Official Protocol Title:	A Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Subjects with Hematologic Malignancies
NCT number:	NCT01953692
Document Date:	16-Apr-2020

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TITLE:

A Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Subjects with Hematologic Malignancies

IND NUMBER: 118604

EudraCT NUMBER: 2013-001603-37

NCT NUMBER: NCT01953692

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-3475-013-09	16-APR-2020	To add a 12-month limit to follow-up after discontinuation to allow for closure of the study.
MK-3475-013-08	21-NOV-2017	This amendment was to discontinue treatment of subjects with combination therapy lenalidomide and pembrolizumab in Cohort 5. On 03-JUL-2017, the United States (US) Food and Drug Administration (FDA) placed on clinical hold KEYNOTE-183 (pembrolizumab/ pomalidomide/dexamethasone for refractory or relapsed and refractory multiple myeloma [MM]), KEYNOTE-185 (pembrolizumab/ lenalidomide/ dexamethasone for treatment naïve MM), and Cohort 1 of KEYNOTE-023 (pembrolizumab/ lenalidomide/ dexamethasone for refractory or relapsed and refractory MM). The FDA determined that the risks of pembrolizumab plus pomalidomide or lenalidomide outweighed any potential benefit for subjects with MM. Based on the summary of data from KEYNOTE-183 and KEYNOTE-185, subjects enrolled in Cohort 5 of KEYNOTE-013 have to discontinue combination therapy with lenalidomide and pembrolizumab. If subjects are experiencing clinical benefit at time of discontinuation, subjects have the option of entering a 90 day transition period where they receive monotherapy pembrolizumab or lenalidomide and then must enter long term safety and survival follow-up. There will be no further enrollment of subjects in this cohort. Additionally, enrollment in Cohort 2 has been completed; all subjects have previously discontinued study treatment and must transition into long-term safety and survival follow-up. There will be no further enrollment of subjects in this cohort.

Document	Date of Issue	Overall Rationale
MK-3475-013-07	25-SEP-2017	This amendment was finalized, but not submitted. The primary rationale was to remove the requirement for reporting immune-related adverse events (AEs) as Events of Clinical Interest (ECTs). Additional updates to align the protocol with current pembrolizumab standard language and to provide clarifications to protocol procedures and timing of assessments and/or procedures were also made.
MK-3475-013-06	13-JUL-2016	This amendment was to clarify the exclusion criteria related to pneumonitis to insure patients who may have a history of pneumonitis are excluded from the study (when applicable).
MK-3475-013-05	20-MAR-2016	This amendment added Cohort 5 to the study to enroll approximately 30-66 additional subjects with relapsed/refractory Diffuse Large B Cell Lymphoma (DLBCL) that have failed, are ineligible for, or refused a stem cell transplant. These subjects will be allocated to receive pembrolizumab 200 mg administered intravenously once every 21 days in combination with lenalidomide taken orally once daily for 21 days + 7 days off. The cycle length is 28 days. This increases the total number of subjects targeted for enrollment in the trial from approximately 156 to approximately 222. Updates were made throughout the protocol to provide entry criteria, study intervention directions, response assessment, dose modification and monitoring guidelines, and statistical analysis plans for this new cohort.

Document	Date of Issue	Overall Rationale
MK-3475-013-04	14-APR-2015	This amendment expanded Cohort 4 to enroll approximately 50 additional subjects with relapsed/refractory Follicular Lymphoma (FL) (Cohort 4C) or Diffuse Large B-Cell Lymphoma (DLBCL) (Cohort 4D) (approximately 25 each) that have failed, are ineligible for, or refused a stem cell transplant. These subjects are not required to have PD-L1 testing to determine eligibility. These subjects will be allocated to receive 200 mg Q3W. This increases the total number of subjects targeted for enrollment in the trial from 106 to approximately 156. Remaining open slots in Cohort 4 will be allocated to MLBCL subjects (Cohort 4A) that will receive 200 mg Q3W instead of 10mg/kg Q2W. The total number of subjects in Cohort 4A and 4B combined will be 28. Subjects enrolled under this amendment in Cohort 2, 4A, 4C and 4D will now receive 200 mg Q3W because the pembrolizumab program has moved to a 200 mg fixed dose regimen given every 3 weeks. Enrollment in Cohort 1 and 3 have been completed. Subjects enrolled prior to this amendment will continue on their current regimen of 10 mg/kg Q2W. The objectives for subjects with relapsed/refractory NHL (Cohort 4) were updated to indicate that in addition to the overall Cohort, the objectives also pertain to disease subtype within the cohort (MLBCL, FL, DLBCL, Other) because it was thought that an adequate number of subjects would be enrolled to obtain preliminary efficacy assessments for these disease subtypes. Objectives and hypothesis testing in NHL subjects (Cohort 4) was also updated to be done regardless of PD-L1 status; where adequate numbers permit, descriptive statistics and/or subject listings will be provided by PD-L1 status. The amendment also added conditions under which an investigator, after consultation with the Sponsor, might continue treatment after confirmed progression in subjects who are clinically stable or clinically improved. Additional updates to provide clarification and correct errors were made.

Document	Date of Issue	Overall Rationale
MK-3475-013-03	30-JAN-2014	This amendment was to add a cohort for relapsed refractory multiple myeloma to the protocol.
MK-3475-013-02	18-DEC-2013	This amendment was primarily made to remove the smoldering multiple myeloma cohort per request of the FDA. Changes were made throughout the protocol to accommodate this update. Additional clarifications and corrections
MK-3475-013-01	21-AUG-2013	The primary reason for this amendment was to address requests made by the US Food and Drug Administration to clarify inclusion and exclusion criteria, revise the dose modification and supportive care guidelines, and clarify the duration of treatment for all cohorts. A criterion for ending the trial due to adverse events reported in this trial or other trials was removed. Additionally, revisions were made to assessment of the efficacy endpoint and to inclusion criterion #16; clarifications were made to subject replacement strategy, to efficacy assessments timing, to timing of imaging procedures, and to the study flow chart.
MK-3475-013-00	14-JUN-2013	Original protocol

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0 2.1	Trial Summary Trial Design	Updated follow-up after treatment discontinuation to add a 12-month duration to follow-up.	To allow for closing of the trial after 12 months of follow-up.
7.2.3.2	Events of Clinical Interest	Updated follow-up after allogeneic stem cell transplant (SCT) to provide for completion of follow-up at the end of the trial.	Follow-up post allogeneic-SCT will end when the trial closes.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
4.2.3.4 7.1.1.1.2 12.2	Future Biomedical Research Consent and Collection of Specimens for Future Biomedical Research Collection and Management of Specimens for Future Biomedical Research	Revised text to omit references to a "sub-trial" for future biomedical research.	Template updates for clarification that future biomedical research is not a sub-trial of this protocol.
6.0 7.1.5.3.2	Trial Flow Chart Efficacy Follow-up Visits	Updated heading/column heading text for Follow-up Visits to include "efficacy."	Template update for clarification.
6.0	Trial Flow Chart	Updated column heading for Post Treatment Safety Follow-up to add "Visit"	Template update for clarification

1.0 TRIAL SUMMARY

Abbreviated Title	A Phase Ib Multi-cohort Trial of MK-3475 (pembrolizumab) in Subjects with Hematological Malignancies
Trial Phase	Ib
Clinical Indication	Cohort 1: The treatment of subjects with intermediate-1, intermediate-2, or high risk myelodysplastic syndrome (MDS) who have failed to respond to at least 4 cycles of prior treatment with a hypomethylating agent. Cohort 2: The treatment of subjects with relapsed refractory or refractory multiple myeloma (MM). Cohort 3: The treatment of subjects with relapsed / refractory nodular sclerosing or mixed cellularity Hodgkin lymphoma (HL) that have failed, are ineligible for, or refused a stem cell transplant and have relapsed after treatment with or failed to respond to brentuximab vedotin. Cohort 4: The treatment of subjects with relapsed / refractory non-Hodgkin Lymphoma (NHL) 1. Cohort 4A: The treatment of subjects with relapsed / refractory mediastinal large B-cell lymphoma (MLBCL) that have failed, are ineligible for, or refused a stem cell transplant. 2. Cohort 4B: Subjects with any other relapsed / refractory programmed cell death ligand 1 (PD-L1) positive NHL that have failed, are ineligible for, or refused a stem cell transplant. 3. Cohort 4C: Irrespective of PD-L1 status, NHL subjects with relapsed / refractory Follicular Lymphoma (FL) that have failed, are ineligible for, or refused a stem cell transplant. 4. Cohort 4D: Irrespective of PD-L1 status, NHL subjects with relapsed / refractory Diffuse Large B-Cell Lymphoma (DLBCL) that have failed, are ineligible for, or refused a stem cell transplant. Cohort 5: Irrespective of PD-L1 status, NHL subjects with relapsed / refractory DLBCL that have failed, are ineligible for, or refused a stem cell transplant.
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Subjects enrolled prior to Amendment 013-04 in Cohorts 1, 2, 3, 4A, and 4B received pembrolizumab 10 mg/kg every 2 weeks. Subjects enrolled under Amendment 013-04 or Amendment 013-05 in Cohort 2, 4A, 4C, and 4D will receive pembrolizumab 200 mg every 3 weeks. Subjects enrolled in Cohort 5 (DLBCL) will receive pembrolizumab 200 mg intravenously once every 21 days in combination with lenalidomide taken orally once daily for 21 days + 7 days off. The cycle length is 28 days.

Number of trial subjects	Approximately 222 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 55 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, eligible subjects will receive treatment on Cycle 1 Day 1. Treatment with pembrolizumab or lenalidomide + pembrolizumab will continue until documented confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons requiring cessation of treatment. Subjects who attain a complete response (CR) or stringent CR (sCR) (MM) 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 the occurrence of adverse events and spontaneously reported pregnancy as described under Section 7.2 of the protocol. Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for at least 12 months 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 at least 12 months after their discontinuation visit for overall survival until death, withdrawal of consent, or the end of the study. Due to the unfavorable results (risks outweighed benefits) of KEYNOTE-183 and KEYNOTE-185 in subjects with MM treated with pembrolizumab plus pomalidomide or lenalidomide, subjects enrolled in Cohort 5 who are still receiving combination treatment are to stop combination treatment immediately, complete the discontinuation visit, and move into the long-term safety and survival follow-up per protocol. If clinically benefitting at time of stopping combination therapy, subjects may enter a transition period remaining on single agent lenalidomide or pembrolizumab for up to 90 days from 15-SEP-2017 and then enter long-term survival and safety follow-up. For Cohort 2, enrollment has been completed and all subjects have previously discontinued study treatment and must transition into long-term and survival follow-up. There will be no further enrollment of subjects in this cohort.

A list of abbreviations used in this document can be found in Section 12.11.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, nonrandomized trial of MK-3475 (pembrolizumab) in subjects with intermediate-1, intermediate-2, or high risk myelodysplastic syndrome (MDS) who have failed

to respond to at least 4 cycles of prior treatment with a hypomethylating agent (HMA) (Cohort 1); subjects with relapse refractory or refractory multiple myeloma (MM, Cohort 2); subjects with relapsed / refractory nodular sclerosing or mixed cellularity Hodgkin lymphoma (HL) that have failed, are ineligible for, or refused a stem cell transplant and have relapsed after treatment with or failed to respond to brentuximab vedotin (Cohort 3); subjects with relapsed / refractory mediastinal large B-cell lymphoma (MLBCL) that have failed, are ineligible for, or refused a stem cell transplant (Cohort 4A); subjects with other relapsed / refractory programmed cell death ligand 1 (PD-L1) positive non-Hodgkin lymphoma (NHL) that have failed, are ineligible for, or refused a stem cell transplant (Cohort 4B); irrespective of PD-L1 status, subjects with relapsed / refractory Follicular Lymphoma (FL, Cohort 4C) or Diffuse Large B-Cell Lymphoma (DLBCL, Cohort 4D) that have failed, are ineligible for, or refused a stem cell transplant.

This multicenter, nonrandomized trial under Amendment 013-05 will also evaluate MK-3475 (pembrolizumab) given in combination with lenalidomide in subjects with relapsed / refractory DLBCL (Cohort 5) who have failed, are ineligible for, or refused a stem cell transplant.

Approximately 222 subjects will be enrolled in this trial to examine the safety and efficacy of pembrolizumab or lenalidomide + pembrolizumab combination. 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 with pembrolizumab or lenalidomide + pembrolizumab combination will continue until documented disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons requiring cessation of treatment. Per the investigator's discretion subjects who attain an investigator-determined confirmed complete response (CR) or stringent complete response (sCR) (MM) may consider stopping trial treatment after receiving at least 24 weeks of therapy. At least two doses of pembrolizumab must be received after CR or sCR (MM) is documented for subjects receiving pembrolizumab monotherapy. An additional 21 consecutive daily doses of lenalidomide + 2 doses of pembrolizumab must be received after CR is documented in subjects in Cohort 5 (DLBCL). These subjects will be eligible for retreatment after they have experienced disease progression at the discretion of the investigator if no cancer treatment was administered since the last dose of trial treatment, the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial remains open (refer to Section 7.1.5.2.1 for further details). After the end of treatment, each subject will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 7.2 of the protocol. Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for at least 12 months 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 at least 12 months after their discontinuation visit for overall survival (OS) until death, withdrawal of consent or the end of the study, whichever comes first.

The primary objectives of the trial are to determine safety, tolerability, and efficacy of pembrolizumab or lenalidomide + pembrolizumab combination in subjects with hematologic malignancies. Secondary objectives include further analysis of various efficacy parameters (time to progression [TTP]/progression-free survival [PFS]/ OS for each respective cohort, as well as an analysis of PD-L1 expression and corresponding efficacy. The pharmacokinetic (PK) properties of pembrolizumab and pembrolizumab when given in combination with lenalidomide, and the relationship of candidate efficacy/resistance biomarkers and anti-tumor activity of pembrolizumab will be investigated as exploratory objectives.

With the initiation of Amendment 013-04, the protocol will be enrolling subjects in the following Cohorts: Cohort 2 (MM), 4A (MLBCL), 4C (FL), and 4D (DLBCL).

With the initiation of Amendment 013-05, subjects will be enrolled in Cohort 5 (DLBCL) to receive lenalidomide + pembrolizumab combination treatment.

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

Due to the unfavorable results (risks outweighed benefits) of KEYNOTE-183 and KEYNOTE-185 in subjects with MM treated with pembrolizumab plus pomalidomide or lenalidomide, subjects enrolled in Cohort 5 who are still receiving combination are to stop combination treatment immediately, complete the discontinuation visit, and move into the long-term safety and survival follow-up per protocol. If clinically benefitting at time of stopping combination therapy, subjects may enter a transition period remaining on single agent lenalidomide or pembrolizumab for up to 90 days from 15-SEP-2017 and then enter long-term survival and safety follow-up.

For Cohort 2, enrollment has been completed and all subjects have previously discontinued study treatment and must transition into long-term safety and survival follow-up. There will be no further enrollment of subjects in this cohort

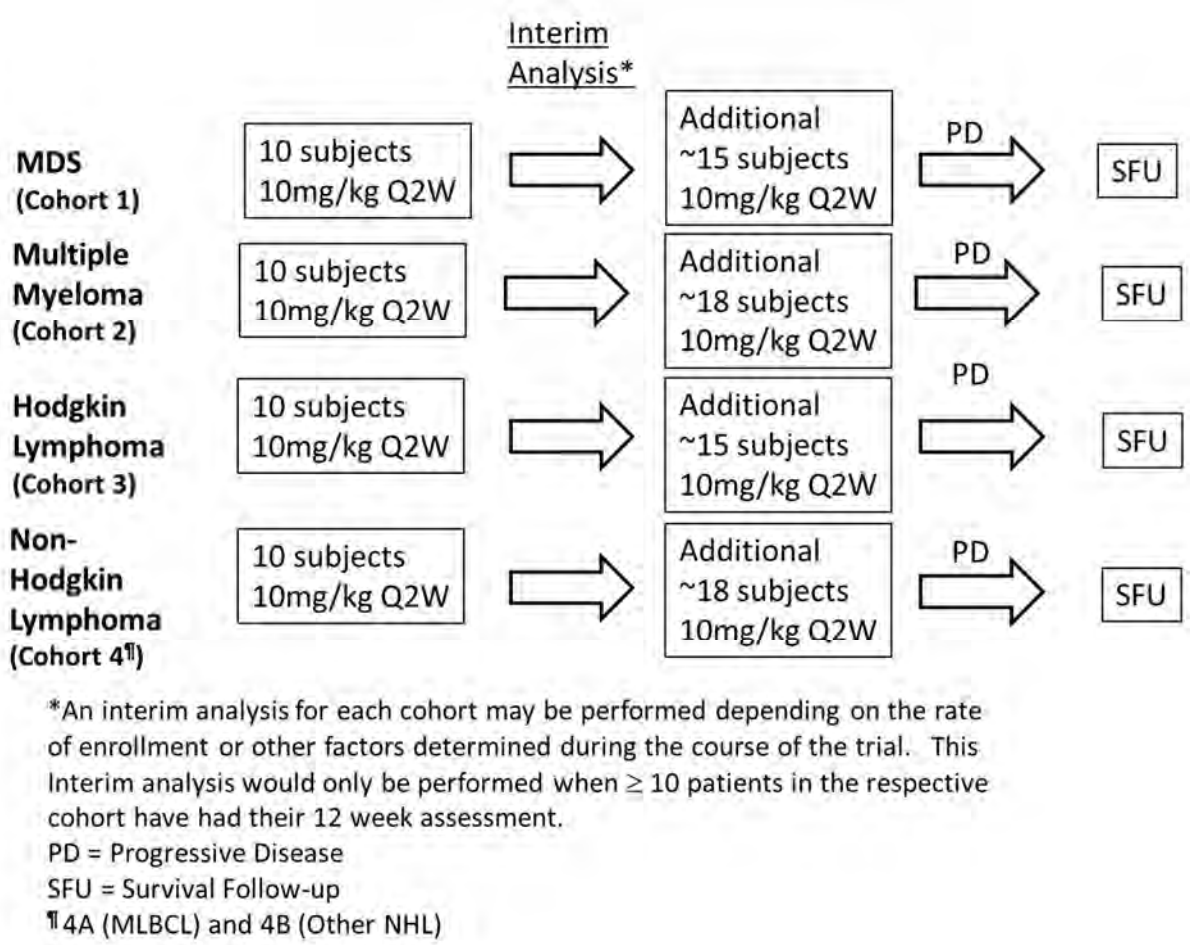
Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

An interim analysis will be performed if fewer than 10 subjects are enrolled in a cohort after being open for 6 months from the time that the first subject is treated in the respective cohort. Results will be reviewed by the study team.

The safety run-in will be conducted on at least the first 12 subjects enrolled in Cohort 5 (DLBCL) to determine the recommended phase II dose (RP2D) for lenalidomide when given in combination with pembrolizumab. The Sponsor will review dose limiting toxicities (DLTs) reported by the investigator during the safety run-in and will determine the appropriate adjustment to the dose of lenalidomide, if necessary.

2.2 Trial Diagram

The trial design for Cohorts 1, 2, 3, and 4 is depicted in Figure 1 and Figure 2.



*An interim analysis for each cohort may be performed depending on the rate of enrollment or other factors determined during the course of the trial. This Interim analysis would only be performed when ≥ 10 patients in the respective cohort have had their 12 week assessment.
PD = Progressive Disease
SFU = Survival Follow-up
¶ 4A (MLBCL) and 4B (Other NHL)

Figure 1 Trial Design Prior to Amendment 013-04

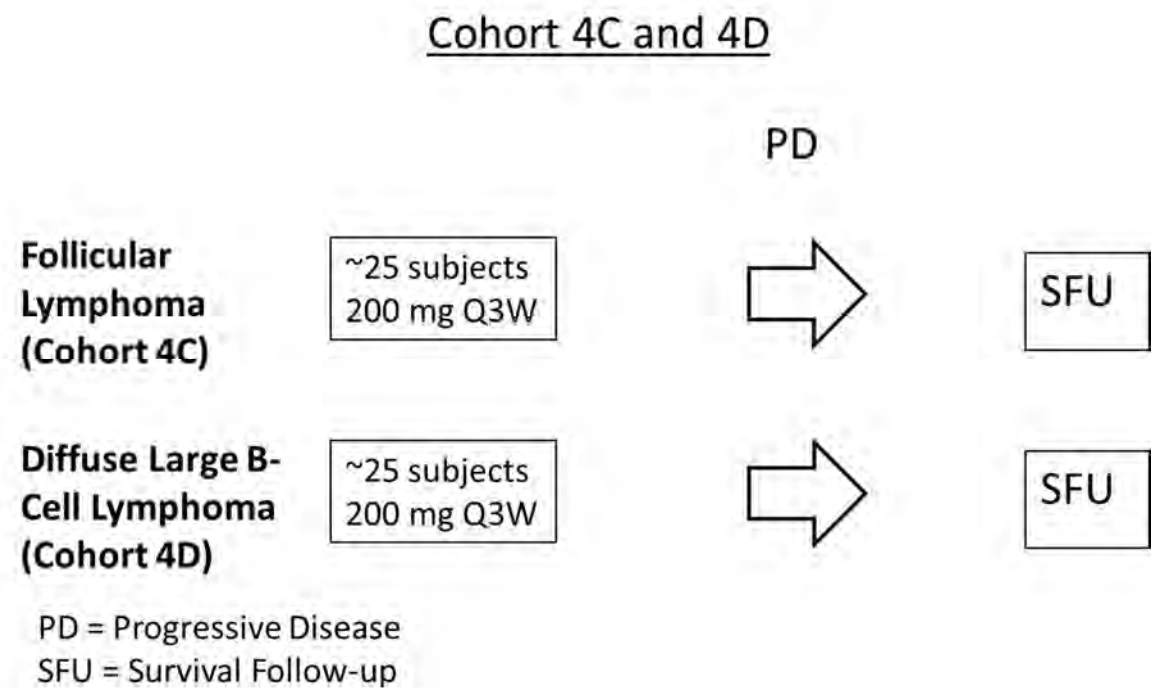


Figure 2 Trial Design Amendment 013-04 (Cohorts 4C and 4D)

The trial design for Cohort 5 (DLBCL) is depicted in Figure 3.

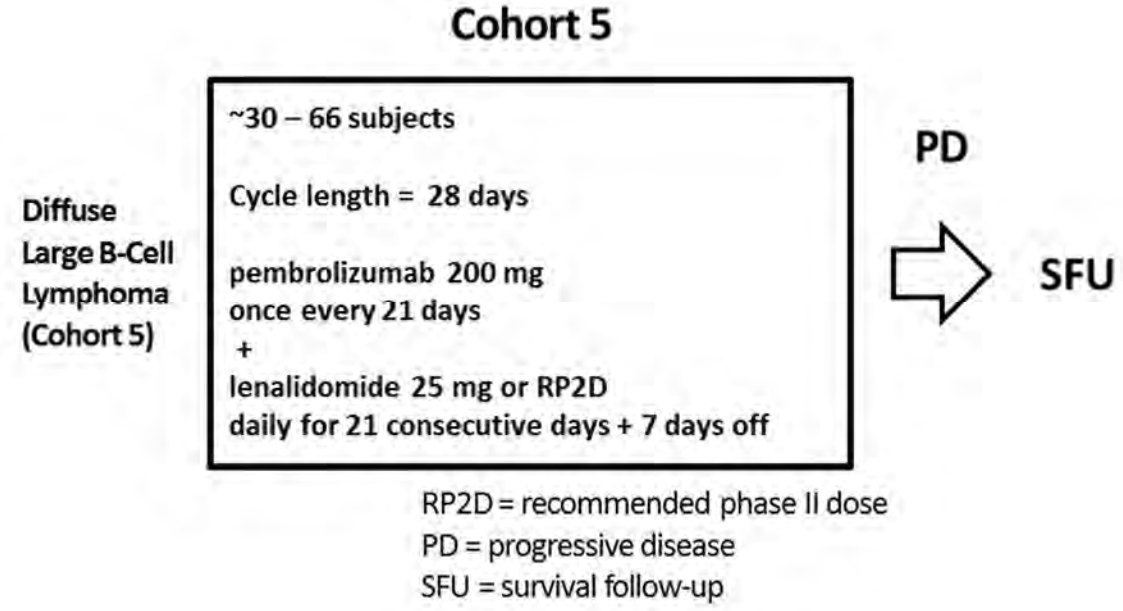


Figure 3 Trial Design Amendment 013-05 (Cohort 5)

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

MDS (Cohort 1)

1) **Objective:** To determine the safety and tolerability of pembrolizumab in subjects with intermediate-1, intermediate-2, or high risk MDS whose disease has failed to respond to at least 4 cycles of a HMA.

2) **Objective:** To evaluate the objective response rate (ORR) of pembrolizumab based on International Working Group (IWG) criteria for MDS in subjects with intermediate-1, intermediate-2, or high risk MDS whose disease has failed to respond to at least 4 cycles of a HMA.

Hypotheses: Intravenous (IV) administration of single agent pembrolizumab to subjects with intermediate-1, intermediate-2, or high risk MDS whose disease has failed to respond to at least 4 cycles of a HMA will result in an ORR greater than 10% based on IWG criteria for MDS.

Multiple Myeloma (Cohort 2)

1) **Objective:** To determine the safety and tolerability of pembrolizumab in subjects with relapse refractory or refractory MM.

2) **Objective:** To evaluate ORR of pembrolizumab based on International Myeloma Working Group (IMWG) 2006 Criteria in subjects with relapse refractory or refractory MM.

