrolizumab exposure may have an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug related toxicities and severe or life-threatening AEs as per [Table 3](#).

In addition, subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures, as described in Section 5.6.1, are also included in [Table 3](#).

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to trial therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on trial therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's trial record.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab

General instructions:				
<ol style="list-style-type: none"> 1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks. 2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks. 3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids. 				
Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). • Participants with \geq Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or increased bilirubin	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	<ul style="list-style-type: none"> Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β -cell failure	Withhold	<ul style="list-style-type: none"> Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia 	<ul style="list-style-type: none"> Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids and initiate hormonal replacements as clinically indicated. 	<ul style="list-style-type: none"> Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue ¹		
Hyperthyroidism	Grade 2	Continue	<ul style="list-style-type: none"> Treat with non-selective beta-blockers (e.g., propranolol) or thioamides as appropriate 	<ul style="list-style-type: none"> Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue ¹		
Hypothyroidism	Grade 2-4	Continue	<ul style="list-style-type: none"> Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care 	<ul style="list-style-type: none"> Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper. 	<ul style="list-style-type: none"> Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Myocarditis	Grade 1 or 2	Withhold	<ul style="list-style-type: none"> Based on severity of AE administer corticosteroids 	<ul style="list-style-type: none"> Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	<ul style="list-style-type: none"> Based on type and severity of AE administer corticosteroids 	<ul style="list-style-type: none"> Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
<p>Abbreviations: AE – adverse event; ALT – alanine transaminase; AST – aspartate transaminase; CTCAE – Common Terminology Criteria for Adverse Events; GI – gastrointestinal; irAE – immune-related adverse event; IV – intravenous; T1DM – type 2 diabetes mellitus.</p> <p>1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.</p> <p>NOTE: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).</p>				

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). Cycle 1 may not be administered until after completion of all screening assessments and randomization. Beginning with Cycle 2 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.

Trial treatments will be administered on an outpatient basis. Inpatient study drug administration may be allowed with sponsor consultation.

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 (i.e., 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 may remain on treatment for up to 35 administrations of pembrolizumab (approximately 2 years) or until confirmed PD.
- Per the investigator's discretion subjects who achieve a CR may stop treatment and are eligible to restart treatment upon documented progression as long as they meet eligibility criteria specified in the protocol (see Section 7.1.5.2.1) and the trial is still ongoing. These subjects will be eligible for retreatment for up to 17 administrations of pembrolizumab (approximately 1 year).

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

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There is one treatment arm.

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 prothrombin time or partial thromboplastin time 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 after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

In subjects with rrRS, additional therapies to treat the underlying CLL (according to treatment guidelines) may be added at the physician's discretion if medically necessary and with Sponsor approval. These therapies must be approved by regulatory authorities for CLL and commercially available.

Corticosteroid use on study for management of AEs, SAEs, and ECIs, as a premedication for IV contrasts, allergies/reactions, or if considered necessary for a subject's welfare is allowed.

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
- Granulocyte Macrophage - Colony Stimulating Factor
- Immunotherapy not specified in this protocol, however Immunoglobulin Therapy (IVIG) is allowed
- Chemotherapy not specified in this protocol

- Investigational agents other than pembrolizumab
- Radiation therapy

Note: Radiation therapy to a symptomatic soft tissue lesion, bone lesions, or to the brain may be allowed after consultation with Sponsor.

Note: Radiation may be administered ONLY to subjects that have CR, PR, or SD who in the opinion of the investigator may have a tumor flare reaction in an isolated area. **Subjects that are progressing with no suspicion of tumor flare and require radiation therapy must be discontinued from study treatment.**

- 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, chickenpox, yellow fever, rabies, Bacillus Calmette-Guerin, and oral typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and are not allowed.

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 AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.2 ([Table 3](#)). Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to [Table 3](#) in Section 5.2.1.2 for guidelines regarding dose modification and supportive care.

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should maintain a normal 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.

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

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

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

OR

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

OR

3. has a congenital or acquired condition that prevents childbearing.

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

1. practice abstinence† from heterosexual activity;

OR

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

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

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

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

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

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

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

5.7.3 Use in Pregnancy

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

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation are important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment period will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5.3 – Post Treatment Visits.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

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

- The subject or subject's legally acceptable representative requests to discontinue treatment.
 - Confirmed radiographic disease progression outlined in Section 7.1.2.7.5 (exception if the Sponsor approves treatment continuation).
 - Unacceptable adverse experiences as described in Section 7.2
 - Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
 - Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
 - Recurrent Grade 2 pneumonitis
 - A confirmed positive serum pregnancy test
 - Noncompliance with trial treatment or procedure requirements
 - Investigator's decision to withdraw the subject

For subjects who are discontinued from treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed.

5.8.2 Withdrawal from the Trial

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

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

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

5.9 Subject Replacement Strategy

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) or the Sponsor ends the trial, whichever occurs first.

5.11 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete,
2. Poor adherence to protocol and regulatory requirements,
3. Plans to modify or discontinue the development of the study drug.
4. Sponsor's decision to terminate the study.

In the event of Sponsor decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Trial Flow Chart

Trial Period	Screening Phase	Treatment Cycles									End of Treatment	Post-treatment		
		To be repeated beyond 9 cycles										Discon	Post-Treatment Safety Follow-up	Follow-up Visits ^a
Treatment Cycle/Title	Screening (Visit 1)	1	2	3	4	5	6	7	8	9	Discon			
Scheduling Window (Day 1 of each cycle + 3 days)	-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 post Discon (±14 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Administrative Procedures														
Informed Consent	X													
Informed Consent for Future Biomedical Research	X													
Inclusion/Exclusion Criteria	X													
Subject Identification Card	X													
Demographics and Medical History	X													
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	
Obtain randomization number and study drug assignment using IVRS/IWRS	X													
Pembrolizumab Administration		X	X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X	X	X
Survival Status ^b		←-----→										←-----→		X ^b
Clinical Procedures/Assessments														
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X ^h
Full Physical Examination	X					X					X			X ^h
Directed Physical Examination		X		X				X						

Trial Period	Screening Phase	Treatment Cycles									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	Follow-up Visits ^a	Survival Follow-up ^b					
Scheduling Window (Day 1 of each cycle + 3 days)	-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 post Discon (±14 days)	Every 12 weeks (±7 days) or as directed by the Sponsor					
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X		X ^h						
12-Lead Electrocardiogram	X																		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X		X ^h						
Neck, Chest, Abdominal, Pelvic PET, CT	X					X ^{c, d}				X ^{c, d}	X ^d		X ^a						
Disease Response Assessment by IWG criteria						X				X	X		X ^a						
Assessment of Lymphoma B Symptoms	X					X				X	X		X ^a						
Laboratory Procedures/Assessments: analysis performed by local laboratory																			
Pregnancy Test – Urine or Serum β-HCG ^e	(≤ 72 hrs)	X	X	X	X	X	X	X	X	X		X							
Bone Marrow Biopsy and Aspirate ^f	X					PRN ^f				PRN ^f									
Bone marrow morphology, Cytogenetics	X																		