Hypotheses: IV administration of single agent pembrolizumab to subjects with relapse refractory or refractory MM will result in an ORR greater than 25% based on IMWG 2006 Criteria.

Hodgkin Lymphoma and Non-Hodgkin Lymphoma – Monotherapy (Cohort 3 and 4)

1) **Objective:** To determine the safety and tolerability of pembrolizumab in subjects with relapsed / refractory nodular sclerosing or mixed cellularity HL, relapsed / refractory MLBCL, and relapsed / refractory NHL, that have failed, are ineligible for, or refused a stem cell transplant.

2) **Objective:** To evaluate complete remission rate (CRR) of pembrolizumab based on the Revised Response Criteria for Malignant Lymphoma in subjects with relapsed / refractory nodular sclerosing or mixed cellularity HL (Cohort 3).

Hypotheses: IV administration of single agent pembrolizumab to subjects with relapsed / refractory nodular sclerosing or mixed cellularity HL will result in a CRR greater than 10% (Cohort 3) based on the Revised Response Criteria for Malignant Lymphoma.

3) **Objective:** To evaluate ORR of pembrolizumab based on the Revised Response Criteria for Malignant Lymphoma in subjects with relapsed / refractory NHL (Cohort 4).

Hypotheses: IV administration of single agent pembrolizumab to subjects with relapsed / refractory NHL will result in an ORR greater than 25% (Cohort 4) based on the Revised Response Criteria for Malignant Lymphoma.

4) **Objective:** To evaluate ORR of pembrolizumab based on the Revised Response Criteria for Malignant Lymphoma in subjects with relapsed / refractory NHL by disease subtype within Cohort 4 (MLBCL, FL, DLBCL, Other).

Non-Hodgkin Lymphoma (DLBCL) – Combination Therapy (Cohort 5)

1) **Objective:** To determine the safety and tolerability of combination lenalidomide + pembrolizumab in subjects with relapsed / refractory DLBCL (Cohort 5) that have failed, are ineligible for, or refused a stem cell transplant.

2) **Objective:** To evaluate the ORR of combination lenalidomide + pembrolizumab based on the Revised Response Criteria for Malignant Lymphoma in subjects with relapsed / refractory DLBCL (Cohort 5).

3.2 Secondary Objective(s) & Hypothesis(es)

MDS (Cohort 1)

1) **Objective**: To evaluate the OS in subjects with intermediate-1, intermediate-2, or high risk MDS whose disease has failed to respond to at least 4 cycles of a HMA.

2) **Objective**: To evaluate Bone Marrow Response in subjects with intermediate-1, intermediate-2, or high risk MDS whose disease has failed to respond to at least 4 cycles of a HMA.

3) **Objective**: To evaluate Hematologic Improvement based on IWG criteria for MDS in subjects with intermediate-1, intermediate-2, or high risk MDS whose disease has failed to respond to at least 4 cycles of a HMA.

4) **Objective**: To evaluate Cytogenetic Response based on IWG criteria for MDS in subjects with intermediate-1, intermediate-2, or high risk MDS whose disease has failed to respond to at least 4 cycles of a HMA.

5) **Objective**: To evaluate Duration of Response (DOR) in subjects with intermediate-1, intermediate-2, or high risk MDS whose disease has failed to respond to at least 4 cycles of a HMA.

6) **Objective**: To compare in bone marrow biopsies the extent of pre- pembrolizumab PD-L1 expression and change in PD-L1 expression after treatment with a HMA for pembrolizumab responders versus non-responders in subjects with intermediate-1, intermediate-2, or high risk MDS whose disease has failed to respond to at least 4 cycles of a HMA.

Multiple Myeloma (Cohort 2)

1) **Objective**: To evaluate complete response and stringent response rate (CR + sCR) based on IMWG 2006 Criteria in subjects with relapse refractory or refractory MM.

2) **Objective**: To evaluate TTP in subjects with relapse refractory or refractory MM.

3) **Objective**: To evaluate DOR in subjects with relapse refractory or refractory MM.

4) **Objective:** To evaluate PFS in subjects with relapse refractory or refractory MM.

5) **Objective:** To evaluate OS in subjects with relapse refractory or refractory MM.

6) **Objective**: To compare in bone marrow biopsies, the extent of pre- pembrolizumab PD-L1 expression for pembrolizumab responders versus non-responders in subjects with relapse refractory or refractory MM.

Hodgkin Lymphoma and Non-Hodgkin Lymphoma – Monotherapy (Cohort 3 and 4)

1) **Objective:** To evaluate PFS in subjects with relapsed / refractory nodular sclerosing or mixed cellularity HL (Cohort 3), relapsed / refractory NHL (Cohort 4) and by disease subtype within Cohort 4 (MLBCL, FL, DLBCL, Other).

2) **Objective**: To evaluate the OS in subjects with relapsed / refractory nodular sclerosing or mixed cellularity HL (Cohort 3), relapsed / refractory NHL (Cohort 4), and by disease subtype within Cohort 4 (MLBCL, FL, DLBCL, Other).

3) **Objective**: To evaluate ORR of pembrolizumab based on the Revised Response Criteria for Malignant Lymphoma in subjects with relapsed / refractory nodular sclerosing or mixed cellularity HL (Cohort 3).

4) **Objective**: To evaluate DOR in subjects with relapsed / refractory nodular sclerosing or mixed cellularity HL (Cohort 3), relapsed / refractory NHL (Cohort 4), and by disease subtype within Cohort 4 (MLBCL, FL, DLBCL, Other).

5) **Objective**: To compare the extent of pre- pembrolizumab PD-L1 expression in tumor biopsies for pembrolizumab responders versus non-responders in subjects with relapsed / refractory nodular sclerosing or mixed cellularity HL (Cohort 3), relapsed / refractory NHL (Cohort 4), and by disease subtype within Cohort 4 (MLBCL, FL, DLBCL, Other).

Non-Hodgkin Lymphoma (DLBCL) – Combination Therapy (Cohort 5)

1) **Objective:** To evaluate PFS of combination lenalidomide + pembrolizumab based on the Revised Response Criteria for Malignant Lymphoma in subjects with relapsed / refractory DLBCL (Cohort 5).

2) **Objective:** To evaluate the OS of combination lenalidomide + pembrolizumab based on the Revised Response Criteria for Malignant Lymphoma in subjects with relapsed / refractory DLBCL (Cohort 5).

3) **Objective:** To evaluate the DOR of combination lenalidomide + pembrolizumab based on the Revised Response Criteria for Malignant Lymphoma in subjects with relapsed / refractory DLBCL (Cohort 5).

4) **Objective:** To compare the extent of pre-pembrolizumab PD-L1 expression in tumor biopsies for combination lenalidomide + pembrolizumab responders versus non-responders in subjects with relapsed / refractory DLBCL (Cohort 5).

3.3 Exploratory Objectives

MDS (Cohort 1)

1) **Objective:** To explore the PK profile of pembrolizumab in this subject population.

2) **Objective:** To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of pembrolizumab utilizing pre and post-treatment bone marrow biopsies/aspirates and blood sampling using flow cytometric technology. Gene sequencing will be evaluated in baseline bone marrow biopsy samples. Utilizing both pre and post treatment bone marrow biopsy samples acquired for purposes of disease assessment change in baseline of candidate biomarkers will also be assessed using multi-parametric immunohistochemistry (IHC) and Nanostring for gene expression.

3) **Objective:** To compare programmed cell death 1 (PD-1) expression on circulating lymphocytes in responders versus non-responders to pembrolizumab utilizing blood sampling pre and post-treatment.

4) **Objective:** To evaluate responses based on International Prognostic Scoring System (IPSS) and Revised International Prognostic Scoring System classifications in this patient population.

Multiple Myeloma (Cohort 2)

1) **Objective:** To explore the PK profile of pembrolizumab in this patient population.

2) **Objective:** To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of pembrolizumab utilizing pre and post-treatment bone marrow biopsies/aspirates and blood sampling using flow cytometric technology. Gene sequencing will be evaluated in baseline bone marrow biopsy samples. Utilizing both pre and post treatment bone marrow biopsy samples acquired for purposes of disease assessment change in baseline of candidate biomarkers will also be assessed using multi-parametric IHC and Nanostring for gene expression.

3) **Objective:** To compare PD-1 expression on circulating lymphocytes in responders versus non-responders to pembrolizumab utilizing blood sampling pre and post-treatment.

Hodgkin Lymphoma and Non-Hodgkin Lymphoma – (Cohort 3, 4, and 5)

1) **Objective:** To explore the PK profile of pembrolizumab, or pembrolizumab when given in combination with lenalidomide, in subjects with relapsed / refractory nodular sclerosing or mixed cellularity HL (Cohort 3), relapsed / refractory NHL (Cohort 4), and by disease subtype within Cohort 4 and Cohort 5 (MLBCL, FL, DLBCL, Other).

2) **Objective:** To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of pembrolizumab, or pembrolizumab when given in combination with lenalidomide, utilizing pre and post-treatment lymph node biopsies and blood sampling in subjects with relapsed / refractory nodular sclerosing or mixed cellularity HL (Cohort 3), relapsed / refractory NHL (Cohort 4), and by disease subtype within Cohort 4 and Cohort 5 (MLBCL, FL, DLBCL, Other). Gene sequencing will be evaluated in baseline tumor biopsies. Utilizing both pre and post treatment tumor biopsies, change in baseline of candidate biomarkers will also be assessed using multi-parametric IHC and Nanostring for gene expression.

3) **Objective:** To compare PD-1 expression on circulating lymphocytes in responders versus non-responders to pembrolizumab, or pembrolizumab when given in combination with lenalidomide, utilizing blood sampling pre and post-treatment in subjects with relapsed / refractory nodular sclerosing or mixed cellularity HL (Cohort 3), relapsed / refractory NHL (Cohort 4), and by disease subtype within Cohort 4 and Cohort 5 (MLBCL, FL, DLBCL, Other).

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on pembrolizumab (MK-3475). Refer to the current version of the local prescribing information for detailed information on lenalidomide.

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. 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 [2] [3].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-

cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to 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 programmed cell death ligand 2 (PD-L2) [4] [5]. The structure of murine PD-1 has been resolved [6]. 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 CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [5] [7] [8] [9]. 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 [10] [11]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer (NK) cells [12] [13]. Expression has also been shown during thymic development on CD4- CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [14]. 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 [15] [16] [17] [18]. 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 [15]. 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 [19]. 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.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2 without antibody-dependent cellular cytotoxicity (ADCC) or complement dependent cytotoxicity activity.

4.1.2 Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma,

melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of interferon (IFN)-γ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [20] [2] [3] [21] [5] [4]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

Recent data of nivolumab (MDX-1106, BMS-936558), an IgG4 antibody against PD-1, have validated PD-1 as an attractive target for clinical therapeutic intervention [22]. Nivolumab was tested in multiple solid tumors and promising clinical activity was noted in melanoma, renal cell carcinoma, and non-small cell lung cancer (NSCLC) at multiple doses. The most common AEs occurring in 25% or more of subjects included fatigue, decreased appetite, diarrhea, nausea, and cough. The most commonly observed immune-related AEs (irAEs) were pruritus, skin rash, and diarrhea. Other irAEs reported include increase of thyroid stimulating hormone, increase of alanine transaminase (ALT)/aspartate transaminase (AST), pneumonitis, infusion reaction, and vitiligo.

4.1.3 Ongoing Pembrolizumab Clinical Trials

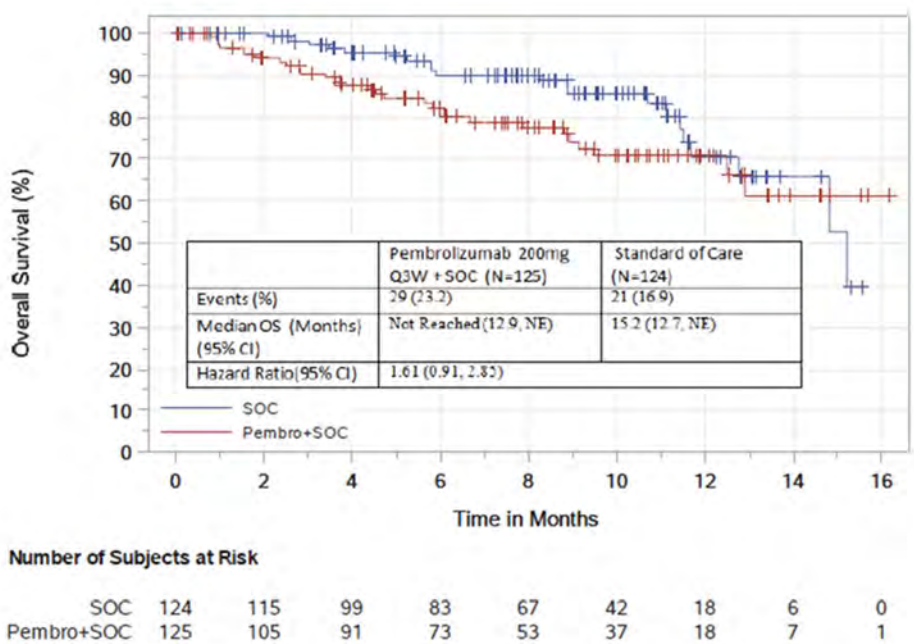
Ongoing clinical trials are being conducted in advanced melanoma, NSCLC, head and neck cancer, urothelial tract cancer, gastric cancer, and triple negative breast cancer. For study details please refer to the IB.

On 03-JUL-2017, the United States (US) Food and Drug Administration (FDA) placed on clinical hold KEYNOTE-183 (pembrolizumab/pomalidomide/dexamethasone for refractory or relapsed and refractory MM), KEYNOTE-185 (pembrolizumab/ lenalidomide/ dexamethasone for treatment naïve MM), and Cohort 1 of KEYNOTE-023 (pembrolizumab/lenalidomide/dexamethasone for refractory or relapsed and refractory MM). The FDA determined that the risks of pembrolizumab plus pomalidomide or lenalidomide outweighed any potential benefit for subjects with MM. Based on the summary of data shown below from KEYNOTE-183 and KEYNOTE-185, subjects enrolled in Cohort 5 of KEYNOTE-013 have to discontinue combination therapy with lenalidomide and pembrolizumab. If subjects are experiencing clinical benefit at time of discontinuation, subjects have the option of entering a 90 day transition period where they receive monotherapy pembrolizumab or lenalidomide and then must enter long-term safety and survival follow-up. There will be no further enrollment of subjects in this cohort. Additionally, enrollment in Cohort 2 has been completed; all subjects have previously discontinued study treatment and must transition into long-term safety and survival follow-up. There will be no further enrollment of subjects in this cohort. A full safety and efficacy analysis based on a 02-JUN-2017 data cutoff date was conducted for studies KEYNOTE-183 and KEYNOTE-185. A summary of these results is presented below.

KEYNOTE-183

KEYNOTE-183 is a phase 3, randomized, controlled trial of pomalidomide and low-dose dexamethasone with or without pembrolizumab in subjects with relapsed and refractory MM who had received at least two prior lines of therapy.

Using a data cutoff date of 02-JUN-2017, a complete evaluation of safety and efficacy was performed. There were 249 randomized subjects included in the analysis (Figure 4). The median follow-up was 8.1 months. For OS, there were 29 deaths on the pembrolizumab-containing investigational arm and 21 deaths on the control arm. The hazard ratio (HR) of the pembrolizumab-containing investigational arm compared to the control arm was 1.61 (95% confidence interval [CI], 0.91-2.85), increasing the relative risk of death by more than 50% compared to the control arm.



Standard of Care(SOC) is pomalidomide and low dose dexamethasone.

Database Cutoff Date: 02JUN2017.

Figure 4 Kaplan-Meier Graph of Overall Survival (Intent to Treat Population)

The ORR was 34% in the investigational arm compared to 40% in the control arm. In an exploratory TTP analysis, an HR of 1.14 (95% CI, 0.75-1.74) was observed (Figure 5).

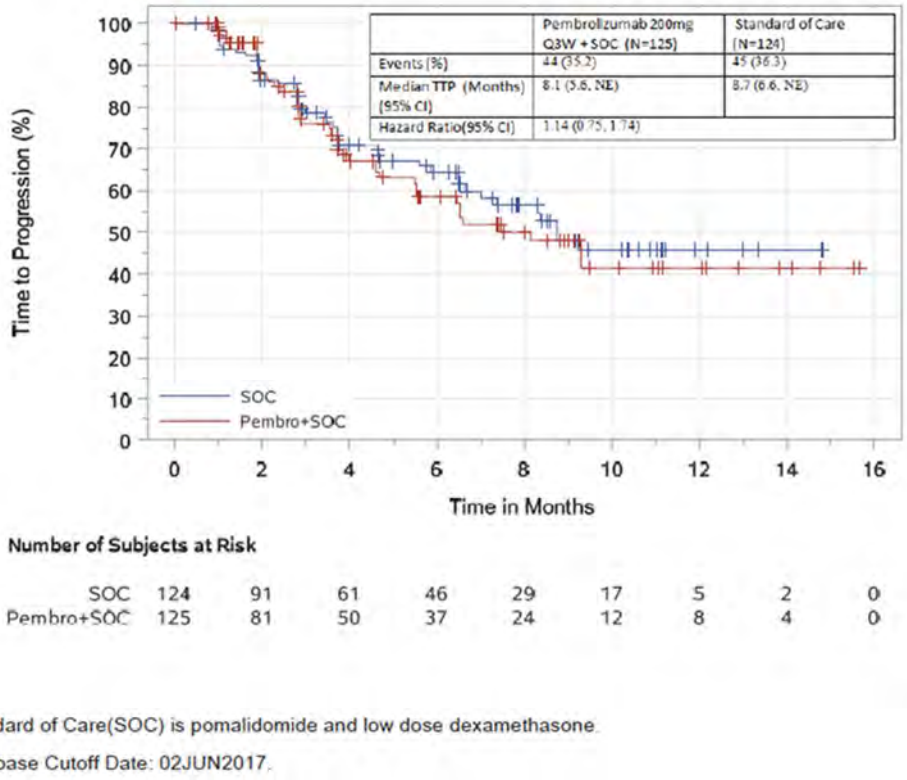


Figure 5 Kaplan-Meier Graph of Time to Progression Per IMWG 2011 Based on Confirmed Investigator Review (Primary Censoring Rule, Intent to Treat Population)

There was an 18% increase of severe, Grade 3 to 5 toxicity (83% vs. 65%, investigational vs. control arm). The incidence of serious adverse events (SAE) was 63% compared to 46% in the control arm. The following non-disease progression causes of death were identified in the pembrolizumab arm: myocarditis, Stevens-Johnson syndrome, myocardial infarction, pericardial hemorrhage, cardiac failure, respiratory tract infection, neutropenic sepsis, sepsis, multiple organ dysfunction, respiratory failure, and unknown.

KEYNOTE-185

KEYNOTE-185 is a phase 3, randomized, controlled trial of lenalidomide and low-dose dexamethasone with or without pembrolizumab in subjects with newly diagnosed MM who are ineligible for autologous stem cell transplant.

The data cutoff date of 02-JUN-2017 was used for these analyses. There were 301 randomized subjects included in the analysis. The median follow-up was 6.6 months. For OS, there

were 19 deaths on the pembrolizumab-containing investigational arm, and 9 deaths on the control arm. The HR of the pembrolizumab-containing investigational arm compared to the control arm was 2.06 (95% CI, 0.93-4.55), more than doubling the relative risk of death compared to the control arm (Figure 6).

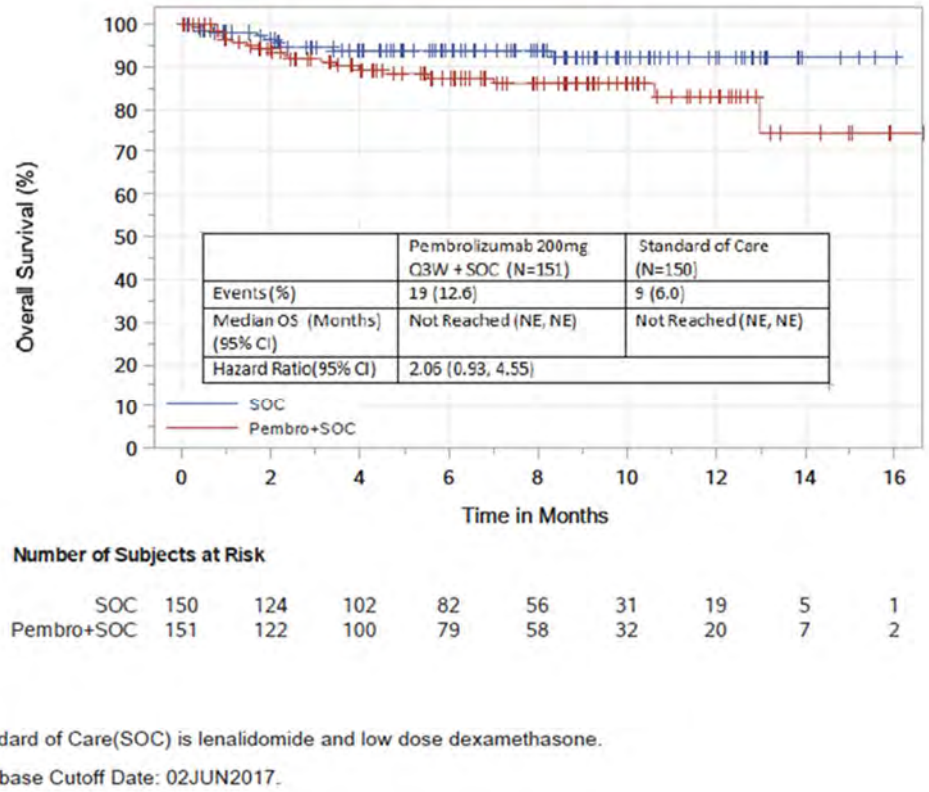


Figure 6 Kaplan-Meier Graph of Overall Survival (Intent to Treat Population)

There was an ORR of 64% in the investigational arm compared to 62% in the control arm. An exploratory TTP analysis (Figure 7) demonstrated an HR of 0.55 (95% CI, 0.20-1.50).

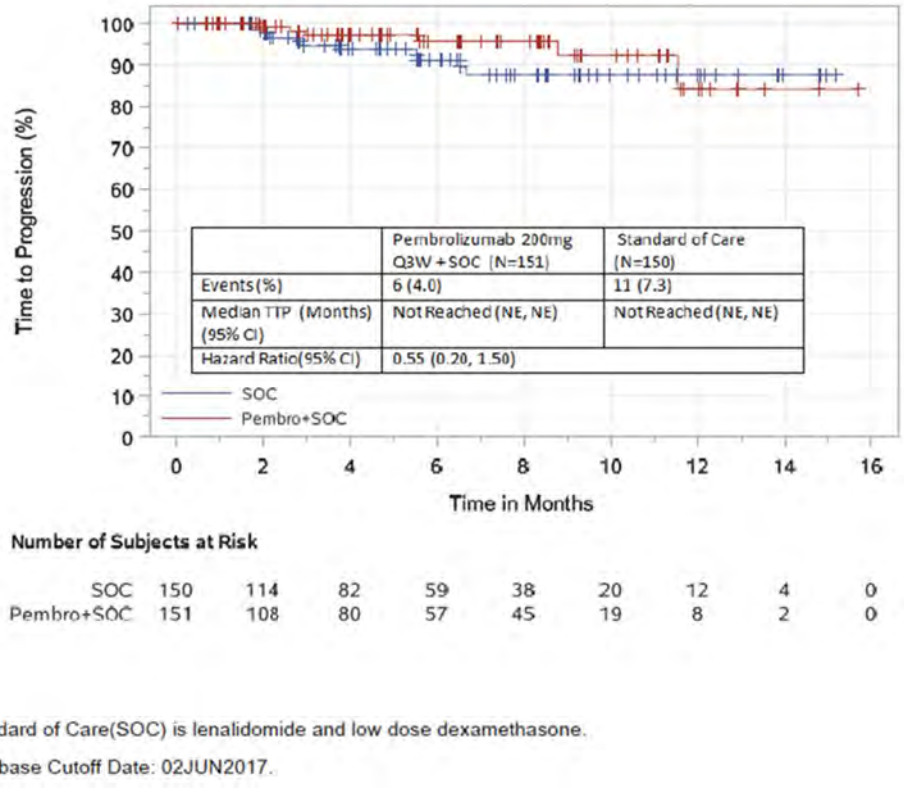


Figure 7 Kaplan-Meier Graph of Time to Progression Per IMWG 2011 Based on Confirmed Investigator Review (Primary Censoring Rule, Intent to Treat Population)

There was a 22% increase of severe, Grade 3 to 5 toxicity (72% vs. 50%, investigational vs. control arm). The incidence of SAEs was 54% compared to 39% in the control arm. There were 19 deaths in the investigational arm and 9 deaths in the control arm. The following non-disease progression causes of death were identified in the pembrolizumab arm: intestinal ischemia, cardio-respiratory arrest, suicide, pulmonary embolism, cardiac arrest, pneumonia, sudden death, myocarditis, large intestine perforation, and cardiac failure.

There is no benefit in efficacy and the risk of death is increased with the investigational regimen when compared to the standard of care in both trials. As noted above, the imbalance in deaths in the investigational treatment arm was driven primarily by a diverse set of AEs.

In conclusion, the benefit-risk profile is unfavorable for:

1. the combination of pembrolizumab, pomalidomide, and dexamethasone in relapsed refractory MM, and
2. the combination of pembrolizumab, lenalidomide, and dexamethasone in newly diagnosed treatment naive MM.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

4.2.1.1 Rationale for Evaluating anti-PD-1 Therapy in Hematologic Malignancies

Hematologic (Heme) malignancies are known to be responsive to a variety of immunotherapies. Allogeneic cellular therapy (bone marrow transplant and donor lymphocyte infusions) is effective in chronic myeloid leukemia, acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and many lymphomas. Some Heme malignancies are also responsive to systemic immunotherapies, such as lenalidomide in multiple myeloma and IFN in chronic myeloid leukemia. While data are currently limited, there is some indication that PD-L1/PD-1 biology may be an important mechanism of tumor immune escape in Heme malignancies. High PD-L1 expression has been reported in literature for MM, AML, CLL, NHL, and HL [23]. Additionally, PD-1 expression on infiltrating or circulating T cells can be associated with Heme malignancies and may contribute to immune escape, as in the cases of MDS, FL, and CLL [24] [25] [26]. Likewise, functional T-cell impairment after bone marrow transplant for AML can be associated with PD-1/PD-L1 expression[27]. The rationale for evaluating MDS, HL, and NHL are detailed below.

4.2.1.2 Myelodysplastic Syndrome

MDS comprises a heterogeneous group of malignant hematopoietic stem cell disorders characterized by dysplastic and ineffective blood cell production and a variable risk of transformation to acute leukemia. Patients often die of complications that arise from cytopenias or from subsequent AML. MDS occurs primarily in the elderly, with a median age of 72 years and male predominance. There are approximately 10,000 cases diagnosed annually in the United States [28]. However, a recent study indicates that the incidence may be as high as 45,000 cases per year, and potentially increasing with an aging population, which would make it the most common type of Heme malignancies [29]. MDS is classified using the World Health Organization (WHO) system based on morphology, immunophenotype, genetics and clinical feature into six entities: refractory cytopenia with unilineage dysplasia, refractory anemia with ringed sideroblasts, refractory anemia with multilineage dysplasia, refractory anemia with excess blasts, MDS with isolated del 5 and MDS, and unclassified [30]. Patients with untreated MDS are categorized into 4 IPSS prognostic risk groups: low, intermediate 1, intermediate 2 and high, which are associated with median survival times of 5.7, 3.1, 1.2, and 0.5 years, respectively [31]. Allogeneic stem cell transplantation (allo-SCT) from a human leukocyte antigen-matched sibling donor is a preferred approach for treating a selected group of patients with MDS, particularly those otherwise healthy patients with high-risk disease [32]. 5-azacytidine (5-Aza), and decitabine have been recently approved by the FDA for treating higher risk MDS patients. Despite these advances, the overall ORR with monotherapy of demethylating agents remains relatively low and the median survival reaches only about 2 years. Outcome after 5-Aza failure in high risk MDS is poor with a median OS of 5.6 months [33].

Aberrant up-regulation of PD-1, PD-L1, PD-L2, and CTLA4 expression has been demonstrated in peripheral blood mononuclear cells from MDS patients. This up-regulation is

further enhanced by therapeutic epigenetic modifiers, such as 5-Aza, and has been associated with poor survival outcome in this patient population [24]. This provides an especially strong rationale for anti-PD-1 therapy after first line 5-Aza failure. Patients with high-risk MDS with excess myeloid blasts (defined as 5%-20%) represent a relatively stable pre-leukemia population in whom an anti-PD-1 therapy would have sufficient time for evaluation before disease progression and death.

4.2.1.3 Hodgkin and non-Hodgkin Lymphoma

HL accounts for approximately 10% of all lymphomas and approximately 0.6% of all cancers diagnosed in the developed world annually [34]. In the United States, HL newly presents in over 8,400 individuals per year accounting for approximately 8.7% of all lymphomas in the US [35] [36]. Classical HL (CHL) is divided into 4 histologic subtypes: Nodular Sclerosis CHL, Mixed cellularity CHL, Lymphocyte rich CHL, and Lymphocyte depleted CHL [37]. Although, HL is curable in 80% of patients diagnosed, new therapies are needed, especially for patients who present with advanced disease. The standard of care for patients with relapsed or refractory HL is salvage chemotherapy and anti-CD-30 therapy followed by autologous stem-cell transplantation (auto-SCT), which can induce long-term remissions in approximately 50% of patients [38] [39]. For patients who experience relapse or progressive HL within 1 year after auto-SCT, especially those who have received newer agents such as brentuximab vedotin (anti-CD-30), the prognosis is exceedingly poor with a median survival time of approximately 1.2 years [40]. Although varied classes of novel agents have demonstrated activity in patients with relapsed / refractory HL who have failed auto-SCT, this patient population has no currently available standard of care and represents an urgent unmet medical need.

The incidence of NHL has increased over the last three decades to represent about 55,000 new cases a year in the United States [41]. At 5 years, the expected OS rate is 60%, and the event-free survival rate is 50% [42] [43]. NHL encompasses multiple entities with distinct clinical features and outcomes. Although the majority of patients with NHL respond to initial therapy, a large number eventually relapse, experience disease progression and death from disease after initial therapy [42] [44]. Auto-SCT has improved survival in patients with aggressive NHL, the treatment of patients who fail to respond to second-line chemotherapy regimens, or who relapse after auto-SCT is generally palliative.

High frequency of expression of PD-L1 by IHC and flow cytometry has been demonstrated in classic HL, and NHL tumor cells including primary mediastinal large B-cell lymphoma (PMLBCL) [27]. A recent integrative analysis reveals selective 9p24.1 amplification, which includes the PD-L1 and PD-L2 loci, increased PD-L1 expression, and further induction via JAK2 in nodular sclerosing HL and PMLBCL [45]. This affords a significant opportunity to define a targeted approach based on a novel biologically defined treatment mechanism such as the PD1/PD-L1 axis, with the goal of improving tolerability and efficacy in this patient population. A phase 1 clinical trial conducted in advanced hematologic malignancies using CT-011, showed clinical responses in 6 of 17 patients including HL and NHL patients [46]. Because the current data related to 9p24.1 amplification provide the strongest rationale for HL and the PMLBCL, other NHL subtypes will be enrolled regardless of PD-L1 positivity by IHC.

4.2.1.3.1 Lenalidomide + Pembrolizumab Combination in Diffuse Large B-Cell Lymphoma

Lenalidomide

Lenalidomide, an analogue of thalidomide, has known immunomodulatory and anti-angiogenic properties. It is currently approved for use in the United States for multiple myeloma, 5q MDS-induced anemia, and mantle cell lymphoma [47], and in the European Union (EU) for MM and 5q deletion MDS-induced anemia [48]. Nonclinical in vitro and in vivo studies have clarified how lenalidomide acts on various hematopoietic tumor types [49] [50] [51] [52] [53]. Recent clinical studies have demonstrated the efficacy of both single-agent [54] [55] [56] and combination lenalidomide therapies [57] [58] [59] [60] [61] in relapsed or refractory DLBCL.

Lenalidomide in vitro inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells, including multiple myeloma, del (5q) MDSs, and mantle cell lymphoma [47]. Enhancement of NK T cells, known to play a role in immune protection from tumors, is also activated by lenalidomide [49]. Although, the exact mechanism of action of lenalidomide is still unknown, early in vitro studies suggest immunomodulatory effects by inhibited Akt and Gab1 phosphorylation and inhibited Gab1 association with tyrosine kinase [50]. Additional immunomodulatory properties, suggested by nonclinical in vivo hematopoietic tumor models, include a delay in tumor growth by activation of T cells and NK cells, increased numbers of NK T cells, and inhibition of proinflammatory cytokines (e.g., tumor necrosis factor-α and interleukin-6 by monocytes [47]. Lenalidomide enhanced NK cell- and monocyte-mediated ADCC CD20+ tumor cells treated with rituximab [51]. More recent investigations of the gene expression changes in specifically activated B-cell-like (ABC) DLBCL suggest that lenalidomide kills ABC DLBCL cells by increasing IFNβ production. This increase, associated with the downregulation of IFN regulatory factor (IRF)-4 and SPIB, prevents IFNβ production by repressing IRF7 and amplifying nuclear factor -κB [52] [53].

Two early phase clinical studies of the efficacy of lenalidomide monotherapy in subjects with relapsed or refractory DLBCL who were not eligible for auto-SCT demonstrated ORRs (CR + unconfirmed CR+ partial response [PR]) of 19% (n=5/26) and 28% (n=30/108) [54] [55]. The most common Grade 3/4 AEs in these single-agent trials were neutropenia, thrombocytopenia, and leukopenia. In a comparison of single-agent lenalidomide in subjects with non-germinal center B-cell-like (GCB) DLBCL (also termed ABC DLBCL) versus GCB DLBCL, the ORR (CR + PR) was significantly higher in the non-GCB group (52.9% [n=9/17]) than in the GCB group (8.7% [n=2/23]), p=0.006; CR in the non-GCB group was 29.4% (n=5/17) compared to 4.3% (n=1/23) in the GCB group [56]. The most common AEs (Medical Dictionary for Regulatory Activities 16.0) reported in 2 or more subjects who received lenalidomide (n=54) were anemia, febrile neutropenia, DLBCL, pyrexia, pneumonia, urinary tract infection, dyspnea, and pulmonary embolism [NCT01197560]. Lenalidomide 25 mg was given orally for the first 21 consecutive days within 28-day cycles. Median ages of the subjects ranged from 65 to 66 years.

Combination treatment with lenalidomide in the DLBCL population has also demonstrated efficacy in 5 clinical studies. Three of these studies, which combined lenalidomide with

rituximab, achieved ORRs (CR + PR) of 35% (n=8/23), 28% (n=9/32), and 41.2% (n=7/17), and [57] [58] [59]. The most common Grade 3/4 hematologic AEs were neutropenia, thrombocytopenia, leukopenia, lymphopenia, and anemia. Subjects were either not eligible to receive auto−SCT or were censored from the analysis from the time of transplant. Lenalidomide 25 mg was given orally for the first 21 consecutive days within 28-day cycles. When lenalidomide was combined with rituximab in elderly subjects with DLBCL, the lenalidomide dose was reduced to 20 mg. Median ages of subjects in these studies ranged from 62 to 69 years.

Lenalidomide combined with R-CHOP-21 (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone every 3 weeks [Q3W]) in 2 frontline studies achieved ORRs (CR + PR) of 98% (95% CI, 91-100) (n=59/60) and 92% (95% CI, 81–97) (n=45/49) [60] [61]. The most common Grade 3/4 hematologic AEs were neutropenia, leukopenia, thrombocytopenia, anemia, and febrile neutropenia. Subjects did not receive auto-SCT during either study. Lenalidomide 25 mg was given orally for the first 10 consecutive days within a 21-day cycle in newly diagnosed subjects, and was reduced to 15 mg given over 14 days in an elderly population. R-CHOP-21 comprised rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (capped at 2.0 mg), all on day 1; and prednisone 100 mg/m^2 per day on days 1 through 5. Median ages of subjects ranged from 65 to 75 years.

The most common AEs in the single-agent and combination treatment studies with lenalidomide were myelosuppression, with most events reversible with dose modifications.

Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD−1 and its ligands, PD-L1 and PD-L2, and is currently approved for use in the United States for unresectable or metastatic melanoma and metastatic NSCLC in tumors that express PD-L1 and in the EU for unresectable or metastatic melanoma [62] [63].

The in vitro and in vivo effects of upregulation of PD-1 in various tumor types and in NHL have already been described (see Section 4.1 and Section 4.2.1.3). DLBCL is a known clinically aggressive type of NHL. Recent studies in the tumor tissue of subjects with DLBCL showed variable expression of PD-L1, which was also found in infiltrating macrophages and in the tumor environment. Overexpression of PD-L1 in DLBCL has been associated with a poor prognosis [64] [65]. Tissue microarray immunostaining showed overexpression of PD-1, PD-L1, PD-L2, and lymphocyte-activation gene 3 in FL and DLBCL tumor tissues, with DLBCL tumor cells co-expressing PD-1, PD−L1 and PD−L2. The ABC DLBCL subtype comprised more PD-L1 and PD-L2 expressing lymphoma cells than did the GCB subtype [66].

Pembrolizumab has a known AE profile, with most events Grade 3 or lower; the exception in clinical studies were rare Grade 4 events of hyperglycemia, increased AST, and anemia. AEs were primarily managed with dose interruptions and, if immune−related, treated with corticosteroids until resolution.

Lenalidomide + Pembrolizumab Combination

In KEYNOTE-023, 33 subjects with relapsed or refractory MM who had failed at least 2 lines of prior therapy, including a proteasome inhibitor (e.g., bortezomib or carfilzomib) and an immunomodulatory imide drug (IMiD [thalidomide, pomalidomide, lenalidomide), received lenalidomide 25 mg daily for 21 days and 7 days off + dexamethasone 40 mg weekly + pembrolizumab 200 mg every 2 weeks (Q2W). Determination and confirmation of maximum tolerated dose in 17 subjects allowed for a total of 50 subjects to receive the combination. An interim efficacy analysis showed an overall response rate for the 17 subjects of 76% (n=13/17) (CR + Very Good PR + PR), a disease control rate of 88% (n=15/17) (CR + Very Good PR + PR + Stable Disease [SD]), and a SD rate of 18% (n=3/17). The most common AEs seen in ≥4 subjects were neutropenia, thrombocytopenia, diarrhea, fatigue, anemia, pruritis, hyperglycemia, muscle spasms, myalgia, constipation, and asthenia; with 46% (n=23/50) experiencing hematologic Grade 3/4 toxicities (neutropenia, thrombocytopenia, anemia) with 6% (n=3/50) experiencing hyperglycemia. No dose modifications or treatment discontinuations were required for the management of reported immune-related events. These preliminary data suggest that a lenalidomide + dexamethasone + pembrolizumab treatment combination has an acceptable safety and tolerability profile [67].

On 03-JUL-2017, the US FDA placed on clinical hold KEYNOTE-183 (pembrolizumab/pomalidomide/dexamethasone for refractory or relapsed and refractory MM), KEYNOTE-185 (pembrolizumab/lenalidomide/dexamethasone for treatment naïve MM), and Cohort 1 of KEYNOTE-023 (pembrolizumab/lenalidomide/dexamethasone for refractory or relapsed and refractory MM). The FDA determined that the risks of pembrolizumab plus pomalidomide or lenalidomide outweighed any potential benefit for subjects with MM. As of Amendment 04 of KEYNOTE-013, use of pembrolizumab as a single agent at a fixed dose of 200 mg Q3W is ongoing. In Amendment 05, combining lenalidomide with pembrolizumab in subjects with DLBCL will explore leveraging the combined known immunomodulatory effects of lenalidomide with the effects of pembrolizumab on PD-L1 within a manageable risk profile.

Note: At least 25 subjects will be enrolled in Cohort 4D before Cohort 5 (DLBCL) is opened for enrollment.

4.2.1.4 Multiple Myeloma

MM is a malignant neoplasm of plasma cells that accumulate in the bone marrow leading to bone destruction and marrow failure. It accounts for 10% of all hematological malignancies, with an incidence of 5 cases per 100,000/year and a median age at onset of 65 to 70 years [68] [69] [70] [71]. The American Cancer Society has estimated 21,700 new cases of MM in the United States in 2012, with an estimated 10,710 deaths [72]. It is diagnosed by the presence of monoclonal plasma cell proliferation with more than 10% plasma cells in the bone marrow, presence of monoclonal proteins in serum, and/or in urine with one or more of end organ effects such as CRAB (hypercalcemia, renal failure, anemia, or bone destruction) [73] [74]. MM is responsive to systemic immunotherapy, lenalidomide. Although, improvements in OS have been achieved with newer therapies such as proteasome inhibitors and IMiDs, myeloma remains an incurable disease. Relapse refractory MM patients have an OS of 9 months, but

only 3 months if they receive no therapy following relapse, thus reflecting the poor outcome among these patients [75] [76] [77].

PD-L1 is expressed on most MM plasma cells [78], and PD-L1 overexpression enhanced MM invasiveness and rendered tumor cells less susceptible to cytotoxic T lymphocytes (CTLs). This effect was alleviated by anti–PD-L1 antibody treatment, demonstrating the importance of the PD-1/PD-L1 pathway in this process [79]. In addition, a recent report demonstrated increased levels of PD-L1 on MM cells together with enhanced PD-1 expression on T cells with an "exhausted" phenotype. The immunosuppressive effects of myeloma are overcome by PD-L1 blockade [80]. A Phase 1 clinical trial conducted in advanced hematologic malignancies using CT-011, showed clinical responses in 6 of 17 patients including SD in MM patients [46].

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for Dose Selection/Regimen for Pembrolizumab (Cohort 1, 2, 3, 4A, 4B)

In the dose escalation phase (1, 3, and 10 mg/kg Q2W) of the first in human study (pembrolizumab KEYNOTE-001), target engagement and objective evidence of tumor size reduction was noted at all dose levels and a maximum tolerated dose was not reached. PK data analysis of pembrolizumab administered Q2W showed slow systemic clearance, limited volume distribution, and a long half-life suggesting that peripheral target engagement is durable (> 21 days); therefore, the Q3W schedule was initially selected for the program. Although, the optimal dose and schedule for pembrolizumab has not been fully defined for melanoma or NSCLC, the highest dose evaluated (10 mg/kg Q2W) has been generally well tolerated.

Data from Bristol-Myers Squibb suggest that some indications, such as NSCLC, may require higher doses than melanoma. Because the optimal dose for new indications in this study cannot be fully informed by clinical data, POC will be evaluated using the maximum administered dose of 10 mg/kg Q2W. This dose was chosen to generate safety data at the highest possible dose and schedule currently in clinical development and may alleviate any doubt about sub-optimal dose compromising clinical efficacy.

4.2.2.2 Rationale for 200 mg Q3W Fixed Dose of Pembrolizumab (Cohort 2, 4A, 4C, 4D, and 5)

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

group. In Cohort B3, advanced melanoma subjects (irrespective of prior ipilimumab therapy) were randomized to receive MK-3475 at 10 mg/kg Q2W versus 10 mg/kg Q3W. Preliminary results demonstrate that the ORR was 32.8% (38/116) in the 10 mg/kg Q2W group and 27.8% (30/108) in the 10 mg/kg Q3W group (FAS Population by immune-related response criteria; data through 28-FEB-2014). The proportion of subjects with drug-related AEs, Grade 3 to 5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. Moreover, population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab (MK-3475) to a clinically meaningful extent. Importantly, the analysis revealed no significant impact of tumor burden on exposure. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model which characterized the influence of body weight and other patient covariates on exposure has been developed using available data from 476 subjects from KEYNOTE-001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings. Thus, with the newly available rationale for a fixed dose, Cohort 2, 4A, 4C and 4D will explore a fixed dose of pembrolizumab 200 mg Q3W in subjects enrolled under Amendment 013-04.

4.2.2.3 Rationale for Selection of Lenalidomide Dose

Lenalidomide is currently approved in the United States for the treatment of MM and mantle cell lymphoma at a dose of 25 mg orally for 21 consecutive days within a 28-day cycle. Lenalidomide at this same dose level was administered as a single agent in subjects with DLBCL in recent clinical studies (see Section 4.2.1.3.1). Given the established efficacy of lenalidomide at the 25-mg level and the preliminary safety data available for the proposed lenalidomide + dexamethasone + pembrolizumab combination seen in KEYNOTE-023, the Amendment 013-05 portion of this study will include a safety run-in as described in Section 5.2.1.3 to confirm the safety and tolerability for lenalidomide daily for 21 days + 7 days off when given in combination with pembrolizumab once Q3W without dexamethasone.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

The primary safety objective of this study is to characterize the safety and tolerability of pembrolizumab or lenalidomide + pembrolizumab in subjects with hematologic malignancies. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, or lenalidomide + pembrolizumab, including SAEs and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes.

4.2.3.2 Efficacy Endpoints

The primary efficacy objective of this study is to evaluate the anti-tumor activity of pembrolizumab in subjects with hematologic malignancies (MDS, MM, HL, and NHL) or lenalidomide + pembrolizumab combination in Cohort 5 (DLBCL).

- The primary efficacy endpoint for MDS will be ORR as assessed by the investigator per the IWG response criteria in MDS [81].
- The primary efficacy endpoint for MM will be ORR as assessed by the investigator per IMWG uniform response criteria [82].
- The primary efficacy endpoint for HL will be CRR as assessed by the investigator Revised Response Criteria for Malignant Lymphoma [83].
- The primary efficacy endpoint for NHL will be ORR as assessed by the investigator Revised Response Criteria for Malignant Lymphoma [83].

For lymphoma subjects, radiographic images will also be transferred to an imaging vendor for retrospective central review and assessment of response by Revised Response Criteria for Malignant Lymphoma if the minimum number of responses required for success for the primary hypothesis is observed. For MDS subjects, if the study meets its primary endpoints of safety and tolerability and efficacy, sites may be asked to submit/provide slides and hematopathology reports for a central review and confirmation.

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 lymphoma disease response assessment criteria may not provide a comprehensive response assessment of

immunotherapeutic agents such as pembrolizumab. Therefore, in the setting where a subject's lymphoma disease response assessment shows progressive disease (PD), trial treatment may be continued at the discretion of the principal investigator in a subject whose clinical condition is stable until repeat imaging performed 4 to 6 weeks later confirms progression. However, imaging should occur at any time where there is clinical suspicion of progression. See Section 7.1.2.7.7 for additional information about the timing of the disease response assessment after PD.

4.2.3.3 Biomarker Research

Bone marrow and lymph node biopsy specimens that are collected will be evaluated at a central laboratory for expression status of PD-L1 by IHC. When available, hematopathology reports should be submitted to the central laboratory performing the IHC analysis. Additional biomarker research to identify factors important for pembrolizumab therapy may also be pursued. For example, pre- and post-dose bone marrow biopsies/aspirates, lymph node biopsies (lymphoma cohorts only), and blood samples from this study may undergo flow cytometric, proteomic, genomic, and transcriptional analyses at a central laboratory. 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/PDL-1 pathway results in enhanced T cell mediated immune response. To test the hypothesis that T cell activation mediated by pembrolizumab treatment correlates with clinical response, T cell subsets in peripheral blood, e.g., PD-1+ T cells, effector, memory and regulatory T cells, will be assessed pre- and post-dose and in both responders and non-responders. In addition, PD-L1 expression on bone marrow mononuclear cells of MDS will be tested.

Multiparametric (Two-Color) IHC

Spatial association of PD-1+ tumor-infiltrating lymphocytes and PD-L1+ cells (tumor and myeloid cells) suggests "induction" of PD-L1. Interferon-gamma production by antigen-specific PD-1+ CD8+ T cells is hypothesized to drive local intratumoral upregulation of PD-L1 on adjacent tumor and myeloid cells, leading to a "stalled CTL" response which may be predictive of response to pembrolizumab therapy. By assessing both of the required elements, i.e., PD-L1 positive cells and PD-1+ T cells, a two-color IHC assay may be a better predictor of response than PD-L1 positivity alone.

Transcriptional Analyses

Messenger ribonucleic acid (RNA) expression profiling in archival material 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 CTL" 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) IFN-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 being 'hypermutated'. 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.

4.2.3.4 Future Biomedical Research

Merck will conduct Future Biomedical Research (FBR) on blood, lymph node and bone marrow specimens collected during this clinical trial. This research may include genetic analyses (deoxyribonucleic acid [DNA]), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or AEs are identified. Genomic markers of disease may also be investigated. Such retrospective PGt studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs, and/or to ensure that subjects receive the correct dose of the correct drug at the correct time. The details of FBR are presented in Section 12.2 - Collection and Management of Specimens for FBR. Additional informational material for institutional review boards/ethics review committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

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

Efficacy and safety information in regard to pembrolizumab are provided in the current version of the IB and in regard to lenalidomide are provided in Section 4.2.1.3.1 and per the most current local prescribing information.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with intermediate-1, intermediate-2, or high risk MDS who have failed at least 4 cycles of HMA treatment (Cohort 1); relapse refractory or refractory MM (Cohort 2); relapsed / refractory HL (Cohort 3); relapsed / refractory MLBCL (Cohort 4A); PD-L1 positive relapsed / refractory NHL (Cohort 4B); irrespective of PD-L1 status, relapsed / refractory FL (Cohort 4C) or DLBCL (Cohort 4D) or (Cohort 5) 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:

MDS (Cohort 1)

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

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

3. Have primary or secondary MDS with IPSS score of Intermediate-1, Intermediate-2, or High and has failed (defined as worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to more advanced MDS FAB subtype than pretreatment) to respond to at least 4 cycles of prior treatment with a HMA (azacitidine and decitabine).

   Per IWG criteria, progression is defined as:

   - Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts
   - 5%-10% blasts: ≥ 50% increase to > 10% blasts
   - 10%-20% blasts: ≥ 50% increase to >20% blasts
   - 20%-30% blasts: ≥ 50% increase to > 30% blasts

   Or any of the following:

   - At least 50% decrement from maximum remission/response in granulocytes or platelets
   - Reduction in Hgb by ≥ 2 g/dL
   - Transfusion dependence

4. Be expected to survive long enough to assess for response or benefit from treatment at investigator's discretion.

5. Have a performance status of 0 or 1 on the ECOG Performance Scale.

6. Be able to provide bone marrow biopsy/aspirate material for biomarker analysis or is willing to provide a newly obtained bone marrow biopsy/aspirate.

7. Demonstrate adequate organ function as defined in Table 1, all screening laboratory tests should be performed within 7 days of treatment initiation.