Trial Period	Screening Phase	Treatment Cycles									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	Follow-up Visits ^a	Survival Follow-up ^b
Scheduling Window (Day 1 of each cycle + 3 days)	-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 post Discon (±14 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Laboratory Procedures/Assessments: analysis performed by central laboratory														
Lymph Node Biopsy (archival or newly obtained sample)	X ^{fg}					X ^h					X th			
Whole Blood for Correlative Studies (RNA/DNA)	X		X			X					X			
Blood for Biomarker Studies (plasma and serum)	X			X		X					X			
Blood for Genetics		X												
PT/INR and aPTT	X													
CBC with Differential	X (-7 days)	X	X	X	X	X	X	X	X	X	X	X	X ⁱ	
Comprehensive Chemistry Panel	X (-7 days)	X	X	X	X	X	X	X	X	X	X	X	X ⁱ	
LDH	X					X								
Urinalysis	X		X		X		X		X			X		
T3 (or FT3 per local standard), FT4 and TSH	X		X		X		X		X			X		
Patient Reported Outcomes														
EuroQoL EQ-5D ^k		X ^j	X ^j	X ^j	X ^j	X ^j				X ^j	X ^j	X ^j		
EORTC QLQ-C30 ^k		X ^j	X ^j	X ^j	X ^j	X ^j				X ^j	X ^j	X ^j		

Abbreviations: aPTT – activated partial thromboplastin time; β -hCG – beta human chorionic gonadotropin; CBC– complete blood count; CLL – chronic lymphocytic leukemia; CR – complete response/remission; CT – computed tomography; DNA – deoxyribonucleic acid; ECOG – Eastern Cooperative Oncology Group; EORTC QLQ C30 – European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; ePRO – electronic patient reported outcome; EQ-5D – European Quality of Life 5-Dimension; FT3 – free triiodothyronine; FT4 – free thyroxine; INR – International Normalized Ratio; IVRS – Integrated Voice Response System; IWG – International Working Group; IWRS – Integrated Web Response System; LDH – lactate dehydrogenase; PET – positron emission tomography; PD – progressive disease; PRO – patient reported outcome; PT – prothrombin time; RNA – ribonucleic acid; RS – Richter Syndrome; T3 – triiodothyronine; TSH – thyroid stimulating hormone.

- a. 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 (\pm 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression by investigator assessment, (3) death, or (4) the end of the study, whichever occurs first.
- b. After the start of new anti-cancer treatment or documented disease progression by investigator assessment, the subject will transition to the Survival Follow-up and should be contacted by telephone (or in person if recent contact for other purposes during window) approximately every 12 weeks to assess survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).
- c. If subjects have stable disease, partial remission, or complete response they should continue on every 12 week (\pm 7 days) assessment schedule as described in section 7.1.2.7.4. Imaging should occur at any time where there is clinical suspicion of progression.
- d. In subjects with an unconfirmed PD assessment who continued study therapy, a radiological assessment should be performed 12 weeks (\pm 7 days) later or 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. However, imaging should occur at any time where there is clinical suspicion of progression.
- e. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to each cycle 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.
- f. For all subjects, collect bone marrow biopsy and aspirate at baseline. Repeat bone marrow biopsy and aspirate as needed to confirm CR. Local results of bone marrow biopsy and aspirate will be used for baseline and to confirm CR (or other reason). Residual bone marrow biopsy sample (all subjects for any sample obtained) should be sent to the central lab for potential future central analysis per sponsor discretion. For RS it is necessary to confirm marrow clearance of RS or lymphoma clone to confirm CR. If indeterminate by morphology, immunohistochemistry should be negative. Residual underlying CLL may persist in node and/or marrow and still qualify as CR.
- g. At screening subjects are required to submit an archival or newly obtained sample of lymph node biopsy. An archival sample is acceptable for subjects in which tumors are inaccessible or contraindicated due to subject safety concerns.
- h. Newly obtained sample of lymph node biopsies at Week 12 (\pm 7 days) and at the time of discontinuation due to disease progression are optional but highly recommended. Newly obtained samples of lymph node biopsies for subjects in which tumors are inaccessible or contraindicated due to subject safety concerns are exempt from this requirement. Detailed instructions for tissue collection, processing, and shipment are provided in the Procedures Manual
- i. To be performed only up to 90 days of the end of treatment or before initiation of a new antineoplastic treatment.
- j. Patient reported outcomes (PROs) are assessed every cycle for the first five cycles and every 4 cycles thereafter until PD or up to 1 year 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. If the subject does not complete the ePROs, the MISS_MODE form must be completed to capture the reason the assessment was not performed. Subjects who are on-study (signed informed consent) before approval of Amendment 01 (which instituted PROs) do not need to complete PROs.

6.2 Trial Flow Chart: Second Course Phase (Retreatment for Post-Complete Response Relapse Only)

Trial Period	Treatment Cycles									End of Treatment	Post-treatment		
	1	2	3	4	5	6	7	8	9		Discon	Post-Treatment Safety Follow-up	Follow-up Visits ^a
	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 ^a	Survival Follow-up ^b
Scheduling Window (Day 1 of each cycle + 3 days)	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post last dose (±3 days)	Every 12 weeks post Discon (±14 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Administrative Procedures													
Eligibility Criteria ^c	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab Administration	X	X	X	X	X	X	X	X	X				
Post-study anticancer therapy status											X	X	X
Survival Status ^b													X ^b
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X ^f	
Full Physical Examination					X				X	X			
Directed Physical Examination	X		X				X						
Vital Signs and Weight	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					X ^{d,e}				X	X ^e		X ^a	
Disease Response Assessment by IWG criteria					X				X	X		X ^a	
Assessment of Lymphoma B Symptoms					X				X	X		X ^a	

Trial Period	Treatment Cycles									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 ^a	Survival Follow-up ^b
Scheduling Window (Day 1 of each cycle + 3 days)	+3	±3	±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days post last dose (±3 days)	Every 12 weeks post Discon (±14 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Laboratory Procedures/Assessments: analysis performed by local laboratory													
Pregnancy Test – Urine or Serum β-HCG	X	X	X	X	X	X	X	X	X		X		
Bone Marrow Biopsy and Aspirate	X												
Laboratory Procedures/Assessments: analysis performed by central laboratory													
Blood for Correlative Studies (DNA/RNA)		X			X								
CBC with Differential		X	X	X	X	X	X	X	X	X	X		
Comprehensive Chemistry Panel		X	X	X	X	X	X	X	X	X	X		
LDH					X				X	X	X		
Urinalysis		X		X		X		X			X		
T3 (or FT3 per local standard), FT4 and TSH		X		X		X		X		X	X		

Abbreviations: aPTT – activated partial thromboplastin time; β -hCG – beta human chorionic gonadotropin; CBC– complete blood count; CLL – chronic lymphocytic leukemia; CR – complete response/remission; CT – computed tomography; DNA – deoxyribonucleic acid; ECOG – Eastern Cooperative Oncology Group; FT3 – free triiodothyronine; FT4 – free thyroxine; INR – International Normalized Ratio; IVRS – Integrated Voice Response System; IWG – International Working Group; IWRS – Integrated Web Response System; LDH – lactate dehydrogenase; PET – positron emission tomography; PD – progressive disease; PT – prothrombin time; RNA – ribonucleic acid; T3 – triiodothyronine; TSH – thyroid stimulating hormone.