Table 1 MDS Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Bone marrow blasts	Blast percentage ≤ 30% [a]
White blood cell count	< 30,000 mcL (Subjects with a rapid increase in WBC indicative of progressive disease per investigator's assessment should be excluded.)
Renal	
Creatinine **OR** Measured or calculated creatinine clearance [b] (GFR can also be used in place of creatinine or CrCl)	≤ 1.5X upper limit of normal (ULN) **OR** ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

[a] The protocol follows FAB classification which allows inclusion of subjects with blasts percentages up to 30%. Please note that per the 2008 WHO classification, subjects with blast counts of 20-30% are considered AML.
[b] Creatinine clearance should be calculated per institutional standard.

8. Female subjects of childbearing potential should 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.

9. 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.

10. 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.

Multiple Myeloma (Cohort 2, enrollment has been completed and no further enrollment will be allowed)

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

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

13. Has a confirmed diagnosis of multiple myeloma based on standard criteria (see Durie 1986 for criteria [84]). See Appendix 12.6 for MM Diagnostic Criteria.

14. Currently has MM with measurable disease, defined as:

    - a monoclonal immunoglobulin spike on serum electrophoresis of at least 0.5 g/dL and/or
    - urine monoclonal protein levels of at least 200 mg/24 hours
    - for subjects without measurable serum and urine M-protein levels, an abnormal free light chain ratio (normal value: 0.26 - 1.65) with involved FLC level ≥10 mg/dL (≥100 mg/L).

15. Has relapse refractory or refractory MM who has failed at least two lines of prior therapy, including a proteasome inhibitor (bortezomib, carfilzomib) and an IMiD (thalidomide, pomalidomide, lenalidomide).

    a. **Relapse Refractory MM** defined as achieving at least a partial response to previous treatment with a proteasome inhibitor or an IMiD, or both, but progressed within 6 months (and had developed progressive disease on or within 60 days after completing their last treatment)
    b. **Refractory MM** defined as progressed on or within 60 days of treatment with a proteasome inhibitor or an IMiD, or both (and had developed progressive disease on or within 60 days after completing their last treatment)

16. Be able to provide archival (if available) and newly obtained bone marrow aspirate/biopsy material for biomarker analysis and disease assessment.

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

18. Must demonstrate adequate organ function as defined by the following table (Table 2). All screening laboratory tests should be performed within 7 days of treatment initiation.

Table 2 Multiple Myeloma Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,000 /mcL
Platelets	≥ 75,000 / mcL
Hemoglobin	≥ 8 g/dL
Renal	
Creatinine **OR** Measured or calculated[1] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) **OR** ≥ 60 mL/min for subject with creatinine levels > 1.5X institutional ULN
Hepatic	
Total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[1] Creatinine clearance should be calculated per institutional standard.	

19. Female subjects of childbearing potential should 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.

20. 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.

21. 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.

Hodgkin Lymphoma (Cohort 3); Mediastinal Large B-Cell Lymphoma (Cohort 4A); any other PD-L1 positive Non-Hodgkin Lymphoma (Cohort 4B); Follicular Lymphoma (Cohort 4C); or Diffuse Large B-Cell Lymphoma (Cohort 4D) and (Cohort 5, enrollment has been discontinued and no further enrollment will be allowed).

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

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

24. Have relapsed / refractory nodular sclerosing or mixed cellularity Hodgkin lymphoma, relapsed / refractory mediastinal large B cell lymphoma, relapsed / refractory PD-L1 positive non-Hodgkin lymphoma, or irrespective of PD-L1 status, non-Hodgkin lymphoma subjects with relapsed / refractory Follicular Lymphoma (FL) or Diffuse Large B-Cell Lymphoma (DLBCL). Subjects must have failed, are ineligible for, or refused a stem cell transplant (where stem cell transplant is standard of care). Hodgkin lymphoma subjects must have relapsed after treatment with or failed to respond to Brentuximab vedotin.

    -Note: Amendment 013-04 will exclusively enroll subjects with relapsed / refractory MLBCL, FL or DLBCL NHL subtypes.

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

26. Cohort 3, 4A, 4C, 4D, and 5: Be able to provide a core or excisional lymph node biopsy for biomarker analysis from an archival or newly obtained biopsy at Screening. In addition, be able to provide additional biopsy at Week 12.

27. For Cohort 4B (PD-L1 positive relapsed / refractory NHL) only: PD-L1 positivity must be confirmed by IHC from an archival sample (if available) or from a newly obtained lymph node biopsy (excision or core needle biopsy) prior to study entry. In addition these subjects must be able to provide additional biopsy material at Screening and the completion of Cycle 7.

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

29. Must demonstrate adequate organ function as defined in Table 3, all screening laboratory tests should be performed within 7 days of treatment initiation.

Table 3 Lymphoma Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,000 /mcL
Platelets	≥ 75,000 / mcL
Hemoglobin	≥ 8 g/dL
Renal	
Creatinine **OR** Measured or calculated [a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) **OR** ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Serum albumin	> 3.0 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard.	

30. Have a life expectancy > 3 months

31. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication or per local requirements as described in the current version of the lenalidomide prescribing information. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

32. 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.

33. 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.

Non-Hodgkin Lymphoma Diffuse Large B Cell Lymphoma (Cohort 5, enrollment has been discontinued and no further enrollment will be allowed)

34. Must demonstrate adequate renal function as confirmed by both a creatinine ≤ 1.5 times the upper limit of normal (ULN) and a creatinine clearance ≥ 60 mL/min obtained per institutional standards.

35. Must be willing to use thromboprophylaxis as selected by the investigator.

36. All subjects must agree to follow the regional requirements for lenalidomide counseling, pregnancy testing, and birth control; and be willing and able to comply with the regional requirements (for example, periodic pregnancy tests, safety laboratory tests, etc.).

5.1.3 Subject Exclusion Criteria

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

MDS (Cohort 1)

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 currently receiving treatment with any colony stimulating factors including G-CSF, GM-CSF, erythropoietin, and other hematopoietic cytokines within 2 weeks of enrollment into trial.

3. 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.

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

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

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

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

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

6. 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]).

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

8. Has known clinically active CNS involvement.

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

10. Has an active infection requiring intravenous systemic therapy.

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

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

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

14. Has a known Human Immunodeficiency Virus (HIV), Hepatitis B (HBV) (e.g., HBsAg reactive), or Hepatitis C (HCV) (e.g., HCV RNA [qualitative] is detected) infection.

15. Has known symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

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

Multiple Myeloma (Cohort 2)

17. 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.

18. Has myeloma and a history of repeated infections, primary amyloidosis, hyperviscosity, plasma cell leukemia, POEMS syndrome, Waldenström's macroglobulinemia, or IgM myeloma.

19. 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.

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

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

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

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

    -Note: Toxicity that has not recovered to ≤ Grade 1 is allowed if it meets the inclusion requirements for laboratory parameters defined in Table 2.

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

23. Has known clinically active CNS involvement.

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

25. Has an active infection requiring intravenous systemic therapy.

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

27. 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.

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

29. Has a known Human Immunodeficiency Virus (HIV), Hepatitis B (HBV) (e.g., HBsAg reactive), or Hepatitis C (HCV) (e.g., HCV RNA [qualitative] is detected) infection.

30. Has a clinically significant coagulopathy per investigator's assessment.

31. Has known symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

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

33. Has received autologous stem cell transplant within 12 weeks before the first infusion.

34. Is planning for or is eligible for allogeneic hematopoietic stem cell transplant.

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

Hodgkin Lymphoma (Cohort 3); Mediastinal Large B-Cell Lymphoma (Cohort 4A); any other PD-L1 positive Non-Hodgkin Lymphoma (Cohort 4B); Follicular Lymphoma (Cohort 4C); or Diffuse Large B-Cell Lymphoma (Cohort 4D) and (Cohort 5).

36. 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.

37. 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.

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

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

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

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

    -Note: Toxicity that has not recovered to ≤ Grade 1 is allowed if it meets the inclusion requirements for laboratory parameters defined in Table 3.

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

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

42. Has known clinically active CNS involvement.

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

44. Has an active infection requiring intravenous systemic therapy.

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

46. 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.

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

48. Has a known Human Immunodeficiency Virus (HIV), Hepatitis B (HBV) (e.g., HBsAg reactive), or Hepatitis C (HCV) (e.g., HCV RNA [qualitative] is detected) infection.

49. Has known symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

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

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 4.

Table 4 Trial Treatment

Drug & Cohort	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab Cohort 1, 2, 3, 4A, and 4B	10 mg/kg	Q2W	IV infusion	Day 1 of each cycle	Experimental
Pembrolizumab Cohort 2, 4A, 4C, 4D	200 mg*	Q3W	IV infusion	Day 1 of each cycle	Experimental
Lenalidomide + Pembrolizumab Cohort 5 (DLBCL)**	25 mg or RP2D 200 mg	Daily Q3W	Oral IV infusion	First 21 consecutive days + 7 days off Every 21 days The cycle length = 28 days	Experimental

Abbreviations: DLBCL=diffuse large B-cell lymphoma; IV=intravenous; Q2W=every 2 weeks; Q3W=every 3 weeks; RP2D=recommended Phase II dose.
See Section 5.2.3 for the expected duration of treatment.
*Applicable after amendment 013-04.
**Applicable after amendment 013-05.

All trial treatments will be administered on an out-patient basis.

All products indicated in Table 4 will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.2.2 Rationale for Dose Selection/Regimen/Modification.

The dose amount required to prepare the pembrolizumab infusion solution will be based on the subject's weight in kilograms (kg) for all subjects receiving 10 mg/kg Q2W in Cohort 1, 2, 3, 4A and 4B enrolled prior to approval of Amendment 013-04. Subjects enrolled in Cohort 2, 4A, 4C and 4D under Amendment 013-04 or 013-05 will receive 200 mg Q3W. Subjects enrolled in Cohort 5 (DLBCL) will be allocated to receive pembrolizumab 200 mg administered intravenously once every 21 days in combination with lenalidomide taken orally once daily for 21 days + 7 days off. The cycle length is 28 days. Details on the dose calculation, preparation, and administration of pembrolizumab are provided in the Pharmacy

Manual. For additional information regarding lenalidomide, please refer to the current version of the local prescribing information.

5.2.1.2 Dose Modification for Pembrolizumab

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

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

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

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • 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	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	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	• Administer corticosteroids (initial dose of 0.5- 1mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2mg/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	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper.	• 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	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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.

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

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

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities (exception MDS) as per Table 6 below.

Table 6 Dose Modification Guidelines for Hematological Pembrolizumab-Related Adverse Events

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Hematological Toxicity	1, 2, 3	No	N/A	N/A
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any life-threatening event*
Abbreviations: N=no; N/A=not applicable; Y=yes				

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

5.2.1.3 Cohort 5 (DLBCL) Lenalidomide + Pembrolizumab Combination Therapy: Safety Run-in and Expansion

The safety evaluation for subjects enrolled in Cohort 5 (DLBCL) will include Part 1 (safety run-in) for a maximum of 12 subjects per dose level of lenalidomide. Once RP2D is established at the end of Part 1, Part 2 (expansion) will enroll up to approximately 30 subjects treated at the RP2D. With 4 potential doses of lenalidomide to be evaluated, the sample size can range from approximately 30 to 66 subjects for this cohort.

5.2.1.3.1 Part 1: Safety Run-In

Amendment 013-05 is using a design based on the toxicity probability intervals method [85]. DLTs will be used to determine the dose level of lenalidomide used in the safety run-in. Pembrolizumab 200 mg is to be administered intravenously once every 21 days in combination with lenalidomide taken orally once daily for 21 days + 7 days off. The cycle length is 28 days. Only the lenalidomide dose level will be reduced by 5-mg increments to a dose no lower than 10 mg; i.e., the dose of pembrolizumab is fixed at 200 mg.

The safety run-in will begin with an enrollment of 6 subjects treated at an initial level of 25 mg lenalidomide. The number of subjects who are evaluable for DLT (columns) versus the number of subjects who developed a DLT during Cycle 1 (rows) will be continuously assessed as shown in Table 7 below as follows:

1) If 2 or fewer of the 6 subjects at the initial level develop a DLT, then enrollment would continue at this level following the rules of the table. There is no elevation beyond 25 mg lenalidomide, so that an "E" (escalate) is considered an "S" (stay) at that dose level.

If a "D" (de-escalate) is reached, then lenalidomide will be reduced to 20 mg and a new cohort of 6 subjects will be enrolled at that level.

2) If 3 of the 6 subjects at the initial level develop a DLT, then a new cohort of 6 subjects would be assessed at the 20 mg lenalidomide level, again following the rules of the table starting at the column for 6 subjects, where an "E" would trigger an increase back to the 25 mg lenalidomide level and evaluation would resume at the number of subjects where it previously left off. If "D" is reached in the table, then a new cohort of 6 subjects would be assessed at the 15 mg lenalidomide level analogously, with further de-escalation to 10 mg lenalidomide if indicated (based on a "D" reached for the 15 mg lenalidomide table).

3) If 4 or more of the 6 (or fewer) subjects at the initial level develop a DLT, then that level is considered unacceptable ("DU") and a new cohort of 6 subjects would be assessed at the 20 mg lenalidomide level as described above. There is no re-escalation allowed to a dose level that was found unacceptable ("DU") according to the table.

Once a DLT is observed, the number of subjects who are enrolled at that dose but are not yet fully evaluable for DLT assessment may not exceed the number of remaining subjects who are at risk of developing a DLT before the dose would be considered unacceptably toxic (denoted as DU in Table 7). For example, if 2/6 subjects have experienced a DLT at a given dose level, no more than an additional 4 subjects should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 4 of the additional subjects experience a DLT (i.e., 6/10 subjects with DLT in Table 7). To find out how many more subjects can be enrolled, one can count steps in diagonal direction (down and to the right) from the cell to the first cell marked DU.

Enrollment would continue until 12 subjects have been evaluated in at least one dose level. When ≤5 of the 12 subjects at a given dose level develop a DLT, then that dose level is taken as the lenalidomide RP2D with pembrolizumab 200 mg. Thus, the RP2D for lenalidomide could be 25, 20, 15, or 10 mg depending on the guidance below.

All decisions regarding dose levels for subject enrollment and dosing will be made by the Sponsor and communicated to the investigators. Note that while 30% has been the target toxicity rate used to generate the guidelines in Table 7, the observed rate of subjects with DLT at the RP2D may be slightly above or below 30%.

Table 7 Monitoring Guidance in Dose Evaluation (Target DLT Rate of 30%)

Number of Toxicities	Number of subjects treated at current dose level						
	6	**7**	**8**	**9**	**10**	**11**	**12**
0	E	E	E	E	E	E	E
1	E	E	E	E	E	E	E
2	S	S	E	E	E	E	E
3	D	S	S	S	S	S	E
4	DU	D	D	S	S	S	S
5	DU	DU	DU	D	D	D	S
6	DU	DU	DU	DU	DU	DU	D
7		DU	DU	DU	DU	DU	DU
8			DU	DU	DU	DU	DU
9				DU	DU	DU	DU
10					DU	DU	DU

E = Escalate to the next higher dose level
S = Stay at the current dose level
D = De-escalate to the next lower dose level
DU = Current dose level is unacceptably toxic
Target DLT rate = 30%; a=.005, b=.005, k1=1.1; k2=0.5; pow=1
Source: [86]

After reaching the RP2D according to the design above, enrollment in the expansion portion will be started, with additional patients treated at the RP2D to achieve 30 subjects treated at that dose (inclusive of those treated at that dose during the safety run-in).

5.2.1.3.2 Part 2: Expansion

During the expansion portion of Cohort 5 (DLBCL), the RP2D level of lenalidomide taken once daily for 21 consecutive days + 7 days off will be administered in combination with pembrolizumab 200 mg once every 21 days. The maximum number of subjects to be enrolled in the expansion portion will be 30 subjects, including those treated at the RP2D during Part 1.

Safety will be evaluated as described in Section 7.2.

Subjects enrolled in the safety-run-in who do not experience DLTs will remain on their initial dose regardless of the RP2D established for the trial.

5.2.1.3.3 Definition of Dose-Limiting Toxicities

All toxicities will be graded using NCI CTCAE, version 4.0 (Section 12.5).

All subjects enrolled during safety run-in will complete all doses of study drug for Cycle 1 before the additional subjects are enrolled.

The occurrence of any of the following toxicities during the safety run-in for subjects enrolled in Cohort 5 (DLBCL) will be considered a DLT if judged by the investigator as related to lenalidomide or pembrolizumab.

- Grade 4 non-hematologic toxicity (not laboratory).
- Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia
    - Grade 4 thrombocytopenia of any duration
    - Grade 3 thrombocytopenia if associated with bleeding
- Febrile neutropenia Grade 3 or Grade 4.
- The use of colony stimulating factor G-CSF for neutropenia.
- Grade 3 non-hematologic toxicity (not laboratory) will be considered a DLT, with the exception of Grade 3 nausea, vomiting, or diarrhea, which will not be considered a DLT unless lasting more than 3 days despite optimal supportive care.
- Any Grade 3 non-hematologic laboratory value if:
    - medical intervention is required to treat the subject, or
    - the abnormality leads to hospitalization, or
    - the abnormality persists for >1 week.
- Any drug-related AE that causes a subject to discontinue treatment during Cycle 1.
- Grade 5 toxicity.
- Any treatment-related toxicity that causes a greater than 1 week delay in initiating Cycle 2.
- Unable to complete at least 80% of either of the 2 treatments during the first course of therapy due to treatment-related toxicity (even if not meeting above DLT criteria).

5.2.1.3.4 Dose Modification for Lenalidomide

Lenalidomide must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 8.

Table 8 Dose Modification Guidelines for Hematologic Lenalidomide-Related Adverse Events

Toxicity	**Grade**	**Hold Treatment (Y/N)**	**Timing for restarting treatment**
Thrombocytopenia	1 or 2	N	Continue to monitor CBC as per protocol.
	3 or 4	Y	Follow CBC weekly until platelet count returns to ≥ 50,000 mcL. Resume lenalidomide at 5 mg less than the previous dose. *If the reduced dose of lenalidomide falls below 10 mg, Sponsor consultation is required to continue the subject on lenalidomide treatment.*
Neutropenia	1 or 2	N	Continue to monitor CBC as per protocol.
	3 for at least 7 days OR 4	Y	Follow CBC weekly until neutrophil count returns to ≥1,000 mcL. Resume lenalidomide at 5 mg less than the previous dose. *If the reduced dose of lenalidomide falls below 10 mg, Sponsor consultation is required to continue the subject on lenalidomide treatment.*
Febrile neutropenia	3	Y	Follow CBC weekly until neutrophil count returns to ≥1,000 mcL. Resume lenalidomide at 5 mg less than the previous dose. *If the reduced dose of lenalidomide falls below 10 mg, Sponsor Consultation is required to continue the subject on lenalidomide treatment.*
	4	Y	Discontinue lenalidomide permanently.
Abbreviations: CBC=complete blood cell count; N=no; Y=yes.			

Dose Modification Guidelines for Non-Hematologic Lenalidomide-Related Adverse Events

Hold treatment for non-hematologic Grade 3/4 toxicities judged to be related to lenalidomide. When the toxicity has resolved to ≤Grade 2, restart lenalidomide at 5 mg less than the previous dose. If the reduced dose of lenalidomide falls below 10 mg, Sponsor Consultation is required to continue the subject on lenalidomide treatment.

In subjects in Cohort 5 (DLBCL) who experience a decrease in renal function, the most current version of the local prescribing information should be followed.

5.2.1.3.5 Replacement of Subjects During Safety Run-in

In order to determine safety, all subjects selected must meet the criteria for evaluability in Cycle 1. Subjects are considered non-evaluable for DLT assessment and will be replaced if:

- they are allocated but not treated,
- they discontinue from the trial prior to completing Cycle 1 for reasons other than treatment-related AEs (if a subject experiences a DLT and does not complete Cycle 1 for any reason this subject will be considered evaluable for DLT assessment), they received <90% of the total pembrolizumab infusion in Cycle 1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT,
- they received <80% of lenalidomide doses in Cycle 1 for reasons other than treatment-related AEs.

Non-evaluable subjects will not be counted toward the cohort total for DLT evaluation.

If a subject experiences a DLT in Cycle 1, the dose of lenalidomide may be reduced or lenalidomide can be discontinued only after discussion and agreement between the Sponsor and investigator. However, if the subject is deriving clinical benefit from pembrolizumab, the subject may be allowed to continue on pembrolizumab as described in Section 7.1.2.7.7.

5.2.2 Timing of Dose Administration

Pembrolizumab should be administered on Day 1 of each cycle for subjects receiving pembrolizumab monotherapy after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis. Administration during in-patient hospitalization requires Sponsor consultation.

Pembrolizumab will be administered as a 30 minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability

of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

Subjects in Cohort 5 (DLBCL) will receive pembrolizumab 200 mg administered intravenously once every 21 days in combination with lenalidomide taken orally once daily for 21 days + 7 days off. The cycle length is 28 days. After RP2D is established for Cohort 5 (DLBCL), treatment should continue for 26 cycles or until confirmed disease progression or unacceptable toxicity.

Because a subject treated with PD-1 inhibitors may have pseudoprogression of disease (there is progression per imaging, but the subject is clinically stable or improving), confirmation of progression should be conducted as follows:

After the first documentation of progression at Week 12, it is at the discretion of the investigator to keep a clinically stable subject on trial treatment or to stop trial treatment until a disease response assessment performed 4 to 6 weeks later confirms progression.

Clinical stability may be defined as:

1) Absence of symptoms and signs indicating clinically significant progression of disease (including worsening of laboratory values) with the exception of M-protein elevation for the multiple myeloma cohort.

2) No decline in ECOG performance status.

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

Subjects that are deemed clinically unstable are not required to have a confirmation assessment.

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 no other anti-tumor therapy (e.g., chemotherapy, radiation, etc.) has been administered.

Subjects should have their next disease response assessment as detailed in the Trial Flow Chart (see Section 6.0). When feasible, subjects should not be discontinued until progression is confirmed.

For subjects who have SD, partial response, or CR following the disease response assessment at Week 12, a confirmation assessment is not required. Disease assessments and imaging should continue per the regular frequency.

5.2.3 Extent of Treatment

- Subjects receiving pembrolizumab monotherapy who experience a partial response or have SD may remain on treatment until unacceptable toxicity or progression. Subjects receiving pembrolizumab monotherapy Q3W may receive up to 35 doses; subjects receiving pembrolizumab monotherapy Q2W may receive up to 52 doses.

- Per the investigator's discretion, subjects receiving pembrolizumab monotherapy who achieve a CR or sCR (MDS subjects must meet both bone marrow and peripheral blood criteria for CR; MM subjects must achieve a sCR) may stop treatment after 24 weeks provided that there are two doses received after the CR was documented. These subjects, with the exception of subjects in Cohort 2 (MM) who are not allowed, 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).

- Subjects receiving pembrolizumab monotherapy who achieve a CR or sCR and choose not to stop therapy may continue treatment until progression. Subjects receiving pembrolizumab monotherapy Q3W may receive up to 35 doses; subjects receiving pembrolizumab monotherapy Q2W may receive up to 52 doses.

- Subjects in Cohort 5 (DLBCL) who receive lenalidomide + pembrolizumab and achieve a PR or SD response may remain on treatment for up to 26 cycles or until unacceptable toxicity or progression. **Note:** Cohorts 5 has been discontinued and all subjects must stop combination treatment immediately, complete the discontinuation visit, and move into the long-term safety and survival follow-up per protocol. If clinically benefitting at time of stopping combination therapy, subjects may enter a transition period remaining on single agent lenalidomide or pembrolizumab for up to 90 days from 15-SEP-2017 and then must transition into long-term survival and safety follow-up.

- Per the investigator's discretion, subjects who achieve a CR in Cohort 5 (DLBCL) may stop treatment after 24 weeks provided they receive an additional 21 consecutive daily doses of lenalidomide + 2 doses of pembrolizumab after CR was documented. These subjects 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). **Note:** Cohorts 5 has been discontinued and all subjects must stop combination treatment immediately, complete the discontinuation visit, and move into the long-term safety and survival follow-up per protocol. If clinically benefitting at time of stopping combination therapy, subjects may enter a transition period remaining on single agent lenalidomide or pembrolizumab for up to 90 days from 15-SEP-2017 and then must transition into long-term survival and safety follow-up. Subjects who achieve a CR in Cohort 5 will not be eligible any longer to restart treatment.

5.2.4 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Subjects participating in this trial will be allocated to trial treatment 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. Listed below are some specific restrictions for concomitant therapy or vaccination during the course of the trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the local Clinical Monitor. 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 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 case report form. 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.

For subjects enrolled in Cohort 5 (DLBCL), digoxin should be administered with caution. Please refer to the current version of the local prescribing information for lenalidomide for additional information.

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
- GM-CSF
- Immunotherapy not specified in this protocol (IV Ig therapy is permissible)
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or lenalidomide
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion, plasmacytoma, bone lesions, or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacille 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., Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
    - Note: Steroid premedications for contrast CTs are permissible.

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with

potential immunologic etiology are outlined in Section 5.2.1.2. 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 the event it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 5 in Section 5.2.1 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.

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

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 9.

Table 9 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; NCI=National Cancer Institute; NSAIDs=non-steroidal anti-inflammatory drugs. Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6.2 Supportive Care Guidelines for Lenalidomide

Supportive care for lenalidomide toxicities is summarized below. Follow the guidance provided in the current version of the lenalidomide local prescribing information for updated information related to supportive care for Grade 3 or Grade 4 AEs related to lenalidomide.

- Hematologic: Subjects may require dose interruption and/or dose reduction. In the mantle cell lymphoma trial, Grade 3 or 4 neutropenia was reported in 43% of the subjects. Grade 3 or 4 thrombocytopenia was reported in 28% of the subjects.
    - Neutropenia: Monitor subjects with neutropenia for signs of infection, and treat appropriately.
    - Thrombocytopenia: Advise subjects to observe for bleeding or bruising, especially with use of concomitant medications that may increase risk of bleeding.
- Venous and arterial thromboembolism: Deep vein thrombosis, pulmonary embolism, and arterial thrombosis events are increased in subjects treated with lenalidomide. However, subjects with mantle cell lymphoma experienced lower rates of thromboembolic events than did subjects with multiple myeloma [47].
    - Thromboprophylaxis is recommended. The regimen of thromboprophylaxis should be based on an assessment of the subject's underlying risks by the investigator.
    - Instruct subjects to report immediately any signs and symptoms suggestive of thrombotic events.
    - Selection of treatment for thromboembolic AEs is at the discretion of the investigator.
    - Erythropoietin-stimulating agents and estrogens may further increase the risk of thrombosis, and their use should be based on a benefit-risk decision in subjects receiving lenalidomide.

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

5.7.2.1 Subjects Enrolled in Cohorts 1, 2, 3, and 4

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 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 follicle stimulating hormone measurement is insufficient.);

OR

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

OR

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

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

(1) practice abstinence[†] from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

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

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

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

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

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

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

Monthly pregnancy testing should be conducted as per local regulations where applicable.

5.7.2.2 Subjects Enrolled in Cohort 5 (DLBCL)

Subjects enrolled in Cohort 5 (DLBCL) receive lenalidomide + pembrolizumab in combination. When both treatments are administered, the contraception, counseling, and dispensing requirements for lenalidomide will apply. If lenalidomide treatment is temporarily withheld, as described in Section 5.2.1.3.4, the contraception requirements for lenalidomide will continue to be followed. If lenalidomide is restarted, the contraception, counseling, and dispensing requirements will apply. If lenalidomide is permanently discontinued, but pembrolizumab is continued, the contraception requirements for lenalidomide will apply for at least 4 weeks after the last dose of lenalidomide. Subsequent to this 4-week period, the

contraception requirements in Section 5.7.2.1 will apply until the subject discontinues from or completes the trial.

Lenalidomide is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes life-threatening human birth defects or embryo-fetal death. An embryo-fetal development study in monkeys indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy. Lenalidomide is only available through the REVLIMID Risk Evaluation and Mitigation Strategy (REMS)™ program or as provided by the Sponsor after the Lenalidomide Education and Counseling Guidance Document is completed and signed by a trained counselor prior to each dispensing of lenalidomide (see Section 12.10). A copy of this document must be maintained in the subject's records for each dispense.

Subjects should be informed that taking study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. Subjects enrolled in Cohort 5 (DLBCL) must follow the contraception requirements detailed in Celgene's REVLIMID REMS program for the duration of the study and during the follow-up period defined in Section 7.2.2 – Reporting of Pregnancy and Lactation to the Sponsor. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study. Please refer to the current versions of the local prescribing information, the Prescriber Guide, the Pharmacy Guide, and the Global Pregnancy Prevention Plan (see Section 12.10) for the REVLIMID REMS program for any updated information.

5.7.2.2.1 Risk Minimization Program

Because of the embryo-fetal risk, lenalidomide is available only through a restricted program under a REMS, the **REVLIMID REMS™** program in the United States and for trial sites not participating in **REVLIMID REMS™** lenalidomide will be provided by the Sponsor. Compliance with the **REVLIMID REMS**™ program in the United States or any protocol-specified requirements is mandatory for all subjects enrolled in this study.

Required components of the REVLIMID REMS program include the following:

- Prescribers must be certified with the REVLIMID REMS program by enrolling and complying with the REMS requirements.
- Study investigators must follow the Global Pregnancy Prevention Plan as detailed in the REVLIMID REMS program (see Section 12.10 for the Global Pregnancy Prevention Plan).
- Subjects must sign a Patient-Physician agreement form and comply with the REVLIMID REMS requirements. In particular, female subjects of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements. Refer to the current version of the local prescribing information.

- Pharmacies must be certified with the REVLIMID REMS program and must dispense only to subjects who are authorized to receive lenalidomide and comply with REVLIMID REMS requirements.

Further information about the REVLIMID REMS program in the United States is available at PPD or by telephone at PPD

5.7.2.2.2 Additional Precautions

- Subjects should be instructed to never give lenalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- No more than a 28-day lenalidomide supply may be dispensed with each cycle of lenalidomide.

5.7.3 Pregnancy

If, while on treatment with lenalidomide + pembrolizumab (Cohort 5), a female subject misses a menstrual period or if there is any abnormality in menstrual bleeding, lenalidomide should be discontinued immediately. The investigator will obtain a pregnancy test and counsel the subject.

If, while on treatment with pembrolizumab (Cohorts 1, 2, 3, and 4) or lenalidomide + pembrolizumab (Cohort 5), a female subject inadvertently becomes pregnant, 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 study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

If a female partner of a male subject enrolled in Cohort 5 (DLBCL) inadvertently becomes pregnant while the male subject is on treatment with lenalidomide + pembrolizumab, the male subject will continue in the trial and will receive additional counseling from the investigator. Refer to section 7.2.2 for additional information regarding reporting pregnancy in a female partner of a male study subject to the Sponsor.

Additionally, for sites in the United States, any suspected embryo-fetal exposure to lenalidomide must be reported immediately to the Sponsor, Celgene Corporation at PPD PPD and the FDA via the MedWatch number at PPD. For sites outside the United

States, any suspected embryo-fetal exposure to lenalidomide must be reported immediately to the Sponsor.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment.
- Confirmed disease progression per respective response assessment criteria

  Note: A subject may be granted an exception to continue on treatment with confirmed progression if clinically stable or clinically improved, please see Section 7.1.2.7.7.

- Unacceptable adverse experiences as described in Section 7.2.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy requires active treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.
- Recurrent Grade 2 pneumonitis
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements

- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6.0 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for AE monitoring (SAEs will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than PD will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression or the start of new antineoplastic therapy each subject will be followed by telephone for OS until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Therapy After CR

Per investigator discretion, subjects who attain an investigator-determined CR or sCR (MM) per respective response criteria may consider stopping pembrolizumab monotherapy after receiving a minimum of 24 weeks of treatment with at least two doses since CR or sCR has been confirmed. Subjects who later experience disease progression, with the exception of subjects in Cohort 2 (MM) who are not allowed, will be eligible for retreatment with pembrolizumab at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.2.1.

Per investigator discretion, subjects who achieve a CR in Cohort 5 (DLBCL) may stop treatment after 24 weeks provided they receive an additional 21 consecutive daily doses of lenalidomide + 2 doses of pembrolizumab after CR was achieved. Cohort 5 has been discontinued and all subjects must stop combination treatment immediately, complete the discontinuation visit, and move into the long-term safety and survival follow-up per protocol. If clinically benefitting at time of stopping combination therapy, subjects may enter a transition period remaining on single agent lenalidomide or pembrolizumab for up to 90 days from 15-SEP-2017 and then must transition into long-term survival and safety follow-up. Subjects who achieve a CR in Cohort 5 will not be eligible any longer to restart treatment.

5.9 Subject Replacement Strategy

Subjects will not be replaced in the trial, with the exception of subjects enrolled in the safety run-in for Cohort 5 (DLBCL) as detailed in Section 5.2.1.3.5. However, additional subjects may be enrolled in a given cohort to ensure that the required number of evaluable subjects in each cohort is achieved in the applicable analysis population. Further details are provided in Section 8.1.3 (Power and Sample Size), Section 8.2.4 (Analysis Populations), and Section 8.2.7 (Sample Size and Power Calculations).

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 Study Flow Chart A: Cohort 1-MDS

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 6 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Administrative Procedures													
Informed Consent	X[e]												
Informed Consent for Future Biomedical Research	X[f]												
Inclusion/Exclusion Criteria	X												
Subject Identification Card	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X[g]	X	X	X	X	X	X	X	X	X	X		
Review Transfusion History [h]	X				X			X					
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X	X
Survival Status		←	—	—	—	—	—	—	→		←	—	→ X
Clinical Procedures/Assessments													
Review Adverse Events [i]	X	X	X	X	X	X	X	X	X	X	X[j]	X[j]	
Full Physical Examination	X			X			X[k]			X			
Directed Physical Examination		X	X		X	X		X	X				
Vital Signs and Weight [l]	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X												

Trial Period:	Screening Phase	Treatment Cycles [a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 6 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Determine FAB classification, WHO Classification, IPSS Score, and IPSS-R Score	X				X			X					
International Working Group criteria for MDS [m]					X			X[n]		X[o]		X[b]	
Laboratory Procedures/Assessments: analysis performed by local laboratory													
Pregnancy Test – Urine or Serum β-HCG [p]	X												
PT/INR and aPTT [q]	X[r]												
CBC with Differential [s]	X[r]		X	X	X	X	X	X	X	X	X[t]		
Comprehensive Chemistry Panel [s]	X[r]			X		X		X		X	X[t]		
Reticulocyte Count [s]	X[r]		X	X	X	X	X	X	X	X	X[t]		
LDH [s]	X[r]			X		X		X		X	X[t]		
Urinalysis [s]	X[r]					X[u]					X[t]		
T3 (or FT3 per local standard), FT4 and TSH [s]	X[r]				X			X[v]			X[t]		
Bone Marrow Biopsy & Aspirate [w,x]	X				X			X					
Bone marrow morphology, Iron stain (at screening only), Blast percentage, Cytogenetics [y]	X				X			X					

Trial Period:	Screening Phase	Treatment Cycles [a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 6 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Laboratory Procedures/Assessments: analysis performed by central laboratory													
Archival Bone Marrow Biopsy Collection [x,z]	X												
Correlative Studies Blood/Bone Marrow Collection [x,aa]	X [aa]				X [aa]			X [aa]					
Anti-pembrolizumab antibodies [bb]		X[bb]	X[b] [b]		X[bb]			X[bb]			X[bb]		
Pharmacokinetics [bb]		X[bb, cc]	X[b] [b]		X[bb]			X[bb]			X[bb]		
Blood for Future Biomedical Research [dd]		X											

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; β-HCG=beta human chorionic gonadotropin; CBC=complete blood cell count; CTCAE=Common Terminology Criteria for Adverse Events; DNA=deoxyribonucleic acid; Discon=discontinuation; ECOG=Eastern Cooperative Oncology Group; ECI=events of clinical interest; FAB=French-American-British; FT3=free triiodothyronine; FT4=free thyroxine; HMA=hypomethylating agent; INR=International Normalized Ratio; IPSS= International Prognostic Scoring System; IPSS-R=Revised International Prognostic Scoring System; LDH=lactate dehydrogenase; MDS=myelodysplastic syndrome; NCI=National Cancer Institute; PD=progressive disease; PK=pharmacokinetic; PT=prothrombin time; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone; WHO=World Health Organization.

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 2 weeks.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status every 6 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone 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

Trial Period:	Screening Phase	Treatment Cycles [a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 6 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

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).

d. In general, the window for each visit is ± 3 days unless otherwise noted.
e. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
f. Signing the informed consent for future biomedical research (FBR) samples is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
g. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
h. Transfusion history should be documented for 3 months prior to start of study and every 6 weeks during response assessment. Transfusion history should be obtained from subject medical records and/or blood bank records.
i. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
j. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.
k. To be repeated every 6 weeks after cycle 6.
l. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.
m. Disease response assessment is made based upon the MDS response criteria and includes CBC and documentation of transfusions. Response assessments should occur at screening, Wk 6, Wk 12, and every 6 weeks (± 7 days). For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. Bone marrow assessments should be performed at Screening, Wk 6 (± 7 days), Wk 12 (± 7 days), and then every 12 weeks or as clinically indicated.
n. Subjects who have progressive disease at the Wk 12 assessment should have a confirmation assessment performed at least 28 days later (after Wk 16). See Section 7.1.2.7.7 for additional details regarding confirmation assessments.

Trial Period:	Screening Phase	Treatment Cycles [a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 6 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

o. In subjects who discontinue study therapy without confirmed disease progression, a response assessment should be performed at the time of treatment discontinuation (i.e. date of discontinuation ± 4 week window). If previous assessment was performed within 4 weeks prior to the date of discontinuation, then a repeat assessment at treatment discontinuation is not mandatory.
p. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
q. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
r. Laboratory tests for screening are to be performed within 7 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
s. After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
t. Unresolved abnormal laboratory tests that are drug related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory tests are within normal range.
u. To be repeated every 4 cycles after Cycle 5.
v. To be repeated every 3 cycles after cycle 7.
w. Detailed instructions for bone marrow collection, processing and shipment are provided in the Procedures Manual. Bone marrow biopsy and aspirate should be collected at screening, Wk 6 (± 7 days), Wk 12 (± 7 days), and every 12 weeks while on study treatment or as clinically indicated. If a subject has disease progression at Wk 12 and a confirmatory assessment is performed at Wk 16, a biopsy and aspirate should be performed as part of the confirmation assessment. A confirmation biopsy does not need to be performed for subjects who have stable disease, partial response, or complete response at Wk 12.
x. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
y. Bone marrow morphology, Blast percentage, and Cytogenetics should be performed with each bone marrow biopsy/aspirate procedure. Iron stain is performed at screening only. Cytogenetics is done to evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If it is not a standard procedure in your region, this test does not need to be performed.
z. If available, bone marrow biopsies will be collected from pre and post HMA treatment.
aa. Correlative study samples should be collected at Screening, at the time of the Wk 6/Wk 12 disease response assessments, and upon progression.

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 6 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

bb. Pre-dose trough and post-dose peak PK samples will be collected at Cycles 1 and 2. Pre-dose trough samples only will be collected at Cycle 4, Cycle 7, every 6 cycles thereafter, 30 days after discontinuation of study drug, and 3 months and 6 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All trough samples should be drawn within 24 hours before infusion of pembrolizumab. All peak samples should be drawn within 30 minutes after the end of the infusion. Anti-pembrolizumab antibodies should be drawn with all pre-dose trough PK samples, 30 days after discontinuation of study drug or until the subject starts new anti-cancer therapy. Procedures for sample collection are described in the Procedures Manual.

cc. An additional single PK sample should be drawn between 24 to 96 hours after Cycle 1 dosing.

dd. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw) as the last sample drawn or at a later date as soon as the informed consent is obtained. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.

6.2 Study Flow Chart B: Cohort 2-Multiple Myeloma (Subjects allocated to 10mg/kg Q2W)

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Administrative Procedures													
Informed Consent	X[e]												
Informed Consent for Future Biomedical Research	X[f]												
Inclusion/Exclusion Criteria	X												
Subject Identification Card	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review [g]	X	X	X	X	X	X	X	X	X	X	X		
International Staging System Criteria [h]	X												
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X	X
Survival Status		⟷									⟷		X
Clinical Procedures/Assessments													
Review Adverse Events [i]	X	X	X	X	X	X	X	X	X	X	X[j]	X[j]	
Full Physical Examination	X						X[k]			X			
Directed Physical Examination		X			X			X					
Vital Signs and Weight [l]	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X												
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Skeletal survey [m]	X												
MRI/CT/PET [m]	X												

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
International Myeloma Working Group Uniform Response Criteria [n]				X		X		X[o]		X[p]		X[b]	
Laboratory Procedures/Assessments: analysis performed by local laboratory													
Pregnancy Test – Urine or Serum β-HCG [q]	X												
PT/INR and aPTT [r]	X[s]												
CBC with Differential [t]	X[s]			X		X		X		X	X[u]		
Comprehensive Chemistry Panel [t]	X[s]			X		X		X		X	X[u]		
LDH [t]	X[s]			X		X		X		X	X[u]		
Urinalysis [t]	X[s]					X[v]					X[u]		
T3 (or FT3 per local standard), FT4 and TSH [t]	X[s]				X			X[w]			X[u]		
Viscosity [t]	X[s]												
Quantitative Serum Immunoglobulin	X[s]			X		X		X					
Serum protein electrophoresis and serum immunofixation	X[s]			X		X		X					
Serum free light chain assay	X[s]			X		X		X					
24 hr urine protein electrophoresis and urine immunofixation	X[s]			X		X		X					
M-protein quantitation (urine and serum)	X[s]			X		X		X					
β2 microglobulin	X[s]												
Archival Bone Marrow Biopsy Collection [x]	X												
Bone Marrow Biopsy & Aspirate [x,y]	X			X				X					

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Bone marrow morphology, IHC, Cytogenetics by standard karyotyping, FISH panel [z,aa]	X			X				X					
Laboratory Procedures/Assessments: analysis performed by central laboratory													
Correlative Studies Blood /Bone Marrow Collection [x,bb]	X			X				X					
Anti-pembrolizumab Antibodies [cc]		X[cc]	X[cc]		X[cc]			X[cc]			X[cc]		
Pharmacokinetics [cc]		X[cc,dd]	X[cc]		X[cc]			X[cc]			X[cc]		
Blood for Future Biomedical Research [ee]		X											

Abbreviations: AE=adverse event; AP=anteroposterior; aPTT=activated partial thromboplastin time; β-HCG=beta human chorionic gonadotropin; CBC=complete blood cell count; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; DNA=deoxyribonucleic acid; Discon=discontinuation; ECOG=Eastern Cooperative Oncology Group; ECI=events of clinical interest; FISH=fluorescence in situ hybridization; FT3=free triiodothyronine; FT4=free thyroxine; IHC=immunohistochemistry; INR=International Normalized Ratio; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; NCI=National Cancer Institute; PA=posterior-anterior; PD=progressive disease; PET=positron emission tomography; PK=pharmacokinetic; PT=prothrombin time; Q2W=every 2 weeks; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone.

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 2 weeks.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status every 12 weeks (±7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone 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).
d. In general, the window for each visit is ± 3 days unless otherwise noted.

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

e. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
f. Signing the informed consent for future biomedical research (FBR) samples is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
g. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
h. Use the International Staging System (ISS) at Screening for subject classification.
i. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
j. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.
k. To be repeated every 6 cycles after cycle 6.
l. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.
m. Skeletal survey should include a chest (PA or AP; lateral), skull (lateral), upper extremities (shoulder to elbow), lower extremities (hip to knee; AP), pelvis (AP), cervical/thoracic/lumbar spine (AP and lateral). A skeletal survey and/or MRI/CT/PET (MRI for subjects with bone disease and CT/PET for plasmacytomas) performed as standard of care prior to signing consent can be used for screening if performed within 28 days of Day 1. For suspected progression to bone disease bidirectional measurement of the target lytic lesions must be performed. During the course of the study or if a subject develops bone pain a skeletal survey and/or MRI/CT/PET (MRI for subjects with bone disease and CT/PET for plasmacytomas) should be performed annually or as clinically indicated. Subjects with measurable plasmacytomas at baseline should have imaging performed every 8 weeks.
n. Disease response assessment is based upon the multiple myeloma response criteria. Disease assessments should occur at Screening and every 4 weeks (± 7 days) while on study treatment. For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. Parameters assessed should include serum protein electrophoresis and serum immunofixation, serum free light chain assay, 24 hr urine protein electrophoresis and urine immunofixation, M-protein quantitation (urine and serum), and urine protein electrophoresis.

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

o. Subjects who have progressive disease at the Wk 12 assessment (Cycle 7) should have a confirmation assessment performed at least 28 days later (after Wk 16). Additionally, for subjects who have progressive disease at the Wk 12 assessment, a bone marrow biopsy/aspirate should be performed as part of the Wk 16 confirmation assessment. See Section 7.1.2.7.7 for additional details regarding confirmation assessments.

p. In subjects who discontinue study therapy without confirmed disease progression, a response assessment should be performed at the time of treatment discontinuation (i.e., date of discontinuation ±4 week window). If previous assessment was performed within 4 weeks prior to the date of discontinuation, then a repeat assessment at treatment discontinuation is not mandatory.

q. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

r. 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.

s. Laboratory tests for screening are to be performed within 7 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.

t. After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests. Viscosity should be performed at Screening and as clinically necessary during the trial.

u. Unresolved abnormal laboratory tests that are drug related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory tests are within normal range.

v. To be repeated every 4 cycles after Cycle 5.

w. To be repeated every 3 cycles after cycle 7.

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

y. Bone marrow biopsy/aspirate should be performed at Screening, Cycle 1 Day 1 (Cycle 1 Day 1 only if Screening Bone Marrow Aspirate/Biopsy was performed greater than 28 days from Day 1 Cycle 1), week 4 (± 7 days), Week 12 (± 7 days), to confirm sCR and CR, or as clinically indicated. For subjects who have progressive disease at the Wk 12 assessment, a bone marrow biopsy/aspirate should be performed as part of the Wk 16 confirmation assessment. A bone marrow biopsy/aspirate performed as part of standard of care prior to signing informed consent may be used for screening if performed within 28 days of Day 1. When a bone marrow biopsy is performed, the paraffin-embedded block must be sent to the central laboratory.

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

z. Bone marrow morphology and IHC should be performed with each bone marrow biopsy. Cytogenetics by standard karyotyping, and FISH panel should be performed at screening only.
aa. FISH panel should include del 1p, del 13, del 17p13, t(4;14), t(11;14), t(14;16), and 1q21 amplification.
bb. Correlative study samples should be collected at Screening, at the time of the Wk 4 and Wk 12 disease response assessments, and upon progression.
cc. Pre-dose trough and post-dose peak PK samples will be collected at Cycles 1 and 2. Pre-dose trough samples only will be collected at Cycle 4, Cycle 7, every 6 cycles thereafter, 30 days after discontinuation of study drug, and 3 months and 6 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All trough samples should be drawn within 24 hours before infusion of pembrolizumab. All peak samples should be drawn within 30 minutes after the end of the infusion. Anti-pembrolizumab antibodies should be drawn with all pre-dose trough PK samples, 30 days after discontinuation of study drug or until the subject starts new anti-cancer therapy. Procedures for sample collection are described in the Procedures Manual.
dd. An additional single PK sample should be drawn between 24 to 96 hours after Cycle 1 dosing.
ee. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw) as the last sample drawn or at a later date as soon as the informed consent is obtained. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.

Note: Cohort 2 has completed enrollment and there will be no further enrollment of subjects. All subjects in Cohort 2 have previously discontinued study treatment and must transition into long-term safety and survival follow-up.

6.3 Study Flow Chart C: Cohort 3, 4A, & 4B-Hodgkin Lymphoma, Mediastinal Large B-Cell Lymphoma, & any-other PD-L1 Positive Non-Hodgkin Lymphoma (Subjects allocated to 10mg/kg Q2W).

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up[c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 8 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Administrative Procedures													
Pre-screening Informed Consent	X [e]												
Informed Consent	X [f]												
Informed Consent for Future Biomedical Research [g]	X												
Inclusion/Exclusion Criteria	X												
Subject Identification Card	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review [h]	X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X	X
Survival Status		⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷		⟷	⟷	X
Clinical Procedures/Assessments													
Review Adverse Events [i]	X	X	X	X	X	X	X	X	X	X	X [j]	X	
Full Physical Examination	X				X			X [k]		X			
Directed Physical Examination				X			X						
Vital Signs and Weight [l]	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X												

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up[c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 8 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Pulmonary Function Test [m]	X												
Neck, Chest, Abdominal, Pelvic PET/CT [n]	X				X [n]			X [o]		X [p]		X [b]	
Disease Response Assessment by Revised Response Criteria for Malignant Lymphoma					X [n]			X		X		X	
Assessment of Lymphoma B Symptoms [n]	X				X [n]			X		X		X	
Laboratory Procedures/Assessments: analysis performed by local laboratory													
Pregnancy Test – Urine or Serum β-HCG [q]	X												
PT/INR and aPTT [r]	X [s]												
CBC with Differential [t]	X [s]			X		X		X		X	X [u]		
Comprehensive Chemistry Panel [t]	X [s]			X		X		X		X	X [u]		
LDH [t]	X [s]			X		X		X		X	X [u]		
Urinalysis [t]	X [s]					X [v]					X [u]		
T3 (or FT3 per local standard), FT4 and TSH[t]	X [s]				X			X [w]			X [u]		
β2 microglobulin [t,x]	X [s]							X					
Bone Marrow Biopsy & Aspirate [y,z]	X												
Bone marrow morphology, IHC, Cytogenetics [aa]	X												

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up[c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 8 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Laboratory Procedures/Assessments: analysis performed by central laboratory													
Archival Lymph Node Biopsy [z]	X												
Lymph Node Biopsy [z, bb]	X							X					
Correlative Studies Blood Collection [z,cc]	X							X					
Anti-pembrolizumab Antibodies [dd]		X[dd]	X[dd]		X[dd]			X[dd]			X[dd]		
Pharmacokinetics [dd]		X[dd, ee]	X[dd]		X[dd]			X[dd]			X[dd]		
Blood for Future Biomedical Research [ff]		X											

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; β-HCG=beta human chorionic gonadotropin; CBC=complete blood cell count; CR=complete response; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; DNA=deoxyribonucleic acid; Discon=discontinuation; ECOG=Eastern Cooperative Oncology Group; ECI=events of clinical interest; FDG=fludeoxyglucose; FEF=forced expiratory flow; FT3=free triiodothyronine; FT4=free thyroxine; FVC=forced vital capacity; HL=Hodgkin lymphoma; IHC=immunohistochemistry; INR=International Normalized Ratio; LDH=lactate dehydrogenase; MLBCL=mediastinal large B-cell lymphoma; NCI=National Cancer Institute; NHL=non-Hodgkin lymphoma; PD=progressive disease; PD-L1=programmed cell death ligand 1; PET=positron emission tomography; PK=pharmacokinetic; PT=prothrombin time; Q2W=every 2 weeks; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone.