- a. 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 (\pm 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.
- b. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone (or in person if recent contact for other purposes during window) 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 subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).
- c. Subjects who attain a CR by independent central review and discontinue treatment may restart trial treatment if they meet the criteria specified in Section 7.1.5.2.1.
- d. If subjects have stable disease, partial remission, or complete response they should continue on every 12 week assessment schedule. Imaging should occur at any time where there is clinical suspicion of progression.
- e. Imaging should occur as described in Section 7.1.2.7.4 In subjects with an unconfirmed PD assessment who continued study therapy, a radiological assessment should be performed 4-6 weeks later or 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. However, imaging should occur at any time where there is clinical suspicion of progression.
- f. To be performed only up to 90 days of the end of treatment or before initiation of a new antineoplastic treatment.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Details regarding the disease for which the subject has enrolled in this trial will be recorded separately and not listed as medical history.

Prior acute or 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. Record all medications taken for SAEs and ECIs as defined in Section 7.2.

7.1.1.5.3 Prior Cancer 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.

7.1.1.5.4 Subsequent Antineoplastic Therapy

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

Collect transplant parameters after study treatment to include the conditioning regimen, date, and type of transplant.

7.1.1.6 Assignment of Screening Number

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

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

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

7.1.1.7 Assignment of Treatment/Randomization Number

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

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

7.1.1.8 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 Oncologic Disease Details

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

7.1.2.2 Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse 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 a potentially immunologic etiology (irAE). See Section 7.2 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.

7.1.2.3 Electrocardiogram

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

7.1.2.4 Physical Exam

7.1.2.4.1 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 (height need be taken at screening only) 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.

7.1.2.4.2 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.

7.1.2.5 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.

7.1.2.6 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.

7.1.2.7 Assessment of Disease and Tumor Imaging

7.1.2.7.1 Tumor Imaging and Criteria for Assessment of Disease

The process for image collection and transmission to the independent central imaging vendor can be found in the Site Imaging Manual. Independent central review based on IWG response criteria (Cheson, 2007 [1]) will be used to determine subject eligibility.

The central imaging vendor will receive all CT/PET images from the sites including baseline images and will confirm eligibility. **Eligibility will be based on the independent central review assessment, rather than site assessment. Expedited confirmation of measurable disease as determined by central review will be communicated to the site.**

Anti-tumor activity of pembrolizumab by CT/PET will be evaluated using the following criteria:

- PMBCL: IWG response criteria (Cheson, 2007 [1]) See Section 12.7.
- RS: IWG response criteria (Cheson, 2007 [1]) with special considerations for RS (Section 12.7). In subjects with rrRS, assessment of disease in the bone marrow will be limited to RS lymphoma.

The IWG will be applied by the independent central imaging vendor as the primary measure for eligibility, assessment of tumor response, and date of disease progression. CT/PET imaging showing subject's eligibility should be submitted to the central imaging vendor immediately. The site will be notified if the independent central review confirms eligibility. Additionally, the investigator will apply the IWG response criteria for assessment of disease response and disease progression. In addition, assessment of lymphoma B symptoms should occur with each lymphoma disease response assessment.

In subjects with RS, assessment of disease in the bone marrow will distinguish changes due to RS or transformed lymphoma from changes due to the pre-existing CLL. RS subjects may be assessed as showing radiographic CR if all lesions resolve on anatomic imaging, or if all remaining lesions show PET avidity lower than normal liver tissue, consistent with complete disappearance of fluorodeoxyglucose (FDG)-avid disease. If radiographic CR is observed (no evidence of active disease on imaging), a final response determination of CR requires marrow clearance of RS (as determined by marrow biopsy and aspirate), as well as

disappearance of other clinical evidence of disease (such as physical exam findings). If the bone marrow is indeterminate by morphology, immunohistochemistry should be negative for RS. Residual underlying CLL may persist in node and/or marrow and still qualify as CR, denoting complete response of RS to pembrolizumab. Additional node biopsies for RS should be considered in the presence of enlarging lymph nodes to determine if due to underlying CLL or RS.

Anti-tumor activity of pembrolizumab will also be evaluated by independent central review as part of the exploratory analyses using the Lugano Classification (Cheson, 2014 [2]), see Section 12.8.

7.1.2.7.2 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 comprehensive response assessment of immunotherapeutic agents such as pembrolizumab. Therefore in the setting where a subject assessment shows unconfirmed PD by investigator assessment, study drug may be continued upon Sponsor consultation, if the investigator considers the subject is deriving clinical benefit and providing subsequent radiographic imaging shows evidence of reduction or stabilization in tumor burden from the prior time point where initial unconfirmed PD was observed. If repeat imaging shows a reduction or stabilization in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued/resumed. If repeat imaging confirms PD by investigator assessment, subjects will be discontinued from study therapy. Imaging should occur at any time where there is clinical suspicion of progression.

7.1.2.7.3 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 assess if the subject has measurable disease as defined in the inclusion criteria and submit CT/PET imaging showing subject's eligibility to the central imaging vendor immediately for confirmation. The site will be notified if the independent central review confirms eligibility 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 as stated in section 7.1.2.7.4 below. For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in follow-up assessments.

7.1.2.7.4 Disease Response Assessments/Imaging During the Trial

Following screening, disease response assessments will occur at Week 12 (± 7 days) and every 12 weeks (± 7 days) as detailed in the Trial Flow Chart in Section 6.0. The first

assessment may be performed earlier than 12 weeks if, in the opinion of the investigator, the subject is clinically progressing.

Imaging assessments should be performed (every 12 weeks from the first dose of study medication). There is a ± 7 day window for assessments performed after entry in the study. If PET and CT scan at Screening are negative for disease involvement in the neck, subsequent CT scans may not include neck. If PET or 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, or to confirm CR and as clinically indicated. PET to confirm PD is strongly encouraged, but not required, if CT clearly demonstrates PD. 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 by investigator assessment, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

During Second Course, imaging should continue to occur every 12 weeks (+/- 7 days) following the same parameters listed above.

7.1.2.7.5 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:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease or progressive tumor at critical anatomical sites (e.g., 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 (e.g., 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.

For subjects who have stable disease, partial remission, or complete response following the first disease response assessment (at Week 12), disease assessments and imaging should continue per the regular frequency every 12 weeks as outlined in the Section 7.1.2.7.4.

7.1.2.7.6 Biopsy Collection and Correlative Studies Blood Collection

All PMBCL subjects should submit an archived lymph node formalin-fixed paraffin embedded (FFPE) biopsy sample or when feasible, a newly obtained core or excisional biopsy (fine needle aspirate [FNA] not adequate) for confirmation of rrPBMCL and characterization of PD-L1 expression at a central lab. Central review for diagnosis is not required prior to enrollment.

Similar lymph node tissue from subjects with rrRS should be submitted, although central review will be determined by the Sponsor. Central review for diagnosis is not required prior to enrollment.

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.

For newly obtained lymph node biopsy, when feasible, 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. Detailed instructions for tissue collection, processing, and shipment are provided in the Procedures Manual.

Baseline tumor tissue for biomarker analysis from a newly obtained core or excisional lymph node biopsy (FNA) not adequate] should be provided if feasible to the central vendor prior to randomization or (if newly obtained biopsy not available) an archival tissue sample could alternatively be collected. Adequacy of the fresh biopsy specimen for PD-L1 biomarker analysis will be confirmed by the central laboratory. Detailed instructions for tissue collection, processing and shipment of the newly obtained sample tissue or archival tumor tissue are provided in the Procedures Manual. If the subject signs the FBR consent, any leftover tissue that would ordinarily be discarded at the end of the study will be retained for FBR (see Section 12.3).