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 2 weeks.

b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 8 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.

c. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone 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).
d. In general, the window for each visit is ± 3 days unless otherwise noted.
e. For Cohort 4B (any-other PD-L1 positive NHL) (Prior to Amendment 013-04): For subjects that have an archival biopsy sample available, pre-screening consent must be obtained prior to sending a biopsy sample to the laboratory for characterization. Subjects that do not have an archival sample available must sign the main study consent prior to undergoing a newly obtained biopsy.
f. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
g. Signing the informed consent for future biomedical research (FBR) samples is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
h. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
i. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
j. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.
k. To be repeated every 6 cycles after cycle 7.
l. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.
m. Pulmonary function tests should include an assessment of forced vital capacity, forced expiratory flow between 25 and 75 percent of FVC (FEF25-75), forced expiratory volume in one second and peak expiratory flow (PEF) and diffusion capacity. Additionally, oxygen saturation as assessed by pulse oximetry is required. These tests should be performed at baseline and subsequently at the discretion of the investigator. Hemoglobin must be obtained within 3 days of pulmonary function testing.
n. Disease response assessment is based upon Revised Response Criteria for Malignant Lymphoma. "Diagnostic quality" CT and PET should be performed at Screening and both should be repeated for subsequent assessments. For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in subsequent assessments. Response assessments should occur at Screening (within 28 days prior to first dose of trial treatment), Wk 12, and every 8 weeks (± 7 days) following the Wk 12 assessment. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. The first assessment may be performed earlier than 12 weeks if in the opinion of the investigator the subject is clinically progressing. Assessment of lymphoma B symptoms should occur with each disease response assessment.
o. Subjects who have progressive disease at the Wk 12 assessment should have a confirmation assessment performed at least 28 days later (after Wk 16) (+7 days). See Section 7.1.2.7.7 for additional details regarding confirmation assessments.
p. In subjects who discontinue study therapy without confirmed disease progression, a radiological assessment should be performed at the time of treatment discontinuation (i.e. date of discontinuation ± 4 week window). If previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation is not mandatory.
q. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

r. 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.
s. Laboratory tests for screening are to be performed within 7 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
t. After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
u. Unresolved abnormal laboratory tests that are drug related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory tests are within normal range.
v. To be repeated every 4 cycles after Cycle 5.
w. To be repeated every 3 cycles after Cycle 7.
x. If β2 microglobulin is elevated at baseline, testing should be repeated every 12 weeks.
y. All subjects will have bone marrow biopsy/aspirate performed at baseline. Subsequent bone marrow assessments will only be performed in subjects who have bone marrow involvement. A bone marrow assessment should be performed to confirm CR (if subject had bone marrow involvement) and as clinically indicated.
z. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
aa. Bone marrow morphology, IHC, and Cytogenetics should be performed with each bone marrow biopsy. Cytogenetics is done to evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If it is not a standard procedure in your region, this test does not need to be performed.
bb. Cohort 3 & 4A: Tumor biopsies are required for HL/MLBCL subjects at Screening and Week 12 (± 7 days). If an archival biopsy is not available a new biopsy must be obtained. Cohort 4B: Tumor biopsies are required at Screening and Week 12 (± 7 days). A newly obtained biopsy is required for Cohort 4B even if a subject has been determined to be PD-L1 positive based on archival material. Tumors that are inaccessible or contraindicated due to subject safety concerns are exempt from this requirement at the Week 12 assessment. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous and the tissue sample should have proper size to enable multiple planned biomarker analyses, but not artificially decrease the longest diameter of the lesion. If a tumor biopsy was of a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. Tumors that are inaccessible or biopsy contraindicated due to subject safety concerns are exempt from this requirement at the Week 12 assessment. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous and the tissue sample should have proper size to enable multiple planned biomarker analyses, but not artificially decrease the longest diameter of the lesion. If a tumor biopsy was of a target lesion during eligibility assessment, it is preferable to obtain a new baseline scan.
cc. Correlative study samples should be collected at Screening, at the time of the Week 12 disease response assessment, and upon progression.
dd. Pre-dose trough and post-dose peak PK samples will be collected at Cycles 1 and 2. Pre-dose trough samples only will be collected at Cycle 4, Cycle 7, every 6 cycles thereafter, 30 days after discontinuation of study drug, and 3 months and 6 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All trough samples should be drawn within 24 hours before infusion of pembrolizumab. All peak samples should be drawn within 30 minutes after the end of the infusion. Anti-pembrolizumab antibodies should be drawn with all pre-dose trough PK samples, 30 days after discontinuation of study drug or until the subject starts new anti-cancer therapy. Procedures for sample collection are described in the Procedures Manual.
ee. An additional single PK sample should be drawn between 24 to 96 hours after Cycle 1 dosing.
ff. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw) as the last sample drawn or at a later date as soon as the informed consent is obtained. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.

6.4 Study Flow Chart D: Cohort 2 Multiple Myeloma (Subjects allocated to 200 mg Q3W)

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Administrative Procedures													
Informed Consent	X[e]												
Informed Consent for Future Biomedical Research	X[f]												
Inclusion/Exclusion Criteria	X												
Subject Identification Card	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review[g]	X	X	X	X	X	X	X	X	X	X	X		
International Staging System Criteria[h]	X												
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X	X
Survival Status		⟷									⟷		X
Clinical Procedures/Assessments													
Review Adverse Events[i]	X	X	X	X	X	X	X	X	X	X	X[j]	X[j]	
Full Physical Examination	X			X		X[k]				X			
Directed Physical Examination			X		X		X		X				
Vital Signs and Weight[l]	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X												
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Skeletal survey[m]	X												
MRI/CT/PET[m]	X												

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
International Myeloma Working Group Uniform Response Criteria [n]			X	X	X	X[o]	X	X	X	X[p]		X[b]	
Laboratory Procedures/Assessments: analysis performed by local laboratory													
Pregnancy Test – Urine or Serum β-HCG [q]	X												
PT/INR and aPTT [r]	X[s]												
CBC with Differential [t]	X[s]		X	X	X	X	X	X	X	X	X[u]		
Comprehensive Chemistry Panel [t]	X[s]		X	X	X	X	X	X	X	X	X[u]		
LDH [t]	X[s]		X	X	X	X	X	X	X	X	X[u]		
Urinalysis [t]	X[s]				X [v]			X			X[u]		
T3 (or FT3 per local standard), FT4 and TSH [t]	X[s]			X		X [w]		X			X[u]		
Viscosity [t]	X[s]												
Quantitative Serum Immunoglobulin	X[s]		X	X	X	X	X	X	X				
Serum protein electrophoresis and serum immunofixation	X[s]		X	X	X	X	X	X	X				
Serum free light chain assay	X[s]		X	X	X	X	X	X	X				
24 hr urine protein electrophoresis and urine immunofixation	X[s]		X	X	X	X	X	X	X				
M-protein quantitation (urine and serum)	X[s]		X	X	X	X	X	X	X				
β2 microglobulin	X[s]												
Archival Bone Marrow Biopsy Collection [x]	X												
Bone Marrow Biopsy & Aspirate [x,y]	X			X		X							

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Bone marrow morphology, IHC, Cytogenetics by standard karyotyping, FISH panel [z,aa]	X			X		X							
Laboratory Procedures/Assessments: analysis performed by central laboratory													
Correlative Studies Blood /Bone Marrow Collection [x,bb]	X			X		X							
Anti-pembrolizumab Antibodies [cc]		X[cc]	X[cc]		X[cc]				X[cc]		X[cc]		
Pharmacokinetics [cc]		X[cc,dd]	X[cc]		X[cc]				X[cc]		X[cc]		
Blood for Future Biomedical Research [ee]		X											

Abbreviations: AE=adverse event; AP=anteroposterior; aPTT=activated partial thromboplastin time; β-HCG=beta human chorionic gonadotropin; CBC=complete blood cell count; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; DNA=deoxyribonucleic acid; Discon=discontinuation; ECOG=Eastern Cooperative Oncology Group; ECI=events of clinical interest; FISH=fluorescence in situ hybridization; FT3=free triiodothyronine; FT4=free thyroxine; IHC=immunohistochemistry; INR=International Normalized Ratio; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; NCI=National Cancer Institute; PA=posterior-anterior; PD=progressive disease; PET=positron emission tomography; PK=pharmacokinetic; PT=prothrombin time; Q3W=every 3 weeks; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone.

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks.

b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status every 12 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.

c. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone 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

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

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).

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

e. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.

f. Signing the informed consent for future biomedical research (FBR) samples is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.

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

h. Use the International Staging System (ISS) at Screening for subject classification.

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

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

k. To be repeated every 4 cycles after cycle 5.

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

m. Skeletal survey should include a chest (PA or AP; lateral), skull (lateral), upper extremities (shoulder to elbow), lower extremities (hip to knee; AP), pelvis (AP), cervical/thoracic/lumbar spine (AP and lateral). A skeletal survey and/or MRI/CT/PET (MRI for subjects with bone disease and CT/PET for plasmacytomas) performed as standard of care prior to signing consent can be used for screening if performed within 28 days of Day 1. For suspected progression to bone disease bidirectional measurement of the target lytic lesions must be performed. During the course of the study or if a subject develops bone pain a skeletal survey and/or MRI/CT/PET (MRI for subjects with bone disease and CT/PET for plasmacytomas) should be performed annually or as clinically indicated. Subjects with measurable plasmacytomas at baseline should have imaging performed every 9 weeks.

n. Disease response assessment is based upon the multiple myeloma response criteria. Disease assessments should occur at Screening and every 3 weeks (± 7 days) while on study treatment. For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. Parameters assessed should

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

include serum protein electrophoresis and serum immunofixation, serum free light chain assay, 24 hr urine protein electrophoresis and urine immunofixation, M-protein quantitation (urine and serum), and urine protein electrophoresis.

o. Subjects who have progressive disease at the Wk 12 assessment (Cycle 5) should have a confirmation assessment performed at least 21 days later (after Wk 15). Additionally, for subjects who have progressive disease at the Wk 12 assessment, a bone marrow biopsy/aspirate should be performed as part of the Wk 15 confirmation assessment. See Section 7.1.2.7.7 for additional details regarding confirmation assessments.

p. In subjects who discontinue study therapy without confirmed disease progression, a response assessment should be performed at the time of treatment discontinuation (i.e., date of discontinuation ± 4 week window). If previous assessment was performed within 4 weeks prior to the date of discontinuation, then a repeat assessment at treatment discontinuation is not mandatory.

q. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

r. 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.

s. Laboratory tests for screening are to be performed within 7 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.

t. After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests. Viscosity should be performed at Screening and as clinically necessary during the trial.

u. Unresolved abnormal laboratory tests that are drug related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory tests are within normal range.

v. To be repeated every 3 cycles after Cycle 4.

w. To be repeated every 2 cycles after cycle 5

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

y. Bone marrow biopsy/aspirate should be performed at Screening, Cycle 1 Day 1 (Cycle 1 Day 1 only if Screening Bone Marrow Aspirate/Biopsy was performed greater than 28 days from Day 1 Cycle 1), Week 6 (± 7 days), Week 12 (± 7 days), to confirm sCR and CR, or as clinically indicated. For subjects who have progressive disease at the Wk 12 assessment, a bone marrow biopsy/aspirate should be performed as part of the Wk 15 confirmation assessment. A bone marrow biopsy/aspirate performed as part of

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

standard of care prior to signing informed consent may be used for screening if performed within 28 days of Day 1. When a bone marrow biopsy is performed, the paraffin-embedded block must be sent to the central laboratory.

z. Bone marrow morphology and IHC should be performed with each bone marrow biopsy. Cytogenetics by standard karyotyping, and FISH panel should be performed at screening only.

aa. FISH panel should include del 1p, del 13, del 17p13, t(4;14), t(11;14), t(14;16), and 1q21 amplification.

bb. Correlative study samples should be collected at Screening, at the time of the Wk 6 and Wk 12 disease response assessments, and upon progression.

cc. Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Cycles 1, 2, 4, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug or until the subject starts new anti-cancer therapy. All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab. Additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab infusion at Cycles 1 and 8. Procedures for sample collection are described in the Procedures Manual.

dd. An additional single PK sample should be drawn between 72 to 168 hours after Cycle 1 dosing.

ee. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw) as the last sample drawn or at a later date as soon as the informed consent is obtained. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.

Note: Cohort 2 has completed enrollment and there will be no further enrollment of subjects. All subjects in Cohort 2 have previously discontinued study treatment and must transition into long-term safety and survival follow-up.

6.5 Study Flow Chart E: Cohort 4A, 4C, 4D Mediastinal Large B-Cell Lymphoma, Follicular Lymphoma (FL), and Diffuse Large B-Cell Lymphoma (DLBCL) (Subjects allocated to 200 mg Q3W)

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

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up[c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 9 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Neck, Chest, Abdominal, Pelvic PET/CT [m]	X			X		X [n]			X	X [o]		X [b]	
Disease Response Assessment by Revised Response Criteria for Malignant Lymphoma				X		X			X	X		X	
Assessment of Lymphoma B Symptoms [m]	X			X		X			X	X		X	
Laboratory Procedures/Assessments: analysis performed by local laboratory													
Pregnancy Test – Urine or Serum β-HCG [p]	X												
PT/INR and aPTT [q]	X [r]												
CBC with Differential [s]	X [r]		X	X	X	X	X	X	X[u]	X	X [t]		
Comprehensive Chemistry Panel [s]	X [r]		X	X	X	X	X	X	X[u]	X	X [t]		
LDH [s]	X [r]		X	X	X	X	X	X	X[u]	X	X [t]		
Urinalysis [s]	X [r]				X[v]						X [t]		
T3 (or FT3 per local standard), FT4 and TSH[s]	X [r]			X		X [w]		X			X [t]		
β2 microglobulin[s,x]	X [r]					X [x]							
Epstein-Barr virus (Cohort D)[y]	X												
Bone Marrow Biopsy & Aspirate [z, aa]	X												
Bone marrow morphology, IHC, Cytogenetics [bb]	X												

Trial Period:	Screening Phase	Treatment Cycles [a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up[c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 9 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Laboratory Procedures/Assessments: analysis performed by central laboratory													
Lymph Node Biopsy [aa, cc]	X					X							
Correlative Studies Blood Collection [aa, dd]	X					X							
Anti-pembrolizumab Antibodies [ee]		X[ee]	X[ee]		X[ee]				X[ee]		X[ee]		
Pharmacokinetics [ee]		X [ee,ff]	X[ee]		X[ee]				X[ee]		X[dd]		
Blood for Future Biomedical Research [gg]		X											

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; β-HCG=beta human chorionic gonadotropin; CBC=complete blood cell count; CR=complete response; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; DNA=deoxyribonucleic acid; Discon=discontinuation; ECOG=Eastern Cooperative Oncology Group; ECI=events of clinical interest; FDG=fludeoxyglucose; FEF=forced expiratory flow; FT3=free triiodothyronine; FT4=free thyroxine; FVC=forced vital capacity; IHC=immunohistochemistry; INR=International Normalized Ratio; LDH=lactate dehydrogenase; NCI=National Cancer Institute; PD=progressive disease; PET=positron emission tomography; PK=pharmacokinetic; PT=prothrombin time; Q3W=every 3 weeks; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone.

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone 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).
d. In general, the window for each visit is ± 3 days unless otherwise noted.
e. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
f. Signing the informed consent for future biomedical research (FBR) samples is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
g. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
h. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
i. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.
j. To be repeated every 4 cycles after cycle 5.
k. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.
l. Pulmonary function tests should include an assessment of forced vital capacity, forced expiratory flow between 25 and 75 percent of FVC (FEF25-75), forced expiratory volume in one second and peak expiratory flow (PEF) and diffusion capacity. Additionally, oxygen saturation as assessed by pulse oximetry is required. These tests should be performed at baseline and subsequently at the discretion of the investigator. Hemoglobin must be obtained within 3 days of pulmonary function testing.
m. Disease response assessment is based upon Revised Response Criteria for Malignant Lymphoma. "Diagnostic quality" CT and PET should be performed at Screening and both should be repeated for subsequent assessments. For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in subsequent assessments. Response assessments should occur at Screening (within 28 days prior to first dose of trial treatment), Wk 6, Wk 12, and every 9 weeks (± 7 days) following the Wk 12 assessment. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. Assessment of lymphoma B symptoms should occur with each disease response assessment. The first assessment may be performed earlier than 12 weeks if in the opinion of the investigator the subject is clinically progressing.
n. Subjects who have progressive disease at the Wk 12 assessment should have a confirmation assessment performed at least 21 days later (after Wk 15) (+7 days). See Section 7.1.2.7.7 for additional details on confirmation assessments.
o. In subjects who discontinue study therapy without confirmed disease progression, a radiological assessment should be performed at the time of treatment discontinuation (i.e., date of discontinuation ± 4 week window). If previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation is not mandatory.
p. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

q. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
r. Laboratory tests for screening are to be performed within 7 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
s. After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
t. Unresolved abnormal laboratory tests that are drug related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory tests are within normal range.
u. CBC with Differential, Comprehensive Chemistry Panel, and LDH should be performed every 6 weeks after Cycle 8.
v. To be repeated every 3 cycles after Cycle 4.
w. To be repeated every 2 cycles after cycle 5.
x. If β2 microglobulin is elevated at baseline, testing should be repeated every 12 weeks.
y. Cohort 4D subjects will have Epstein-Barr virus status collected at Screening.
z. All subjects will have bone marrow biopsy/aspirate performed at baseline. Subsequent bone marrow assessments will only be performed in subjects who have bone marrow involvement. A bone marrow assessment should be performed to confirm CR (if subject had bone marrow involvement) and as clinically indicated.
aa. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
bb. Bone marrow morphology, IHC, and Cytogenetics should be performed with each bone marrow biopsy. Cytogenetics is done to evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If it is not a standard procedure in your region, this test does not need to be performed. See Section 7.1.2.7.8 for additional details.
cc. Tumor biopsies are required for subjects at Screening and Week 12 (± 7 days). If an archival biopsy is not available a new biopsy must be obtained. Tumors that are inaccessible or contraindicated due to subject safety concerns are exempt from this requirement at the Week 12 assessment. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous and the tissue sample should have proper size to enable multiple planned biomarker analyses, but not artificially decrease the longest diameter of the lesion. If a tumor biopsy was of a target lesion during eligibility assessment, it is preferable to obtain a new baseline scan.
dd. Correlative study samples should be collected at Screening, at the time of the Week 12 disease response assessment, and upon progression. See Section 7.1.2.7.8 and the Procedures Manual for additional details.
ee. Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Cycles 1, 2, 4, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug, or until the subject starts new anti-cancer therapy. All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab. Additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab infusion at Cycles 1 and 8. Procedures for sample collection are described in the Procedures Manual.
ff. An additional single PK sample should be drawn between 72 and 168 hours after Cycle 1 dosing.
gg. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw) as the last sample drawn or at a later date as soon as the informed consent is obtained. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.

6.6 Study Flow Chart F: Cohort 5 Diffuse Large B-Cell Lymphoma (DLBCL) (Subjects allocated to pembrolizumab 200 mg administered intravenously once every 21 days in combination with lenalidomide taken orally once daily for 21 days + 7 days off. The cycle length is 28 days.)

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**						**End of Treatment**	**Post-treatment**		
		To be repeated beyond 3 cycles									
Treatment Cycle/Title: (28-day cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon	Post-Treatment Safety Follow-up Visit[b]	Efficacy Follow-up Visits[c]	Survival Follow-up[d]
Cycle Day (visit day) (± 3 days after Day 1 of Cycle 1 unless otherwise specified)	(-28 to -1 days)	**1**	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Administrative Procedures											
Informed consent[e]	X										
Informed consent for future biomedical research[f]	X										
Inclusion/exclusion criteria	X										
Subject identification card	X										
Demographics and medical history	X										
Prior and concomitant medication review[g]	X	X	X	X	X	X	X	X	X		
Register subject in REVLIMID REMS™ program where applicable[h]	X										
Combination treatments											
Pembrolizumab administration[i]		**See Section 6.6.1**									
Lenalidomide administration[j]											
Post-study anticancer therapy status										X	X
Survival status		⟷							⟷		X
Clinical Procedures/Assessments											
Review adverse events[k]	X	X	X	X	X	X	X	X	X	X	
Full physical examination[l]	X	X						X			
Directed physical examination[l]		X									

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**						**End of Treatment**	**Post-treatment**		
		To be repeated beyond 3 cycles									
Treatment Cycle/Title: (28-day cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon	Post-Treatment Safety Follow-up Visit[b]	Efficacy Follow-up Visits[c]	Survival Follow-up[d]
Cycle Day (visit day) (± 3 days after Day 1 of Cycle 1 unless otherwise specified)	(-28 to -1 days)	**1**	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Vital signs and height[m]	X	X	X	X	X	X	X	X			
12-lead electrocardiogram	X										
Pulmonary function test[n]	X										
ECOG performance status[o]	X	X	X		X		X	X			
Neck, chest, abdominal, pelvic PET/CT[p]	X	X ±7 days						X		X	
Lymphoma disease response assessment by Revised Response Criteria for Malignant Lymphoma [87][q, r]		X[s] ±7 days						X		X	
Assessment of lymphoma B symptoms[t]	X	X ±7 days						X		X	
Laboratory Procedures/Assessments: analysis performed by <u>local</u> laboratory[u]											
Pregnancy test – urine or serum β-HCG[v,w]	X[v]	X[w]									
PT/INR and aPTT[x]	X	X						X	X		
CBC with differential[y]	X	X						X	X		
Comprehensive blood chemistry panel[z]	X	X						X	X		
LDH[z]	X	X						X	X		
Urinalysis[z]	X	X							X		
T3, (or FT3 per local standard), FT4 and TSH[aa]	X	X							X		
Creatinine clearance	X										
β2 microglobulin[bb]	X										
Epstein-Barr virus[cc]	X										
Bone marrow biopsy & aspirate[dd]	X										

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**						**End of Treatment**	**Post-treatment**		
		To be repeated beyond 3 cycles									
Treatment Cycle/Title: (28-day cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon	Post-Treatment Safety Follow-up Visit[b]	Efficacy Follow-up Visits[c]	Survival Follow-up[d]
Cycle Day (visit day) (± 3 days after Day 1 of Cycle 1 unless otherwise specified)	(-28 to -1 days)	**1**	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Bone marrow morphology, IHC, cytogenetics[dd]	X										
Laboratory Procedures/Assessments: analysis performed by central laboratory											
Lymph node biopsy[ee]	X	X									
Correlative studies blood collection[ff]	X	X									
Anti-pembrolizumab antibodies[gg]		X	X		X				X		
Pembrolizumab pharmacokinetics[gg]		X	X		X				X		
Blood for Future Biomedical Research[hh]		X									

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; β-HCG=beta human chorionic gonadotropin; CBC=complete blood cell count; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; DNA=deoxyribonucleic acid; Discon=discontinuation; ECOG=Eastern Cooperative Oncology Group; FDG=fludeoxyglucose; FT3=free triiodothyronine; FT4=free thyroxine; IHC=immunohistochemistry; INR=International Normalized Ratio; LDH=lactate dehydrogenase; NCI=National Cancer Institute; PD=progressive disease; PET=positron emission tomography; PK=pharmacokinetic; PT=prothrombin time; REMS=Risk Evaluation and Mitigation Strategy; RP2D=recommended Phase II dose; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone.

a. Treatments and assessments are based on 28-day cycles.
b. After the end of treatment, each subject will be followed for 30 days for AE monitoring. Serious adverse events will be collected for 90 days after the end of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, and spontaneously reported pregnancy will be collected for 120 days after the end of treatment. Serious adverse events and spontaneously reported pregnancy will be reported for 30 days after the end of treatment if the subject initiates new anticancer therapy. See Section 7.2 for additional details.
c. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
d. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone 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).