- **Newly Obtained Tumor Tissue**

This sample should be sent to the vendor in formalin (strongly preferred) or as a FFPE block. If slides are submitted they must be sent to designated laboratory within 14 days of being sectioned.

- **Archival Tumor Tissue (if available)**

Archival tissue sample should be provided in the form of FFPE tissue block (preferred). Unstained/freshly cut slides cut from FFPE tissue block may be accepted. If slides are submitted they must be sent to designated laboratory within 14 days of being sectioned. Refer to the Procedures Manual for number of slides and instructions.

• **Bone Marrow**

For all subjects, collect bone marrow biopsy and aspirate at baseline. Repeat bone marrow biopsy and aspirate as needed to confirm CR. Local results of bone marrow biopsy and aspirate will be used for baseline and to confirm CR (or other reason). Residual bone marrow biopsy sample (all subjects for any sample obtained) should be sent to the central lab for potential future central analysis per sponsor discretion.

For RS it is necessary to confirm marrow clearance of RS or lymphoma clone to confirm CR. If indeterminate by morphology, immunohistochemistry should be negative. Residual underlying CLL may persist in node and/or marrow and still qualify as CR

Bone marrow and lymph node biopsies will be collected as per [Table 4](#).

Table 4 Bone Marrow and Lymph Node Biopsy Assessments

Indication	Timing of Biopsy
Lymph Node Biopsy	<p>Screening biopsy (archival or newly obtained sample) is required. Biopsy at Week 12 (\pm 7 days) and at the time of discontinuation due to progression are optional but highly recommended.</p> <p>Additional node biopsies for RS should be considered in the presence of enlarging lymph nodes to determine if due to underlying CLL or RS.</p>
<p>Bone marrow biopsy and aspirate</p> <p>(All subjects will have bone marrow biopsy and aspirate performed at Screening. Subsequent bone marrow assessments will only be performed in subjects who have bone marrow involvement.)</p>	<p>Screening, to confirm CR (if subject has baseline bone marrow involvement), and as clinically indicated.</p> <p>For RS, CR can be confirmed by clearance of the RS or lymphoma clone on marrow biopsy and aspirate. Residual underlying CLL may persist in node and/or marrow and still qualify as CR. Bone marrow morphology and cytogenetics should be performed at Screening. 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.</p>
Abbreviations: CLL – chronic lymphocytic leukemia; CR – complete response; RS – Richter syndrome.	

Blood for correlative biomarker studies should be collected as per [Table 5](#).

Table 5 Blood for Correlative Studies

Indication	Timing of Correlative Blood Collection
Whole Blood for RNA/DNA:	Screening, pre-dose on Cycle 2 Day 1, Week 12 assessment, and upon progression.
Abbreviations: DNA – deoxyribonucleic acid; RNA – ribonucleic acid.	

7.1.2.8 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 are administered prior to drug administration, AE evaluation and disease status notification. The PROs are completed in the following order: EuroQol EQ-5D first, then EORTC QLQ-C30 at the time points specified in the Trial Flow Chart. Subjects who are on-study (signed informed consent) before approval of Amendment 1 (which instituted PROs) do not need to complete PROs.

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)

Applicable laboratory tests are specified in [Table 6](#).

Table 6 Laboratory Tests

Hematology^f	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β -human chorionic gonadotropin (β -hCG) ^a
Hemoglobin	Alkaline phosphatase	Glucose	Prothrombin time (PT) International Normalized Ratio (INR) ^d
Platelet count	Alanine aminotransferase (ALT)	Protein	Activated partial thromboplastin time (aPTT) ^d
White blood cell count (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total Triiodothyronine (T3) ^e
Red Blood Cell Count	Calcium	Microscopic exam, if abnormal results are noted	Free thyroxine (free T4)
Absolute Neutrophil Count	Bicarbonate/Carbon dioxide ^b	Urine pregnancy test ^a	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count			Blood for Future Biomedical Research (FBR)
	Chloride		Blood for Proteomics
	Creatinine		Blood for Genetics
	Glucose		Blood for Transcriptional Analysis
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above upper limit of normal (ULN)		
	Total protein		
	Blood Urea Nitrogen		
	Uric acid		
	Urea ^c		

a. Perform on women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy test is to be done within 72 hours of each cycle of trial treatment and 30 days post-treatment.

b. Test only if part of Standard of Care locally.

c. Blood Urea Nitrogen is preferred; if not available urea may be tested.

d. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

e. Total T3 is preferred, if not available free T3 may be tested.

f. Absolute values or percentage.

All laboratory tests will be performed by a central laboratory. Prior to pembrolizumab infusion, specific laboratory tests could be performed locally as clinically indicated per investigator assessment, in parallel to central laboratory testing, if necessary to ensure subject's safety prior to treatment. Subjects may be enrolled based on local laboratory results with central laboratory results pending. Treatment decisions may be made on local laboratory tests.

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 Pregnancy Test

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of each cycle of trial treatment and 30 days post-treatment. If a urine test is positive or not evaluable, a serum test will be required. Subjects must be excluded/discontinued from the trial in the event of a positive or borderline-positive test result.

7.1.3.3 Pharmacokinetic/Pharmacodynamic Evaluations

The accumulation of robust PK and anti-drug antibody (ADA) data has allowed for the adequate characterization of the clinical pharmacology of pembrolizumab across indications. Therefore, upon approval of Amendment 04 each site is to stop the collection of PK and ADA samples for all subjects. Blood samples for PK and ADA collected prior to Amendment 04 may only be stored. Analysis will be performed only if required.

7.1.3.4 Planned Genetic Analysis Sample Collection

This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR. Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the procedure manual.

7.1.3.5 Future Biomedical Research Sample Collection

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 tissue samples
- Leftover lymph node biopsies

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the 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 confirmed by independent central review may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (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 (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

7.1.4.1.2 Lost to Follow-up

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

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

- The investigator or designee must make every effort to regain contact with the subject at each missed visit (e.g., phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.
- Note: A subject is not considered lost to follow up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines.

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 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, Procedures Manual, Pharmacy Manual and Site Imaging Manual.

7.1.5 Visit Requirements

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

7.1.5.1 Screening

Approximately 28 days prior to treatment allocation, 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 confirmation of diagnosis, 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.

7.1.5.2.1 Second Course Phase (Retreatment Period for Post-Complete Remission Relapse ONLY)

Subjects who achieved a CR confirmed by independent central review and decided to stop initial treatment, at the time of recurrence may be eligible to receive pembrolizumab in the Retreatment Period of this study if the study remains open and the subject meets all of the following conditions:

- Stopped initial treatment with pembrolizumab after attaining a confirmed CR by independent central review according to IWG response criteria.
- Received at least 8 administrations of 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 at each cycle 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 restart treatment will be retreated at the same dose frequency as when they last received pembrolizumab for a treatment duration of a maximum of 17 additional administrations (approximately 1 year). Visit requirements are outlined in Section 6.0 – 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 7.1.5.2.1) 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 confirmed disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (\pm 14 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 until disease progression or up to 90 days of the end of treatment or before initiation of a new antineoplastic treatment. Every effort should be made to collect information regarding disease response status until the start of new antineoplastic therapy, documented disease progression by investigator assessment, death, end of the study, or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.2.1. Information regarding post-study antineoplastic treatment will be collected if new treatment is initiated.

For subjects who achieve CR determined by independent central review 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 7.1.5.2.1 will move from the follow-up phase to the Second Course Phase. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment.

7.1.5.4.1 Follow-Up Post-Allogeneic Stem Cell Transplantation

For subjects who receive allogeneic SCT within 24 months of last dose of pembrolizumab, the following events will be collected as ECIs through 18 months from the date of the allogeneic transplant, unless the trial closes earlier: graft-versus-host-disease, febrile syndrome treated with steroids, pulmonary complications, hepatic veno-occlusive disease and/or sinusoidal syndrome, immune-mediated adverse events, critical illness, and transplant-related mortality. Additional medically important AEs post-allogeneic SCT may be submitted at the investigator's discretion (Section 7.2.3.2). If available and relevant to an event post-allogeneic SCT, concomitant medications and/or laboratory results may also be reported.

Guidance on details to be collected and suggested events to be reported can be found in the Procedure Manual.

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 by telephone (or in person if recent contact for other purposes during window) approximately every 12 weeks (\pm 7 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.5.5 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 interim and/or final analysis. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be

contacted for their survival status (excluding subjects who have a previously recorded death event in the collection tool).

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

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

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

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

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

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

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

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

For the time period beginning at treatment allocation/randomization through 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:

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

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

7.2.3.2.1 Follow-Up Post-Allogeneic Stem Cell Transplantation

For subjects who receive allogeneic SCT within 24 months of last dose of pembrolizumab, the following events will be collected as ECIs through 18 months from the date of the allogeneic transplant, unless the trial closes earlier: graft-versus-host-disease, febrile syndrome treated with steroids, pulmonary complications, hepatic veno-occlusive disease and/or sinusoidal syndrome, immune-mediated adverse events, critical illness, and transplant-related mortality. Additional medically important AEs post-allogeneic SCT may be submitted at the investigator's discretion (Section 7.2.3.2). If available and relevant to an event post-allogeneic SCT, concomitant medications and/or laboratory results may also be reported.

Guidance on details to be collected and suggested events to be reported can be found in the Procedure Manual.

Post-allogeneic-SCT ECIs that occur after the normal safety follow-up period must be assessed for seriousness and causality and reported to the Sponsor as follows: within 24 hours if serious regardless of causality, or if non-serious and considered to be drug-related; and 5 calendar days if non-serious and not considered to be drug-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. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

Table 7 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

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 International Council for Harmonisation [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 Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will also be identified in the CSR. Due to the RS cohort being closed early, statistical analyses may be modified and changes will be reported in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized in [Table 8](#); the comprehensive plan is provided in Sections 8.2 to 8.12.

Table 8 Statistical Analysis Plan Summary

Study Design Overview	This study, entitled “A Study of Pembrolizumab (MK 3475) in Subjects with Relapsed or Refractory Primary Mediastinal Large B-cell Lymphoma (rrPMBCL) or relapsed or refractory Richter syndrome (rrRS)” is a multicenter, single arm, nonrandomized trial of pembrolizumab (MK-3475) in subjects with rrPMBCL or rrRS.
Treatment Assignment	Subjects meeting inclusion/exclusion criteria will be assigned to each cohort and receive 200 mg of pembrolizumab every 3 weeks (Q3W).
Analysis Populations	The primary analysis population for both efficacy and safety assessments is the “All Subjects as Treated” (ASaT) population, defined as all subjects who receive at least one dose of study medication (pembrolizumab).
Primary Endpoint(s)	The primary efficacy endpoint is the Objective Response Rate (ORR), defined as the proportion of subjects in the analysis population who have complete remission (CR) or partial remission (PR) using International Working Group (IWG) criteria, Cheson 2007 at any time during the study. Response for the primary analysis will be determined by central review.
Key Secondary Endpoints	<ol style="list-style-type: none"> 1. Progression-Free Survival (PFS) 2. Duration of Response (DOR) 3. Disease Control Rate (DCR) 4. Overall Survival (OS)
Statistical Methods for Key Efficacy Analyses	<p>rrPMBCL: The primary hypothesis will be evaluated by comparing ORR for pembrolizumab to a fixed historical control rate using a binomial exact test. The ORR will be estimated as well as a 95% 2-sided exact confidence interval using the Clopper-Pearson method.</p> <p>rrRS: The ORR will be estimated, along with the 90% 2-sided confidence interval using the Clopper-Pearson method.</p>

Statistical Methods for Key Safety Analyses	Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate.
Interim Analyses	rrPMBCL: An interim analysis will be conducted when between 50%-60% of the ASaT population is evaluable for response; see Section 8.7 for details. rrRS: Interim analyses may be conducted as needed to monitor study efficacy and safety, e.g., when 40% of subjects are evaluable for response; see Section 8.7 for details.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	The planned sample size is 50 subjects for the primary analysis in each cohort. Assuming ~6% of those enrolled will not be treated, approximately 53 subjects for each cohort will be enrolled into the study to obtain 50 subjects in the primary analysis population (ASaT). With 50 subjects in the primary analysis population for the rrPMBCL cohort, there is at least 88% statistical power (1-sided nominal 2.5% alpha) to detect a 35% or higher ORR for the pembrolizumab arm compared to a fixed control rate of 15% using the exact binomial test; see Section 8.8 for details.

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 single arm, open-label study, i.e., 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, hypothesis, and associated estimations of the study are stated in Section 3.

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 ORR for each cohort, defined as the proportion of subjects in the analysis population who have CR or PR at any time during the study, prior to disease progression. For rrPMBCL, response assessment will be based on IWG criteria (Cheson, 2007 [1]) using independent central review. For subjects with rrRS, IWG criteria with special considerations for RS will be used (Section 12.7). A secondary efficacy endpoint is ORR based on investigator assessment.

Other secondary efficacy endpoints include: (1) PFS, defined as the time from first dose of pembrolizumab to the first documented disease progression or death due to any cause, whichever occurs first; (2) DOR, defined as time from first response (CR, PR) to disease progression in subjects who achieve a PR or better, (3) DCR, defined as the proportion of subjects in the analysis population who have CR, PR, or SD at any time during the study prior to disease progression and (4) OS, defined as time from first dose to date of death.

PFS, DOR, and DCR will be based both on central review (primary) and investigator assessment (secondary).

Exploratory efficacy endpoints include ORR, PFS, DOR, and DCR, incorporating response assessments for subjects continuing pembrolizumab treatment after initial progression. An additional exploratory endpoint is the ORR based on the Lugano classification [2] using independent central review.

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, i.e., subjects will be included if they receive at least one dose of study medication (pembrolizumab).

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 PD/drug related AE.

8.5.2 Safety Analysis Population

The 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 (pembrolizumab). 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

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 10](#) below. The primary evaluation will be by central review for ORR, DCR, PFS, and DOR.

8.6.1.1 Objective Response Rate

The primary efficacy endpoint for this study is the ORR for each cohort, defined as the proportion of subjects who have response (CR or PR) prior to disease progression. In the rrPMBCL cohort, an exact binomial test will be conducted versus a fixed control rate. In both cohorts, the final analysis for the primary endpoint will be conducted when the last subject has reached the Week 12 response assessment or has discontinued study therapy.