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**						**End of Treatment**	**Post-treatment**		
		To be repeated beyond 3 cycles									
Treatment Cycle/Title: (28-day cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon	Post-Treatment Safety Follow-up Visit[b]	Efficacy Follow-up Visits[c]	Survival Follow-up[d]
Cycle Day (visit day) (± 3 days after Day 1 of Cycle 1 unless otherwise specified)	(-28 to -1 days)	**1**	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

e. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
f. Signing the informed consent for future biomedical research samples is optional. Detailed instructions for the collection and management of specimens for future biomedical research are provided in the Procedures Manual and Section 12.2.
g. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
h. Lenalidomide must be prescribed through and in compliance with the REVLIMID REMS™ program or protocol specified requirements. Refer to local prescribing information.
i. Pembrolizumab will be given by intravenous infusion over 30 minutes at a fixed dose of 200 mg. Each dose will be administered once every 3 weeks within each 28-day cycle. See Section 5.2 and Section 7.1.5.2 for additional details. See Section 12.9 for additional dose timing details.
j. Lenalidomide will be given orally once daily at the RP2D established during the safety run-in. Each dose will be administered for the first 21 consecutive days of each 28-day cycle. See Section 5.2 and Section 7.1.5.2 for additional details. See Section 12.9 for additional dose timing details.
k. Adverse events and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. See Section 7.1.2.1 and Section 7.2 for additional details.
l. A physical examination will be performed before each administration of pembrolizumab. A full physical examination will be performed at Week 12, and every 12 weeks thereafter, and directed physical exams will be conducted before administration of pembrolizumab at each of the other visits.
m. Vitals signs will include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at Screening only.
n. Pulmonary function tests should include an assessment of forced vital capacity, forced expiratory flow between 25 and 75 percent of forced vital capacity, forced expiratory volume in 1 second, peak expiratory flow, and diffusion capacity. Additionally, oxygen saturation as assessed by pulse oximetry is required. These tests should be performed at baseline and subsequently at the discretion of the investigator. Hemoglobin must be obtained within 3 days of pulmonary function testing.
o. ECOG performance status will be performed before administration of each dose of pembrolizumab.
p. Diagnostic quality CT and PET should be performed at Screening, Week 12, and every 12 weeks following Week 12. For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in subsequent assessments. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of treatment cycle frequencies. In subjects who discontinue study therapy without confirmed disease progression, a radiological assessment should be performed at the

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**						**End of Treatment**	**Post-treatment**		
		To be repeated beyond 3 cycles									
Treatment Cycle/Title: (28-day cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon	Post-Treatment Safety Follow-up Visit[b]	Efficacy Follow-up Visits[c]	Survival Follow-up[d]
Cycle Day (visit day) (± 3 days after Day 1 of Cycle 1 unless otherwise specified)	(-28 to -1 days)	**1**	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

time of treatment discontinuation (i.e., date of discontinuation ±4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation is not mandatory. See Section 7.1.2.7 and the Site Imaging Manual for additional details regarding scan requirements and timing.

q. Lymphoma disease response assessments [87]should occur at Week 12, and every 12 weeks (±7 days) following the Week 12 assessment. For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. The first assessment may be performed earlier than 12 weeks if, in the opinion of the investigator, the subject is clinically progressing. See Section 7.1.2.7 for additional details regarding assessment requirements and timing.

r. Subjects who have progressive disease at the Week 12 assessment should have a confirmation assessment performed at least 4-6 weeks later. See Section 7.1.2.7.7 for additional details on confirmation assessments.

s. Lymphoma disease response assessments [87]should occur at Week 12, and every 12 weeks (±7 days) following the Week 12 assessment. Disease assessments or scans should not be delayed for delays in cycle starts.

t. Lymphoma B assessments should be performed at Screening and at the time of each disease response assessment. See Section 7.1.2.7.6 for additional details.

u. Laboratory tests for screening that are performed at a local laboratory should be completed within 7 days prior to the first dose (Cycle 1) of trial treatment. Subsequent laboratory safety evaluations should be completed within 72 hours of any subsequent trial treatments (i.e., should be available before the subject receives the scheduled dose). See Section 7.1.3.1 for details regarding laboratory safety evaluations.

v. In females of childbearing potential, two negative pregnancy tests (sensitivity of at least 25 mIU/mL) must be obtained prior to initiating therapy in female subjects enrolled in Cohort 5 (DLBCL). The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing lenalidomide therapy.

w. Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide. Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.

x. Coagulation factors will be obtained at Screening and repeated during the trial as per the prescribing information for the selected thromboprophylaxis/thromboembolism therapy.

y. CBC with differential is performed weekly for Cycle 1, every 2 weeks for Cycles 2-4, and on Day 1 of each cycle thereafter (monthly). Subjects may require dose interruption and/or dose reduction.

z. LDH, comprehensive chemistry panel, and urinalysis should be performed on Day 1 of Cycles 1-8, and every 8 weeks thereafter. Tests may be performed within ±7 days after Day 1 of Cycle 1.

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**						**End of Treatment**	**Post-treatment**		
		To be repeated beyond 3 cycles									
Treatment Cycle/Title: (28-day cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon	Post-Treatment Safety Follow-up Visit[b]	Efficacy Follow-up Visits[c]	Survival Follow-up[d]
Cycle Day (visit day) (± 3 days after Day 1 of Cycle 1 unless otherwise specified)	(-28 to -1 days)	**1**	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

aa. Thyroid function tests (T3, FT4, and TSH) should be performed at Week 4, Week 8, Week 12, and every 12 weeks thereafter. Tests may be performed within ±7 days after Day 1 of Cycle 1.
bb. If β2 microglobulin is elevated at baseline, testing should be repeated every 12 weeks.
cc. All subjects will have Epstein-Barr virus status collected at Screening.
dd. All subjects will have a bone marrow biopsy/aspirate, bone marrow morphology, IHC, and cytogenetics performed at baseline. Cytogenetics is done to evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If it is not a standard procedure in your region, this test does not need to be performed. See Section 7.1.2.7.8 for additional details.
ee. Tumor biopsies are required for subjects at Screening and Week 12 (± 7 days). If an archival biopsy is not available a new biopsy must be obtained. See Section 7.1.2.7.8 and the Procedures Manual for additional details. Tumors that are inaccessible or contraindicated due to subject safety concerns are exempt from this requirement at the Week 12 assessment. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous and the tissue sample should have proper size to enable multiple planned biomarker analyses, but not artificially decrease the longest diameter of the lesion. If a tumor biopsy was of a target lesion during eligibility assessment, it is preferable to obtain a new baseline scan.
ff. Correlative study samples should be collected at Screening, at the time of the Week 12 lymphoma disease response assessment, and upon progression. See Section 7.1.2.7.8 and the Procedures Manual for additional details.
gg. Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Day 1 of Cycle 1, Day 22 of Cycle 1, Day 15 of Cycle 2, Day 15 of Cycle 5, every 4th pembrolizumab infusion thereafter, and 30 days after discontinuation of study drug (or until the subject starts new anti-cancer therapy).
hh. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose on Day 1 (or with the next scheduled blood draw) as the last sample drawn or at a later date as soon as the informed consent is obtained. Detailed instructions for the collection and management of specimens for future biomedical research are provided in the Procedures Manual and Section 12.2.

Note: Cohort 5 has been discontinued and there will be no further enrollment of subjects. All subjects in Cohort 5 must stop combination treatment immediately, complete the discontinuation visit and move into the long-term safety and survival follow-up per protocol. If clinically benefitting at time of stopping combination therapy, subjects may enter a transition period remaining on single agent lenalidomide or pembrolizumab for up to 90 days from 15-SEP-2017 and then must transition into long-term survival and safety follow-up.

6.6.1 Study Dose Chart F2: Cohort 5 Diffuse Large B-Cell Lymphoma (DLBCL) (Subjects allocated to pembrolizumab 200 mg administered intravenously once every 21 days in combination with lenalidomide taken orally once daily for 21 days + 7 days off. The cycle length is 28 days.)

	Each Cycle = 28 Days (To be repeated beyond 3 cycles)											
	Cycle 1				Cycle 2				Cycle 3			
Trial Treatment/ Cycle Day (± 3 days)	Days 1-7	Days 8-14	Days 15-21	Days 22-28	Days 1-7	Days 8-14	Days 15-21	Days 22-28	Days 1-7	Days 8-14	Days 15-21	Days 22-28
Pembrolizumab (Q3W)[a]	1			22			15			8		
Lenalidomide[b]	1 to 21				1 to 21				1 to 21			
Pill count for Lenalidomide[c]	1				1				1			
Pregnancy Prevention Counseling and Dispensing of Lenalidomide[d]	X											

Abbreviations: IV=intravenous; PO=per orem; Q3W=every 3 weeks; REMS=Risk Evaluation and Mitigation Strategy; RP2D=recommended Phase II dose.

a. Pembrolizumab will be administered as 200 mg every 21 days (3 weeks) as an IV infusion over 30 minutes.

b. Lenalidomide will be administered as RP2D PO, once daily on Days 1 to 21 of repeated 28-day cycles. Lenalidomide must be prescribed through and in compliance with the REVLIMID REMS™ program. Refer to local prescribing information.

c. Site should document drug accountability as per their institutional guidelines.

d. The Lenalidomide Education and Counseling Guidance Document must be completed for all subjects and signed by a trained counselor prior to each dispensing of lenalidomide (see Section 12.10). A copy of this document must be maintained in the subject's records for each dispense. Lenalidomide will be dispensed every 3-4 weeks as per local requirements.

Note: Cohort 5 has been discontinued and there will be no further enrollment of subjects. All subjects in Cohort 5 must stop combination treatment immediately, complete the discontinuation visit and move into the long-term safety and survival follow-up per protocol. If clinically benefitting at time of stopping combination therapy, subjects may enter a transition period remaining on single agent lenalidomide or pembrolizumab for up to 90 days from 15-SEP-2017 and then must transition into long-term survival and safety follow-up.

6.7 Study Flow Chart G: Cohort 1-MDS Second Course Phase (Retreatment for Post-Complete Response Relapse Only)

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 6 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Administrative Procedures													
Eligibility Criteria	X												
Interim Medical History	X												
Prior and Concomitant Medication Review	X[e]	X	X	X	X	X	X	X	X	X	X		
Review Transfusion History [f]	X				X			X					
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X	X
Survival Status		←							→		←	→	X
Clinical Procedures/Assessments													
Review Adverse Events [g]	X	X	X	X	X	X	X	X	X	X	X [h]	X [h]	
Full Physical Examination	X			X			X[i]			X			
Directed Physical Examination		X	X		X	X		X	X				
Vital Signs and Weight [j]	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X												
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Determine FAB classification, WHO Classification, IPSS Score, and IPSS-R Score	X				X			X					
International Working Group criteria for MDS [k]					X			X[l]		X[m]		X[b]	

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 6 weeks post Discon (±7 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 [n]	X												
PT/INR and aPTT [o]	X[p]												
CBC with Differential [q]	X[p]		X	X	X	X	X	X	X	X	X[r]		
Comprehensive Chemistry Panel [q]	X[p]			X		X		X		X	X[r]		
Reticulocyte Count [q]	X[p]		X	X	X	X	X	X	X	X	X[r]		
LDH [q]	X[p]			X		X		X		X	X[r]		
Urinalysis [q]	X[p]					X[s]					X[r]		
T3 (or FT3 per local standard), FT4 and TSH [q]	X[p]				X			X[t]			X[r]		
Bone Marrow Biopsy & Aspirate [u,v]	X				X			X					
Bone marrow morphology, Iron stain (at screening only), Blast percentage, Cytogenetics [w]	X				X			X					
Laboratory Procedures/Assessments: analysis performed by central laboratory													
Correlative Studies Blood/Bone Marrow Collection [v,x]	X[x]				X[x]			X[x]					
Anti-pembrolizumab Antibodies [y]		X[x]	X[x]					X[y]			X[y]		

Trial Period:	Screening Phase	Treatment Cycles [a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 6 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Pharmacokinetics [y]		X [y]	X [y]					X [y]			X [y]		

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; β-HCG=beta human chorionic gonadotropin; CBC=complete blood cell count; CTCAE=Common Terminology Criteria for Adverse Events; Discon=discontinuation; ECOG=Eastern Cooperative Oncology Group; ECI=events of clinical interest; FAB=French-American-British; FT3=free triiodothyronine; FT4=free thyroxine; INR=International Normalized Ratio; IPSS= International Prognostic Scoring System; IPSS-R=Revised International Prognostic Scoring System; LDH=lactate dehydrogenase; MDS=myelodysplastic syndrome; NCI=National Cancer Institute; PD=progressive disease; PK=pharmacokinetic; PT=prothrombin time; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone; WHO=World Health Organization.

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 2 weeks.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status every 6 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone 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).
d. In general, the window for each visit is ± 3 days unless otherwise noted.
e. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
f. Transfusion history should be documented for 3 months prior to start of study and every 6 weeks during response assessment. Transfusion history should be obtained from subject medical records and/or blood bank records.
g. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
h. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.
i. To be repeated every 6 weeks after cycle 6.

Trial Period:	Screening Phase	Treatment Cycles [a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 6 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

j. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.
k. Disease response assessment is made based upon the MDS response criteria and includes CBC and documentation of transfusions. Response assessments should occur at screening, Week 6, Week 12, and every 6 weeks (+/- 7 days). For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. Bone marrow assessments should be performed at Screening, Week 6 (± 7 days), Week 12 (± 7 days), and then every 12 weeks or as clinically indicated.
l. Subjects who have progressive disease at the Week 12 assessment should have a confirmation assessment performed at least 28 days later (after Week 16). See Section 7.1.2.7.7 for additional details regarding confirmation assessments.
m. In subjects who discontinue study therapy without confirmed disease progression, a response assessment should be performed at the time of treatment discontinuation (i.e. date of discontinuation ± 4 week window). If previous assessment was performed within 4 weeks prior to the date of discontinuation, then a repeat assessment at treatment discontinuation is not mandatory.
n. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
o. 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.
p. Laboratory tests for screening are to be performed within 7 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
q. After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
r. Unresolved abnormal laboratory tests that are drug related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory tests are within normal range.
s. To be repeated every 4 cycles after Cycle 5.
t. To be repeated every 3 cycles after Cycle 7.
u. Detailed instructions for bone marrow collection, processing and shipment are provided in the Procedures Manual. Bone marrow biopsy and aspirate should be collected at screening, Wk 6 (± 7 days), Wk 12 (± 7 days), and every 12 weeks while on study treatment or as clinically indicated. If a subject has disease progression at Wk 12 and a confirmatory assessment is performed at Wk 16, a biopsy and aspirate should be performed as part of the confirmation assessment. A confirmation biopsy does not need to be performed for subjects who have stable disease, partial response, or complete response at Wk 12.

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 6 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

v. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
w. Bone marrow morphology, Blast percentage, and Cytogenetics should be performed with each bone marrow biopsy/aspirate procedure. Iron stain is performed at screening only. Cytogenetics is done to evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If it is not a standard procedure in your region, this test does not need to be performed.
x. Correlative study samples should be collected at Screening, at the time of the Wk 6/Wk 12 disease response assessments, and upon progression.
y. Pre-dose trough PK samples will be collected at Cycles 1, 2, 7, every 6 cycles thereafter, 30 days after discontinuation of study drug, and 3 months and 6 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All trough samples should be drawn within 24 hours before infusion of pembrolizumab. Anti-pembrolizumab antibodies should be drawn with all pre-dose trough PK, 30 days after discontinuation of study drug or until the subject starts new anti-cancer therapy. Procedures for sample collection are described in the Procedures Manual.

6.8 Study Flow Chart H: Cohort 2-Multiple Myeloma Second Course Phase (Retreatment for Post-Stringent Complete Response (sCR) Relapse Only) (Subjects allocated to 10mg/kg Q2W)

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Administrative Procedures													
Eligibility Criteria	X												
Interim Medical History	X												
Prior and Concomitant Medication Review [e]	X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X	X
Survival Status		⟷									⟷		X
Clinical Procedures/Assessments													
Review Adverse Events [f]	X	X	X	X	X	X	X	X	X	X	X [g]	X [g]	
Full Physical Examination	X						X [h]			X			
Directed Physical Examination		X			X			X					
Vital Signs and Weight [i]	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X												
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Skeletal survey [j]	X												
MRI/CT/PET *(only for subjects with bone disease/plasmacytoma)* [j]	X												
International Myeloma Working Group Uniform Response Criteria [k]				X		X		X[l]		X[m]		X[b]	

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 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 [n]	X												
PT/INR and aPTT [o]	X[p]												
CBC with Differential [q]	X[p]			X		X		X		X	X[r]		
Comprehensive Chemistry Panel [q]	X[p]			X		X		X		X	X[r]		
LDH [q]	X[p]			X		X		X		X	X[r]		
Urinalysis [q]	X[p]					X[s]					X[r]		
T3 (or FT3 per local standard), FT4 and TSH [q]	X[p]				X			X[t]			X[r]		
Viscosity [q]	X[p]												
Quantitative Serum Immunoglobulin	X[p]			X		X		X					
Serum protein electrophoresis and serum immunofixation	X[p]			X		X		X					
Serum free light chain assay	X[p]			X		X		X					
24 hr urine protein electrophoresis and urine immunofixation	X[p]			X		X		X					
M-protein quantitation (urine and serum)	X[p]			X		X		X					
β2 microglobulin	X[p]												

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Bone Marrow Biopsy & Aspirate [u, v]	X			X				X					
Bone marrow morphology, IHC, Cytogenetics by standard karyotyping, FISH panel [w,x]	X			X				X					
Laboratory Procedures/Assessments: analysis performed by central laboratory													
Correlative Studies Blood /Bone Marrow Collection [u,y]	X			X				X					
Anti-pembrolizumab Antibodies [z]		X [z]	X [z]					X [z]			X [z]		
Pharmacokinetics [z]		X [z]	X [z]					X [z]			X [z]		

Abbreviations: AE=adverse event; AP=anteroposterior; aPTT=activated partial thromboplastin time; β-HCG=beta human chorionic gonadotropin; CBC=complete blood cell count; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; Discon=discontinuation; ECOG=Eastern Cooperative Oncology Group; ECI=events of clinical interest; FISH=fluorescence in situ hybridization; FT3=free triiodothyronine; FT4=free thyroxine; IHC=immunohistochemistry; INR=International Normalized Ratio; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; NCI=National Cancer Institute; PA=posterior-anterior; PD=progressive disease; PET=positron emission tomography; PK=pharmacokinetic; PT=prothrombin time; Q2W=every 2 weeks; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone.

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 2 weeks.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status every 12 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone 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

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

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).

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

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

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

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

h. To be repeated every 6 cycles after cycle 6.

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

j. Skeletal survey should include a chest (PA or AP; lateral), skull (lateral), upper extremities (shoulder to elbow), lower extremities (hip to knee; AP), pelvis (AP), cervical/thoracic/lumbar spine (AP and lateral). A skeletal survey and/or MRI/CT/PET (MRI for subjects with bone disease and CT/PET for plasmacytomas) performed as standard of care prior to signing consent can be used for screening if performed within 28 days of Day 1. For suspected progression to bone disease bidirectional measurement of the target lytic lesions must be performed. During the course of the study or if a subject develops bone pain a skeletal survey and/or MRI/CT/PET (MRI for subjects with bone disease and CT/PET for plasmacytomas) should be performed annually or as clinically indicated. Subjects with measurable plasmacytomas at baseline should have imaging performed every 8 weeks.

k. Disease response assessment is based upon the multiple myeloma response criteria. Disease assessments should occur at Screening and every 4 weeks (± 7 days) while on study treatment. For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. Parameters assessed should include serum protein electrophoresis and serum immunofixation, serum free light chain assay, 24 hr urine protein electrophoresis and urine immunofixation, M-protein quantitation (urine and serum), and urine protein electrophoresis.

l. Subjects who have progressive disease at the Wk 12 assessment should have a confirmation assessment performed at least 28 days later (after Wk 16). Additionally, for subjects who have progressive disease at the Wk 12 assessment, a bone marrow biopsy/aspirate should be performed as part of the Wk 16 confirmation assessment. See Section 7.1.2.7.7 for additional details regarding confirmation assessments.

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

m. In subjects who discontinue study therapy without confirmed disease progression, a response assessment should be performed at the time of treatment discontinuation (i.e. date of discontinuation ± 4 week window). If previous assessment was performed within 4 weeks prior to the date of discontinuation, then a repeat assessment at treatment discontinuation is not mandatory.
n. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
o. 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.
p. Laboratory tests for screening are to be performed within 7 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
q. After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests. Viscosity should be performed at Screening and as clinically necessary during the trial.
r. Unresolved abnormal laboratory tests that are drug related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory tests are within normal range.
s. To be repeated every 4 cycles after Cycle 5.
t. To be repeated every 3 cycles after Cycle 7.
u. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
v. Bone marrow biopsy/aspirate should be performed at Screening, Cycle 1 Day 1 (Cycle 1 Day 1 only if Screening Bone Marrow Aspirate/Biopsy was performed greater than 28 days from Day 1 Cycle 1), Week 4 (± 7 days), Week 12 (± 7 days), to confirm sCR and CR, or as clinically indicated. For subjects who have progressive disease at the Week 12 assessment, a bone marrow biopsy/aspirate should be performed as part of the Week 16 confirmation assessment. A bone marrow biopsy/aspirate performed as part of standard of care prior to signing informed consent may be used for screening if performed within 28 days of Day 1. When a bone marrow biopsy is performed, the paraffin-embedded block must be sent to the central laboratory.
w. Bone marrow morphology and IHC should be performed with each bone marrow biopsy. Cytogenetics by standard karyotyping and FISH panel should be performed at screening only.
x. FISH panel should include del 1p, del 13, del 17p13, t(4;14), t(11;14), t(14;16), and 1q21 amplification.
y. Correlative study samples should be collected at Screening, at the time of the Week 4 and Week 12 disease response assessments, and upon progression.

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

z. Pre-dose trough PK samples will be collected at Cycles 1, 2, 7, every 6 cycles thereafter, 30 days after discontinuation of study drug, and 3 months and 6 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All trough samples should be drawn within 24 hours before infusion of pembrolizumab. Anti-pembrolizumab antibodies should be drawn with all pre-dose trough PK, 30 days after discontinuation of study drug or until the subject starts new anti-cancer therapy. Procedures for sample collection are described in the Procedures Manual.

Note: Cohort 2 subjects are no longer eligible for second course treatment phase.

6.9 Study Flow Chart I: Cohort 3, 4A, 4B Hodgkin Lymphoma, Mediastinal Large B-Cell Lymphoma, & any-other PD-L1 Positive Non-Hodgkin Lymphoma Second Course Phase (Retreatment for Post-Complete Response Relapse Only) (Subjects allocated to 10 mg/kg Q2W)

Trial Period:	**Screening Phase**	**Treatment Cycles** [a]								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 8 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Administrative Procedures													
Eligibility Criteria	X												
Interim Medical History	X												
Prior and Concomitant Medication Review [e]	X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X	X
Survival Status		⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷		⟷	⟷	X
Clinical Procedures/Assessments													
Review Adverse Events [f]	X	X	X	X	X	X	X	X	X	X	X [g]	X	
Full Physical Examination	X				X			X [h]		X			
Directed Physical Examination				X			X						
Vital Signs and Weight [i]	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X												
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Pulmonary Function Test [j]	X												

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 8 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Neck, Chest, Abdominal, Pelvic PET/CT [k]	X				X [k]			X [l]		X [m]		X [b]	
Disease Response Assessment by Revised Response Criteria for Malignant Lymphoma					X [k]			X		X		X	
Assessment of Lymphoma B Symptoms [k]	X				X [k]			X		X		X	
Laboratory Procedures/Assessments: analysis performed by local laboratory													
Pregnancy Test – Urine or Serum β-HCG [n]	X												
PT/INR and aPTT [o]	X [p]												
CBC with Differential [q]	X [p]			X		X		X		X	X [r]		
Comprehensive Chemistry Panel [q]	X [p]			X		X		X		X	X [r]		
LDH [q]	X [p]			X		X		X		X	X [r]		
Urinalysis [q]	X [p]					X [s]					X [r]		
T3 (or FT3 per local standard), FT4 and TSH [q]	X [p]				X			X [t]			X [r]		
β2 microglobulin [q,u]	X [p]							X [u]					
Bone Marrow Biopsy & Aspirate [v,w]	X												

Trial Period:	Screening Phase	Treatment Cycles [a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 8 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Bone marrow morphology, IHC, Cytogenetics [x]	X												
Laboratory Procedures/Assessments: analysis performed by central laboratory													
Lymph Node Biopsy [w, y]	X							X					
Correlative Studies Blood Collection [w,z]	X							X					
Anti-pembrolizumab Antibodies [aa]		X[aa]	X[aa]					X[aa]			X[aa]		
Pharmacokinetics [aa]		X[aa]	X[aa]					X[aa]			X[aa]		

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; β-HCG=beta human chorionic gonadotropin; CBC=complete blood cell count; CR=complete response; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; Discon=discontinuation; ECOG=Eastern Cooperative Oncology Group; ECI=events of clinical interest; FDG=fludeoxyglucose; FEF=forced expiratory flow; FT3=free triiodothyronine; FT4=free thyroxine; FVC=forced vital capacity; IHC=immunohistochemistry; INR=International Normalized Ratio; LDH=lactate dehydrogenase; NCI=National Cancer Institute; PD=progressive disease; PD-L1=programmed cell death ligand 1; PET=positron emission tomography; PK=pharmacokinetic; PT=prothrombin time; Q2W=every 2 weeks; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone.

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 2 weeks.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 8 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone 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

Trial Period:	Screening Phase	Treatment Cycles [a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 8 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

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).

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

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

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

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

h. To be repeated every 6 cycles after cycle 7.

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

j. Pulmonary function tests should include an assessment of forced vital capacity, forced expiratory flow between 25 and 75 percent of FVC (FEF25-75), forced expiratory volume in one second and peak expiratory flow (PEF) and diffusion capacity. Additionally, oxygen saturation as assessed by pulse oximetry is required. These tests should be performed at baseline and subsequently at the discretion of the investigator. Hemoglobin must be obtained within 3 days of pulmonary function testing.

k. Disease response assessment is based upon Revised Response Criteria for Malignant Lymphoma. “Diagnostic quality” CT and PET should be performed at Screening and both should be repeated for subsequent assessments. For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in subsequent assessments. Response assessments should occur at Screening (within 28 days prior to first dose of trial treatment), Week 12, and every 8 weeks (± 7 days) following the Week 12 assessment. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. Assessment of lymphoma B symptoms should occur with each disease response assessment. The first assessment may be performed earlier than 12 weeks if in the opinion of the investigator the subject is clinically progressing.

l. Subjects who have progressive disease at the Week 12 assessment should have a confirmation assessment performed at least 28 days later (after Week 16) (+7 days). See Section 7.1.2.7.7 for additional details regarding confirmation assessments.