The analysis will consist of the point estimate and 95% (90% for rrRS cohort) 2-sided exact CI using the Clopper-Pearson method which will have at least 95% (90% for rrRS cohort) coverage of the true rate.

Since an investigator may still continue to treat subjects with pembrolizumab who have progressed according to IWG criteria, exploratory analyses (point estimate and 90% 2-sided exact confidence interval) will be conducted for ORR to consider these subjects who later achieve PR or CR post-progression as responders. An additional exploratory analysis for ORR will be conducted based on the Lugano classification (Cheson, 2014 [2]).

8.6.1.2 Disease Control Rate

The DCR, defined as the proportion of subjects in the analysis population who have achieved a CR, PR or SD response prior to disease progression. The analysis will consist of the point estimate and 90% 2-sided exact CI; analogous to ORR, an exploratory analysis of DCR will be performed to consider subjects who continue to receive pembrolizumab and later achieve PR, CR or SD following initial progression.

8.6.1.3 Progression-Free Survival

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

Since disease progression is assessed periodically, 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.

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 discontinuation of treatment or initiation of new anticancer treatment, whichever occurs later, to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in [Table 9](#).

Table 9 Censoring rules for Primary and Sensitivity Analyses of Progression-Free Survival

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No progressive disease (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; 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 assessment	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	Censored at last disease assessment	Progressed at date of lost to follow-up

Analogous to other efficacy endpoints, an exploratory analysis will be performed on PFS incorporating additional response assessments where subjects are treated with pembrolizumab following initial progression; details on this analysis will appear in the sSAP.

8.6.1.4 Duration of Response

DOR 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 PD for subjects who do not have tumor progression and are still on study at the time of an analysis, are given antitumor treatment other than the study treatment, or are removed from study prior to documentation of tumor progression.

An exploratory analysis will be performed including response duration for those subjects who continue to receive pembrolizumab following progression and later achieve CR or PR.

8.6.1.5 Overall Survival

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

Table 10 Efficacy Analysis Methods for Primary and Secondary Efficacy Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Objective Response Rate (ORR) <ul style="list-style-type: none"> Central review 	rrPMBCL: Exact test of binomial parameter; Point Estimate and 2-sided 95% exact CI rrRS: Point estimate and 2-sided 90% exact CI	ASaT/FAS	Subjects with missing data are considered non-responders
Secondary:			
Objective Response Rate (ORR) <ul style="list-style-type: none"> Investigator Assessment 	Point estimate; 2-sided 90% exact CI	ASaT/FAS	Subjects with missing data are considered non-responders
Progression-free survival (PFS) <ul style="list-style-type: none"> Central review Investigator assessment 	Summary statistics using Kaplan-Meier method	ASaT/FAS	Censored at last assessment (see Table 9 for sensitivity analyses based on alternative censoring)
Duration of Response (DOR) <ul style="list-style-type: none"> Central review Investigator assessment 	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
Disease Control Rate (DCR) <ul style="list-style-type: none"> Central review Investigator assessment 	Point Estimate; 2-sided 90% exact CI	ASaT/FAS	Subjects with missing data are considered non-responders
Overall survival (OS)	Summary statistics using Kaplan-Meier method	ASaT/FAS	Censored at last assessment
Abbreviations: ASaT – All Subjects as Treated; CI – confidence interval; FAS – Full Analysis Set; rrPMBCL – relapsed or refractory primary mediastinal B-cell lymphoma; rrRS – relapsed or refractory Richter Syndrome;			

For the rrPMBCL cohort, efficacy updates for the parameters in the above table will be conducted using a data cut-off based on when the last subject remaining on study has completed approximately 9 months and 12 months of efficacy assessments and then at 2 years after the last subject initiated treatment, which corresponds to the end of the protocol-specified treatment period. No formal statistical testing is planned. Subsequent yearly analyses will be conducted (i.e., 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 AEs, ECIs, 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. 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 (e.g., age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by descriptive statistics or categorical tables.

8.6.3.2 Other Analyses

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

Additional exploratory analyses will be described in the sSAP.

8.7 Interim Analysis

rrPMBCL:

An interim analysis will be conducted after all subjects (approximately 50) have enrolled into the rrPMBCL cohort and will consist of between 50% to 60% of the treated population who are evaluable for response, i.e., up to and including that subject at the cut-off who have reached the Week 12 assessment or have discontinued study therapy prior to Week 12. The selection of at least half of the treated population as the minimum is intended to minimize statistical bias and corresponds to a rejection boundary greater than twice that of the historical control (15%), which would be clinically meaningful. The actual boundaries used for the interim and final analyses will be based on the actual number of response evaluable subjects in the interim analysis as well as the total known treated subjects using the corresponding alpha-spending function.

[Table 11](#) below summarizes the timing and decision guidance for the interim and final analysis for ORR.

Table 11 Decision Guidance at Each Efficacy rrPMBCL Analysis

Analysis	Criteria for Conduct of Analysis	Value	Efficacy §
Interim ORR	50-60% of treated subjects are evaluable* for response	P-value** at bound ORR at bound Number of responders	0.0029 36.7% 11
Final ORR	All treated subjects are evaluable* for response	P-value** at bound ORR at bound Number of responders	0.0132 28.0% 14

Abbreviations: ORR – objective response rate; rrPMBCL – relapsed or refractory primary mediastinal B-cell lymphoma.
 Note: O’Brien-Fleming Type I error spending function used to construct boundaries (see Section 8.9)
 § Assumes 30 response evaluable subjects in interim analysis and a total of 50 treated subjects in rrPMBCL
 * Treated subjects who have reached Week 12 assessment or have discontinued study therapy prior to Week 12
 ** One-sided

There is no planned stopping early for futility or superiority; the study will continue to enroll the rrPMBCL cohort completely.

8.8 Sample Size and Power Calculation

Efficacy for each cohort will be analyzed separately; the proposed sample size in each cohort is 50 subjects in the primary analysis population (ASaT). To obtain 50 subjects in each cohort, approximately 53 subjects will need to be enrolled in the study assuming that approximately 6% of enrolled subjects are not treated.

rrPMBCL:

With 50 subjects in the primary analysis population, there is at least 88% statistical power (1-sided nominal 2.5% alpha) to detect a 35% or higher ORR for the pembrolizumab arm compared to a fixed control rate of 15% using the exact binomial test.

The selection of 15% as a fixed control rate is based on historical data in previously conducted studies in rrPMBCL where response rates ranged between 13% to 17% [53, 54] for subjects who received brentuximab vedotin after at least 2 prior lines of therapy and were ineligible or had failed autologous stem cell transplant.

rrRS:

The primary objective for this cohort is the estimation of ORR. With a sample size of 50, the maximum half-width of the two-sided 90% exact confidence interval for ORR is 12%. [Table 12](#) describes examples of 90% CIs per cohort across a possible range of ORRs.

Table 12 Precision (90% Confidence Intervals) for range of observed ORR (30%- 70%)

Number of responses/ Number of treated subjects (ORR)	90% 2-sided Confidence Interval*
15/50 (30%)	(19%, 42%)
25/50 (50%)	(38%, 62%)
35/50 (70%)	(58%, 81%)
Abbreviation: ORR – objective response rate *Exact (Clopper-Pearson) confidence limit for the binomial proportion	

8.9 Multiplicity

Given the single hypothesis for the rrPMBCL cohort, no adjustment for multiplicity (i.e., Type I error) is required for multiple hypotheses. An O’Brien-Fleming Type I error spending function will be used to construct group sequential boundaries to control the Type I error rate for the interim and final analyses of the single rrPMBCL hypothesis.

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 90% CI) will be provided and plotted within each category of the following classification variables:

- Age category (≤ 65 vs. >65 years)
- Sex (female vs. male)
- Race (white vs. non-white)
- Region (US, ex-US)
- Prior auto-SCT (failed, ineligible/refused)

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.

8.12 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in [Table 13](#).

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

Table 13 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
pembrolizumab (MK-3475) 50 mg/vial (25 mg/mL reconstituted)	Lyophilized Powder for IV Injection / Infusion	Provided centrally by the Sponsor
pembrolizumab (MK-3475) 100 mg/4 mL vial (25 mg/mL)	Liquid for IV Injection / Infusion	Provided centrally by the Sponsor

Abbreviation: IV – intravenous.

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

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

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

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

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

- a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.¹
- b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.²
- c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.²
- d. DNA: Deoxyribonucleic acid.
- e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.5 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

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

c. **eCRF Documentation for Future Biomedical Research Specimens**

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

d. **Future Biomedical Research Specimen Collections**

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

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

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

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

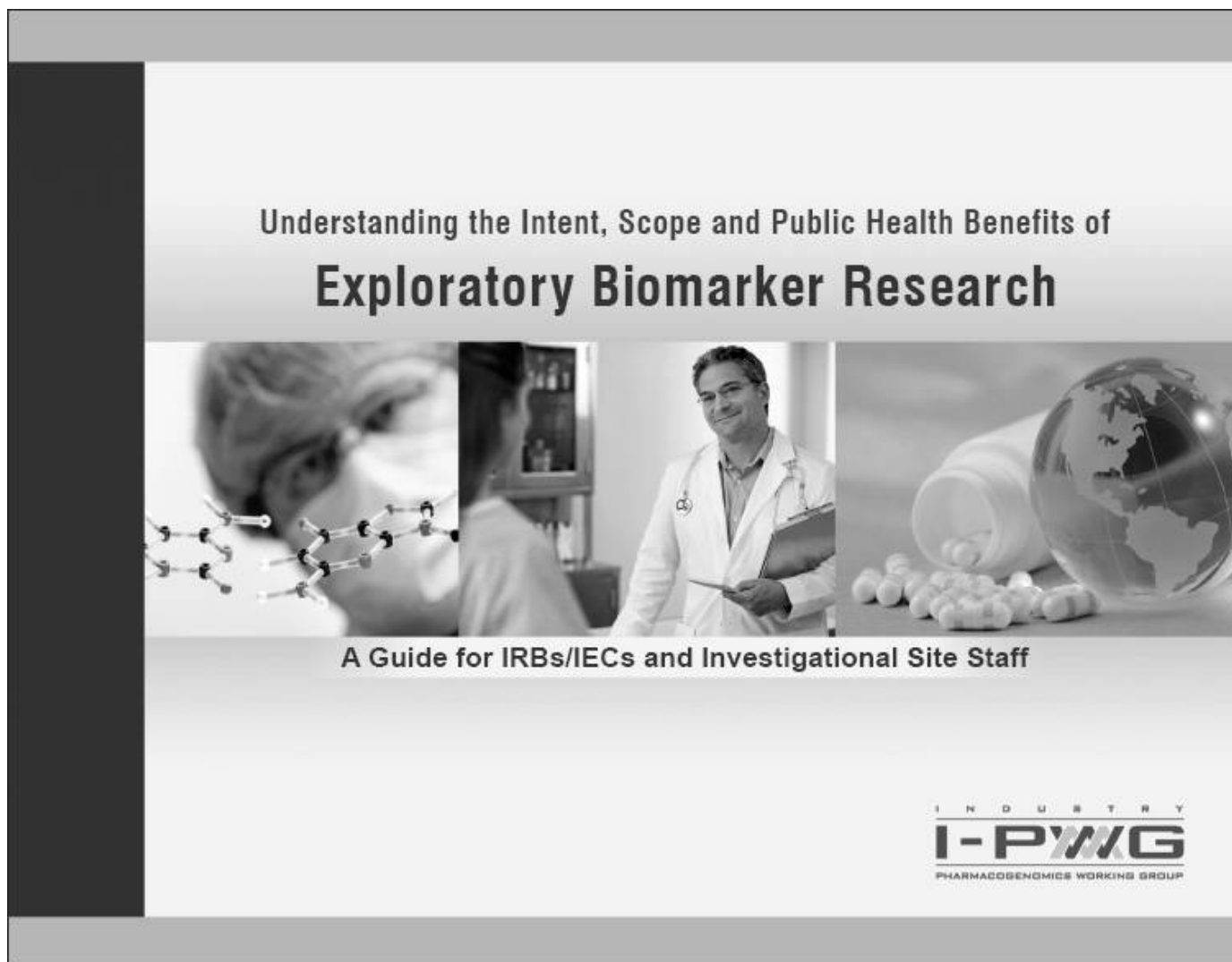
12. Questions

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

13. References

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

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



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

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

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

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

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure² and ICH Guidance E15³ 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.

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.

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 (Erbix[®]) 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 sur-

rogates 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

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.²⁶⁻³¹

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

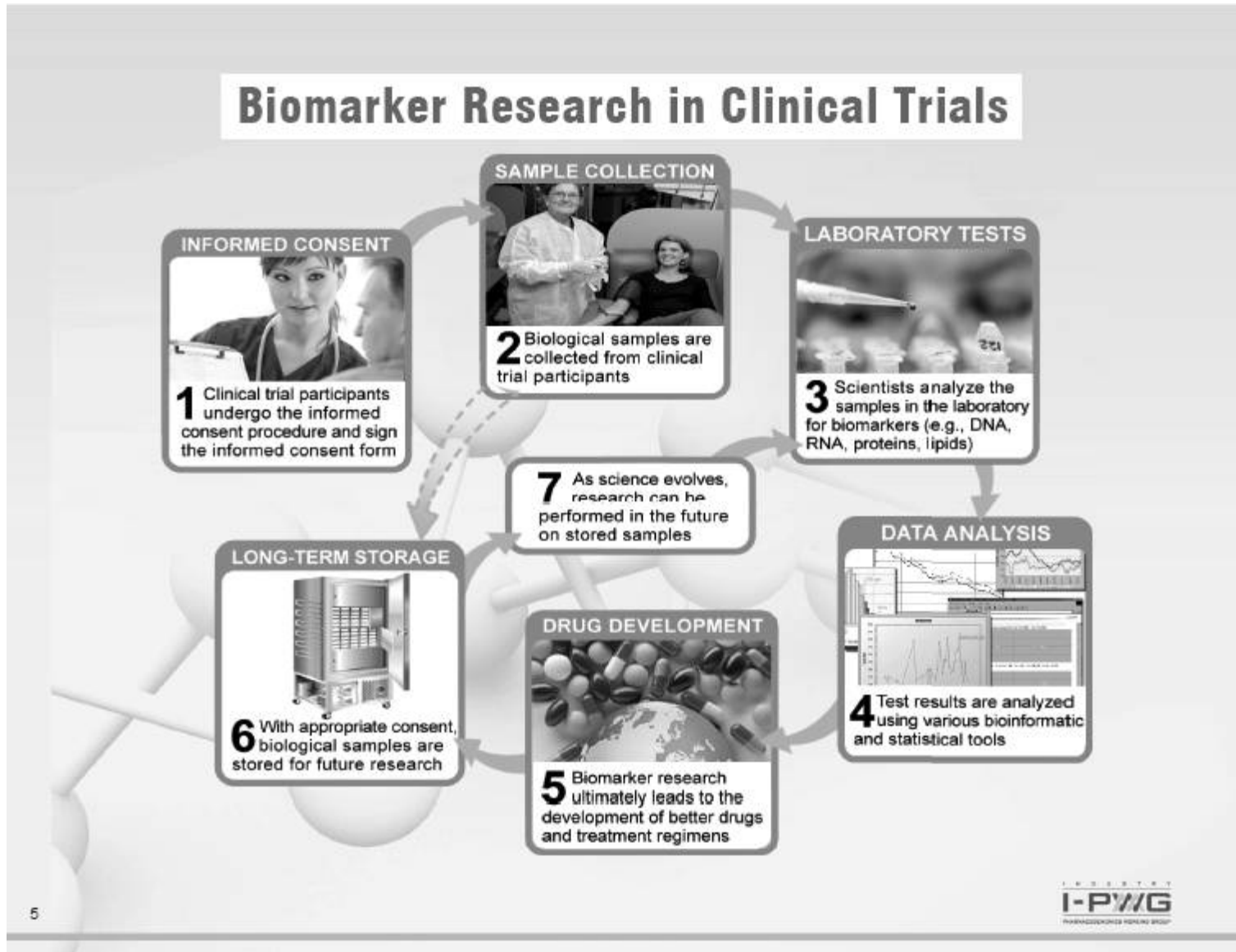
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants 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:³⁰

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.



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.³⁴⁻³⁶

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 (Erbix[®]) 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.^{28,35} 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

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-

biomarkers in drug development, regulation and clinical practice: A US regulatory practice. *Biomarkers Med.* 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/bmm/2008/00000002/00000003/art00010?crawler=true)

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27. Predictive Safety Testing Consortium. (Accessed at: www.c-path.org/psct.cfm)

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http://www.gateaccess.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=fpubl233.110.pdf)

38. Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials. FDA October 2008 www.fda.gov/OHRMS/DOCKETS/98th/FDA-2008-D-0576-gdl.pdf

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12.4 Abbreviations

Abbreviation/Term	Definition
AE	Adverse Event
ADA	Anti-Drug Antibodies
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
ASaT	All Subjects as Treated
AST	Aspartate Aminotransferase
auto-SCT	autologous-Stem Cell Transplant
ABVD	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
β-HCG	Beta Human Chorionic Gonadotropin
CIITA	Class II Transactivator
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CHL	Classical Hodgkin Lymphoma
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CNS	Central Nervous System
CR	Complete Response/Remission
CRF	Case Report Form
CSR	Clinical Study Report
CSR CI	Clinical Study Report Coordinating Investigator
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
DCR	Disease Control Rate
DLBCL	Diffuse Large B-Cell Lymphoma
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items
EQ-5D	European Quality of Life 5-Dimension
ERC	Ethics Review Committee
EU	European Union
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
FDG	Fluorodeoxyglucose
FFPE	Formalin-fixed paraffin embedded
FNA	Fine needle aspirate
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GEL-TAMO	Grupo Espanol de Linfomas y Transplante Autologo de Medula Osea
GI	Gastrointestinal
GVHD	Graft Versus Host Disease

Abbreviation/Term	Definition
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
IB	Investigator's Brochure
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INR	International Normalized Ratio
irAE	Immune-Related Adverse Event
IRB	Institutional Review Board
ITSM	Immunoreceptor Tyrosine-based Switch Motif
IV	Intravenous
IVRS	Integrated Voice Response System
IWRS	Integrated Web Response System
IWG	International Working Group
MACOP-B	Methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-The-Counter
PBPK	Physiologically based pharmacokinetic
PD	Progressive Disease
PD-1	Programmed cell death 1 receptor
PD-L1	Programmed cell death ligand 1 receptor
PD-L2	Programmed cell death ligand 2 receptor
PET	Positron Emission Tomography
PFS	Progression Free Survival
PIN	Personal Identification Number
PK	Pharmacokinetic
PMBCL	Primary Mediastinal B-Cell Lymphoma
PR	Partial Remission/Response
PRO	Patient Reported Outcome
Protocol CI	Protocol Coordinating Investigator
PT	Prothrombin Time
R-CHOP	Rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone
R-EPOCH	rituximab, etoposide phosphate, prednisone, vincristine sulfate (Oncovin), cyclophosphamide, doxorubicin hydrochloride (Hydroxydaunorubicin)
R-ICE	rituximab, ifosfamide, carboplatin, etoposide
RNA	Ribonucleic Acid
rr	Relapsed or Refractory
RS	Richter Syndrome
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
SAE	Serious Adverse Events
sSAP	Supplemental Statistical Analysis Plan
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedures

Abbreviation/Term	Definition
sSAP	supplemental Statistical Analysis Plan
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

12.5 ECOG Performance Status

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

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

12.6 Common Terminology Criteria for Adverse Events V4.0

The descriptions and grading scales found in the revised NCI 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 BD, Pfistner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. *J Clin Oncol.* 2007; 25:579-586.

Additional information is located in the Site Imaging Charter.

Criteria for lymphoma disease assessment:

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 measurable 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 identified 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, [¹⁸F]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.

Special considerations for RS:

In subjects with RS, assessment of disease in the bone marrow will distinguish changes due to RS or transformed lymphoma from changes due to the pre-existing CLL.

For RS, CR requires clearance of the RS on marrow biopsy and aspirate. If radiographic CR is observed (no evidence of active disease on imaging), a final response determination of CR requires marrow clearance of RS, as well as disappearance of other clinical evidence of disease (such as physical exam findings). If the bone marrow is indeterminate by morphology, immunohistochemistry should be negative for RS. Residual underlying CLL may persist in node and/or marrow and still qualify as CR, denoting complete response of RS to pembrolizumab.

For RS, PET positive is defined as a lesion with uptake greater than that of the normal liver uptake. PET must be positive at baseline and must be negative (no lesions with uptake greater than that of the normal liver) to be CR.

12.8 Lugano Classification

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification, *J Clin Oncol.* 2014; Sep 20;32(27):3059-68.

Additional information is located in the Site Imaging Charter.

Revised Criteria for Response Assessment

Response and Site	PET-CT Based Response	CT-Based Response
<u>Complete</u>	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
<u>Partial</u>	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

Response and Site	PET-CT Based Response	CT-Based Response
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
<u>No response or stable disease</u>	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
<u>Progressive disease</u>	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 $\geq 50\%$ 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.
<u>Nonmeasured lesions</u>	None	New or clear progression of preexisting nonmeasured lesions

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
<p>• 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.</p> <p>• * 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).</p> <p>• † 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</p>		

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	