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 8 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

m. In subjects who discontinue study therapy without confirmed disease progression, a radiological assessment should be performed at the time of treatment discontinuation (i.e. date of discontinuation ± 4 week window). If previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation is not mandatory.
n. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
o. 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.
p. Laboratory tests for screening are to be performed within 7 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
q. After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
r. Unresolved abnormal laboratory tests that are drug related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory tests are within normal range.
s. To be repeated every 4 cycles after Cycle 5.
t. To be repeated every 3 cycles after Cycle 7.
u. If β2 microglobulin is elevated at baseline, testing should be repeated every 12 weeks.
v. All subjects will have bone marrow biopsy/aspirate performed at baseline. Subsequent bone marrow assessments will only be performed in subjects who have bone marrow involvement. A bone marrow assessment should be performed to confirm CR (if subject had bone marrow involvement) and as clinically indicated.
w. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
x. Bone marrow morphology, IHC, and Cytogenetics should be performed with each bone marrow biopsy. Cytogenetics is done to evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If it is not a standard procedure in your region, this test does not need to be performed.
y. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous and the tissue sample should have proper size to enable multiple planned biomarker analyses, but not artificially decrease the longest diameter of the lesion. If a tumor biopsy was of a target lesion during eligibility

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 8 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

assessment, it is preferred to obtain a new baseline scan. Newly obtained tumor biopsies are required for all lymphoma subjects at Screening and Week 12 (± 7 days). Tumors that are inaccessible or contraindicated due to subject safety concerns are exempt from this requirement.

z. Correlative study samples should be collected at Screening, at the time of the Wk 12 disease response assessment, and upon progression.

aa. Pre-dose trough PK samples will be collected at Cycles 1, 2, 7, every 6 cycles thereafter, 30 days after discontinuation of study drug, and 3 months and 6 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All trough samples should be drawn within 24 hours before infusion of pembrolizumab. Anti-pembrolizumab antibodies should be drawn with all pre-dose trough PK, 30 days after discontinuation of study drug or until the subject starts new anti-cancer therapy. Procedures for sample collection are described in the Procedures Manual.

6.10 Study Flow Chart J: Multiple Myeloma (Cohort 2) Second Course Phase (Retreatment for Post-Stringent Complete Response (sCR) Relapse Only) (For subjects allocated to 200 mg Q3W)

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Administrative Procedures													
Eligibility Criteria	X												
Interim Medical History	X												
Prior and Concomitant Medication Review [e]	X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X	X
Survival Status		⟷									⟷		X
Clinical Procedures/Assessments													
Review Adverse Events [f]	X	X	X	X	X	X	X	X	X	X	X[g]	X[g]	
Full Physical Examination	X			X		X[h]				X			
Directed Physical Examination			X		X		X		X				
Vital Signs and Weight [i]	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X												
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Skeletal survey [j]	X												
MRI/CT/PET [j]	X												
International Myeloma Working Group Uniform Response Criteria [k]			X	X	X	X[l]	X	X	X	X[m]		X[b]	

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 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 [n]	X												
PT/INR and aPTT [o]	X[p]												
CBC with Differential [q]	X[p]		X	X	X	X	X	X	X	X	X[r]		
Comprehensive Chemistry Panel [q]	X[p]		X	X	X	X	X	X	X	X	X[r]		
LDH [q]	X[p]		X	X	X	X	X	X	X	X	X[r]		
Urinalysis [q]	X[p]				X [s]			X			X[r]		
T3 (or FT3 per local standard), FT4 and TSH [q]	X[p]			X		X [t]		X			X[r]		
Viscosity [q]	X[p]												
Quantitative Serum Immunoglobulin	X[p]		X	X	X	X	X	X	X				
Serum protein electrophoresis and serum immunofixation	X[p]		X	X	X	X	X	X	X				
Serum free light chain assay	X[p]		X	X	X	X	X	X	X				
24 hr urine protein electrophoresis and urine immunofixation	X[p]		X	X	X	X	X	X	X				
M-protein quantitation (urine and serum)	X[p]		X	X	X	X	X	X	X				
β2 microglobulin	X[p]												
Bone Marrow Biopsy & Aspirate [u,v]	X			X		X							
Bone marrow morphology, IHC, Cytogenetics by standard karyotyping, FISH panel [w,x]	X			X		X							

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Laboratory Procedures/Assessments: analysis performed by central laboratory													
Correlative Studies Blood /Bone Marrow Collection [u,y]	X			X		X							
Anti-pembrolizumab Antibodies [z]		Xᶻ	Xᶻ		Xᶻ				Xᶻ		Xᶻ		
Pharmacokinetics [z]		Xᶻ	Xᶻ		Xᶻ				Xᶻ		Xᶻ		

Abbreviations: AE=adverse event; AP=anteroposterior; aPTT=activated partial thromboplastin time; β-HCG=beta human chorionic gonadotropin; CBC=complete blood cell count; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; Discon=discontinuation; ECOG=Eastern Cooperative Oncology Group; ECI=events of clinical interest; FISH=fluorescence in situ hybridization; FT3=free triiodothyronine; FT4=free thyroxine; IHC=immunohistochemistry; INR=International Normalized Ratio; LDH=lactate dehydrogenase; NCI=National Cancer Institute; PA=posterior-anterior; PD=progressive disease; PET=positron emission tomography; PK=pharmacokinetic; PT=prothrombin time; Q3W=every 3 weeks; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone.

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status every 12 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone 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).
d. In general, the window for each visit is ± 3 days unless otherwise noted.
e. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
f. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

g. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.
h. To be repeated every 4 cycles after cycle 5.
i. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.
j. Skeletal survey should include a chest (PA or AP; lateral), skull (lateral), upper extremities (shoulder to elbow), lower extremities (hip to knee; AP), pelvis (AP), cervical/thoracic/lumbar spine (AP and lateral). A skeletal survey and/or MRI/CT/PET (MRI for subjects with bone disease and CT/PET for plasmacytomas) performed as standard of care prior to signing consent can be used for screening if performed within 28 days of Day 1. For suspected progression to bone disease bidirectional measurement of the target lytic lesions must be performed. During the course of the study or if a subject develops bone pain a skeletal survey and/or MRI/CT/PET (MRI for subjects with bone disease and CT/PET for plasmacytomas) should be performed annually or as clinically indicated. Subjects with measurable plasmacytomas at baseline should have imaging performed every 9 weeks.
k. Disease response assessment is based upon the multiple myeloma response criteria. Disease assessments should occur at Screening and every 3 weeks (± 7 days) while on study treatment. For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. Parameters assessed should include serum protein electrophoresis and serum immunofixation, serum free light chain assay, 24 hr urine protein electrophoresis and urine immunofixation, M-protein quantitation (urine and serum), and urine protein electrophoresis.
l. Subjects who have progressive disease at the Week 12 assessment (Cycle 5) should have a confirmation assessment performed at least 21 days later (after Week 15). Additionally, for subjects who have progressive disease at the Week 12 assessment, a bone marrow biopsy/aspirate should be performed as part of the Week 15 confirmation assessment. See Section 7.1.2.7.7 for additional details regarding confirmation assessments.
m. In subjects who discontinue study therapy without confirmed disease progression, a response assessment should be performed at the time of treatment discontinuation (i.e. date of discontinuation ± 4 week window). If previous assessment was performed within 4 weeks prior to the date of discontinuation, then a repeat assessment at treatment discontinuation is not mandatory.
n. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

Trial Period:	Screening Phase	Treatment Cycles[a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

o. 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.
p. Laboratory tests for screening are to be performed within 7 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
q. After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests. Viscosity should be performed at Screening and as clinically necessary during the trial.
r. Unresolved abnormal laboratory tests that are drug related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory tests are within normal range.
s. To be repeated every 3 cycles after Cycle 4.
t. To be repeated every 2 cycles after cycle 5
u. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
v. Bone marrow biopsy/aspirate should be performed at Screening, Cycle 1 Day 1 (Cycle 1 Day 1 only if Screening Bone Marrow Aspirate/Biopsy was performed greater than 28 days from Day 1 Cycle 1), Week 6 (± 7 days), Week 12 (± 7 days), to confirm sCR and CR, or as clinically indicated. For subjects who have progressive disease at the Week 12 assessment, a bone marrow biopsy/aspirate should be performed as part of the Week 15 confirmation assessment. A bone marrow biopsy/aspirate performed as part of standard of care prior to signing informed consent may be used for screening if performed within 28 days of Day 1. When a bone marrow biopsy is performed, the paraffin-embedded block must be sent to the central laboratory.
w. Bone marrow morphology and IHC should be performed with each bone marrow biopsy. Cytogenetics by standard karyotyping, and FISH panel should be performed at screening only.
x. FISH panel should include del 1p, del 13, del 17p13, t(4;14), t(11;14), t(14;16), and 1q21 amplification.
y. Correlative study samples should be collected at Screening, at the time of the Week 6 and Week 12 disease response assessments, and upon progression.
z. Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Cycles 1, 2, 4, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug, or until the subject starts new anti-cancer therapy. All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab. Additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab infusion at Cycles 1 and 8. Procedures for sample collection are described in the Procedures Manual.

Note: Cohort 2 subjects are no longer eligible for second course treatment phase.

6.11 Study Flow Chart K: Cohort 4A, 4C, 4D Mediastinal Large B-Cell Lymphoma, Follicular Lymphoma (FL), and Diffuse Large B-Cell Lymphoma (DLBCL) Second Course Phase (Retreatment for Post-Complete Response Relapse Only) (Subjects allocated to 200 mg Q3W).

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 9 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Administrative Procedures													
Eligibility Criteria	X												
Interim Medical History	X												
Prior and Concomitant Medication Review [e]	X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X	X
Survival Status		←							→		←	→	X
Clinical Procedures/Assessments													
Review Adverse Events [f]	X	X	X	X	X	X	X	X	X	X	X [g]	X	
Full Physical Examination	X			X		X [h]				X			
Directed Physical Examination			X		X		X		X				
Vital Signs and Weight [i]	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X												
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Pulmonary Function Test [j]	X												
Neck, Chest, Abdominal, Pelvic PET/CT [k]	X			X		X [l]			X	X [m]		X [b]	

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 9 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Disease Response Assessment by Revised Response Criteria for Malignant Lymphoma				X		X			X	X		X	
Assessment of Lymphoma B Symptoms [k]	X			X		X			X	X		X	
Laboratory Procedures/Assessments: analysis performed by local laboratory													
Pregnancy Test – Urine or Serum β-HCG [n]	X												
PT/INR and aPTT [o]	X [p]												
CBC with Differential [q]	X [p]		X	X	X	X	X	X	X[s]	X	X [r]		
Comprehensive Chemistry Panel [q]	X [p]		X	X	X	X	X	X	X[s]	X	X [r]		
LDH [q]	X [p]		X	X	X	X	X	X	X[s]	X	X [r]		
Urinalysis [q]	X [p]				X[t]						X [r]		
T3 (or FT3 per local standard), FT4 and TSH[q]	X [p]			X		X [u]		X			X [r]		
β2 microglobulin[q,v]	X [p]					X [v]							
Bone Marrow Biopsy & Aspirate [w,x]	X												
Bone marrow morphology, IHC, Cytogenetics [y]	X												

Trial Period:	Screening Phase	Treatment Cycles [a]								End of Treatment	Post-treatment		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 9 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Laboratory Procedures/Assessments: analysis performed by central laboratory													
Lymph Node Biopsy [x, z]	X					X							
Correlative Studies Blood Collection[x, aa]	X					X							
Anti-pembrolizumab Antibodies [bb]		X[bb]	X[bb]		X[bb]				X[b b]		X[bb]		
Pharmacokinetics [bb]		X[bb]	X[bb]		X[bb]				X[b b]		X[bb]		

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; β-HCG=beta human chorionic gonadotropin; CBC=complete blood cell count; CR=complete response; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; Discon=discontinuation; ECOG=Eastern Cooperative Oncology Group; ECI=events of clinical interest; FDG=fludeoxyglucose; FEF=forced expiratory flow; FT3=free triiodothyronine; FT4=free thyroxine; FVC=forced vital capacity; IHC=immunohistochemistry; INR=International Normalized Ratio; LDH=lactate dehydrogenase; NCI=National Cancer Institute; PD=progressive disease; PET=positron emission tomography; PK=pharmacokinetic; PT=prothrombin time; Q3W=every 3 weeks; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone.

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.

c. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone 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).
d. In general, the window for each visit is ± 3 days unless otherwise noted.
e. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
f. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
g. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.
h. To be repeated every 4 cycles after cycle 5.
i. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.
j. Pulmonary function tests should include an assessment of forced vital capacity, forced expiratory flow between 25 and 75 percent of FVC (FEF25-75), forced expiratory volume in one second and peak expiratory flow (PEF) and diffusion capacity. Additionally, oxygen saturation as assessed by pulse oximetry is required. These tests should be performed at baseline and subsequently at the discretion of the investigator. Hemoglobin must be obtained within 3 days of pulmonary function testing.
k. Disease response assessment is based upon Revised Response Criteria for Malignant Lymphoma. “Diagnostic quality” CT and PET should be performed at Screening and both should be repeated for subsequent assessments. For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in subsequent assessments. Response assessments should occur at Screening (within 28 days prior to first dose of trial treatment), Week 6, Week 12, and every 9 weeks (± 7 days) following the Week 12 assessment. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. Assessment of lymphoma B symptoms should occur with each disease response assessment. The first assessment may be performed earlier than 12 weeks if in the opinion of the investigator the subject is clinically progressing.
l. Subjects who have progressive disease at the Week 12 assessment should have a confirmation assessment performed at least 21 days later (after Week 15) (+7 days). See Section 7.1.2.7.7 for additional information on confirmation assessments. See Section 7.1.2.7.7 for additional details regarding confirmation assessments.
m. In subjects who discontinue study therapy without confirmed disease progression, a radiological assessment should be performed at the time of treatment discontinuation (i.e. date of discontinuation ± 4 week window). If previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation is not mandatory.
n. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
o. 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.
p. Laboratory tests for screening are to be performed within 7 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
q. After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
r. Unresolved abnormal laboratory tests that are drug related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory tests are within normal range.
s. CBC with Differential, Comprehensive Chemistry Panel, and LDH should be performed every 6 weeks after Cycle 8.
t. To be repeated every 3 cycles after Cycle 4.
u. To be repeated every 2 cycles after cycle 5.

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-treatment**		
						To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Post-Treatment Safety Follow-up Visit	Efficacy Follow-up Visits [b]	Survival Follow-up [c]
Scheduling Window (Days) [d]:	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post Discon (±3 days)	Every 9 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

v. If β2 microglobulin is elevated at baseline, testing should be repeated every 12 weeks.
w. All subjects will have bone marrow biopsy/aspirate performed at baseline. Subsequent bone marrow assessments will only be performed in subjects who have bone marrow involvement. A bone marrow assessment should be performed to confirm CR (if subject had bone marrow involvement) and as clinically indicated.
x. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
y. Bone marrow morphology, IHC, and Cytogenetics should be performed with each bone marrow biopsy. Cytogenetics is done to evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If it is not a standard procedure in your region, this test does not need to be performed. See section 7.1.2.7.8 for additional details.
z. Tumor biopsies are required for subjects at Screening and Week 12 (± 7 days). If an archival biopsy is not available a new biopsy must be obtained.
aa. Correlative study samples should be collected at Screening, at the time of the Week 12 disease response assessment, and upon progression. See section 7.1.2.7.8 and the Procedures Manual for additional details.
bb. Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Cycles 1, 2, 4, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug or until the subject starts new anti-cancer therapy. All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab. Additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab infusion at Cycles 1 and 8. Procedures for sample collection are described in the Procedures Manual.

6.12 Study Flow Chart L: Cohort 5 Diffuse Large B-Cell Lymphoma (DLBCL) Second Course Phase (Retreatment for Post-Complete Response Relapse Only) (Subjects allocated to pembrolizumab 200 mg administered intravenously once every 21 days in combination with lenalidomide taken orally once daily for 21 days + 7 days off. The cycle length is 28 days.)

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**						**End of Treatment**	**Post-treatment**		
		To be repeated beyond 3 cycles									
Treatment Cycle/Title: (28-day cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon	Post-Treatment Safety Follow-up Visit[b]	Efficacy Follow-up Visits[c]	Survival Follow-up[d]
Cycle Day (visit day) (± 3 days after Day 1 of Cycle 1 unless otherwise specified)	(-28 to -1 days)	**1**	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Administrative Procedures											
Inclusion/exclusion criteria	X										
Subject identification card	X										
Demographics and interim medical history	X										
Prior and concomitant medication review[e]	X	X	X	X	X	X	X	X	X		
Reconfirm subject registration in REVLIMID REMS™ program where applicable[f]	X										
Combination treatments											
Pembrolizumab administration[g]		**See Section 6.12.1**									
Lenalidomide administration[h]											
Post-study anticancer therapy status										X	X
Survival status		⟷							⟷		X
Clinical Procedures/Assessments											
Review adverse events[i]	X	X	X	X	X	X	X	X	X	X	
Full physical examination[j]	X	X						X			
Directed physical examination[j]		X									
Vital signs[k]	X	X	X	X	X	X	X	X			
12-lead electrocardiogram	X										

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**						**End of Treatment**	**Post-treatment**		
		To be repeated beyond 3 cycles									
Treatment Cycle/Title: (28-day cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon	Post-Treatment Safety Follow-up Visit[b]	Efficacy Follow-up Visits[c]	Survival Follow-up[d]
Cycle Day (visit day) (± 3 days after Day 1 of Cycle 1 unless otherwise specified)	(-28 to -1 days)	**1**	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Pulmonary function test[l]	X										
ECOG performance status[m]	X	X	X		X		X	X			
Neck, chest, abdominal, pelvic PET/CT[n]	X	X ±7 days						X		X	
Lymphoma disease response assessment by Revised Response Criteria for Malignant Lymphoma [87][o,p]		X[q] ±7 days						X		X	
Assessment of lymphoma B symptoms[r]	X	X ±7 days						X		X	
Laboratory Procedures/Assessments: analysis performed by <u>local</u> laboratory[s]											
Pregnancy test – urine or serum β-HCG[t,u]	X[t]	X[u]									
PT/INR and aPTT[v]	X	X						X	X		
CBC with differential[w]	X	X						X	X		
Comprehensive blood chemistry panel[x]	X	X						X	X		
LDH[x]	X	X						X	X		
Urinalysis[x]	X	X							X		
T3, (or FT3 per local standard), FT4 and TSH[y]	X	X							X		
Creatinine clearance	X										
β2 microglobulin[z]	X										
Epstein-Barr virus[aa]	X										
Bone marrow biopsy & aspirate[bb]	X										
Bone marrow morphology, IHC, cytogenetics[bb]	X										

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**						**End of Treatment**	**Post-treatment**		
		To be repeated beyond 3 cycles									
Treatment Cycle/Title: (28-day cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon	Post-Treatment Safety Follow-up Visit[b]	Efficacy Follow-up Visits[c]	Survival Follow-up[d]
Cycle Day (visit day) (± 3 days after Day 1 of Cycle 1 unless otherwise specified)	(-28 to -1 days)	**1**	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor
Laboratory Procedures/Assessments: analysis performed by central laboratory											
Lymph node biopsy[cc]	X	X									
Correlative studies blood collection[dd]	X	X									
Anti-pembrolizumab antibodies[ee]		X	X		X				X		
Pembrolizumab pharmacokinetics[ee]		X	X		X				X		

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; β-HCG=beta human chorionic gonadotropin; CBC=complete blood cell count; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; Discon=discontinuation; ECOG=Eastern Cooperative Oncology Group; FDG=fludeoxyglucose; FT3=free triiodothyronine; FT4=free thyroxine; IHC=immunohistochemistry; INR=International Normalized Ratio; LDH=lactate dehydrogenase; NCI=National Cancer Institute; PD=progressive disease; PET=positron emission tomography; PK=pharmacokinetic; PT=prothrombin time; REMS=Risk Evaluation and Mitigation Strategy; RP2D=recommended Phase II dose; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone.

a. Treatments and assessments are based on 28-day cycles.
b. After the end of treatment, each subject will be followed for 30 days for AE monitoring. Serious adverse events will be collected for 90 days after the end of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, and spontaneously reported pregnancy will be collected for 120 days after the end of treatment. Serious adverse events and spontaneously reported pregnancy will be reported for 30 days after the end of treatment if the subject initiates new anticancer therapy. See Section 7.2 for additional details.
c. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
d. After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone 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).
e. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.

Trial Period:	Screening Phase	Treatment Cycles[a]						End of Treatment	Post-treatment		
		To be repeated beyond 3 cycles									
Treatment Cycle/Title: (28-day cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon	Post-Treatment Safety Follow-up Visit[b]	Efficacy Follow-up Visits[c]	Survival Follow-up[d]
Cycle Day (visit day) (± 3 days after Day 1 of Cycle 1 unless otherwise specified)	(-28 to -1 days)	**1**	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

f. Lenalidomide must be prescribed through and in compliance with the REVLIMID REMS™ program or protocol-specified requirements. Refer to local prescribing information.
g. Pembrolizumab will be given by intravenous infusion over 30 minutes at a fixed dose of 200 mg. Each dose will be administered once every 3 weeks within each 28-day cycle. See Section 5.2 and Section 7.1.5.2 for additional details. See Section 12.9 for additional dose timing details.
h. Lenalidomide will be given orally once daily at the RP2D established during the safety run-in. Each dose will be administered for the first 21 consecutive days of each 28-day cycle. See Section 5.2 and Section 7.1.5.2 for additional details. See Section 12.9 for additional dose timing details.
i. Adverse events and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. See Section 7.1.2.1 and Section 7.2 for additional details.
j. A physical examination will be performed before each administration of pembrolizumab. A full physical examination will be performed at Week 12, and every 12 weeks thereafter, and directed physical exams will be conducted before administration of pembrolizumab at each of the other visits.
k. Vitals signs will include temperature, pulse, respiratory rate, weight, and blood pressure.
l. Pulmonary function tests should include an assessment of forced vital capacity, forced expiratory flow between 25 and 75 percent of forced vital capacity, forced expiratory volume in 1 second, peak expiratory flow, and diffusion capacity. Additionally, oxygen saturation as assessed by pulse oximetry is required. These tests should be performed at baseline and subsequently at the discretion of the investigator. Hemoglobin must be obtained within 3 days of pulmonary function testing.
m. ECOG performance status will be performed before administration of each dose of pembrolizumab.
n. Diagnostic quality CT and PET should be performed at Screening, Week 12, and every 12 weeks following Week 12. For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in subsequent assessments. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of treatment cycle frequencies. In subjects who discontinue study therapy without confirmed disease progression, a radiological assessment should be performed at the time of treatment discontinuation (i.e., date of discontinuation ±4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation is not mandatory. See Section 7.1.2.7 and the Site Imaging Manual for additional details regarding scan requirements and timing.
o. Lymphoma disease response assessments [87] should occur at Week 12, and every 12 weeks (±7 days) following the Week 12 assessment. For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. The first assessment may be performed earlier than 12 weeks if, in the opinion of the investigator, the subject is clinically progressing. See Section 7.1.2.7 for additional details regarding assessment requirements and timing.
p. Subjects who have progressive disease at the Week 12 assessment should have a confirmation assessment performed 4-6 weeks later. See Section 7.1.2.7.7 for additional details on confirmation assessments.

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**						**End of Treatment**	**Post-treatment**		
		To be repeated beyond 3 cycles									
Treatment Cycle/Title: (28-day cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon	Post-Treatment Safety Follow-up Visit[b]	Efficacy Follow-up Visits[c]	Survival Follow-up[d]
Cycle Day (visit day) (± 3 days after Day 1 of Cycle 1 unless otherwise specified)	(-28 to -1 days)	**1**	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

q. Lymphoma disease response assessments [87] should occur at Week 12, and every 12 weeks (±7 days) following the Week 12 assessment. Disease assessments or scans should not be delayed for delays in cycle starts.
r. Lymphoma B assessments should be performed at Screening and at the time of each disease response assessment.
s. Laboratory tests for screening that are performed at a local laboratory should be completed within 7 days prior to the first dose (Cycle 1) of trial treatment. Subsequent laboratory safety evaluations should be completed within 72 hours of any subsequent trial treatments (i.e., should be available before the subject receives the scheduled dose). See Section 7.1.3.1 for details regarding laboratory safety evaluations.
t. In females of childbearing potential, two negative pregnancy tests (sensitivity of at least 25 mIU/mL) must be obtained prior to initiating therapy in female subjects enrolled in Cohort 5 (DLBCL). The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing lenalidomide therapy.
u. Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide. Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.
v. Coagulation factors will be obtained at Screening and repeated during the trial as per the prescribing information for the selected thromboprophylaxis/thromboembolism therapy.
w. CBC with differential is performed weekly for Cycle 1, every 2 weeks for Cycles 2-4, and on Day 1 of each cycle thereafter (monthly).
x. LDH, comprehensive chemistry panel, and urinalysis should be performed on Day 1 of Cycles 1-8, and every 8 weeks thereafter. Tests may be performed within ±7 days after Day 1 of Cycle 1.
y. Thyroid function tests (T3, FT4, and TSH) should be performed at Week 4, Week 8, Week 12, and every 12 weeks thereafter. Tests may be performed within ±7 days after Day 1 of Cycle 1.
z. If β2 microglobulin is elevated at baseline, testing should be repeated every 12 weeks.
aa. All subjects will have Epstein-Barr virus status collected at Screening.
bb. All subjects will have a bone marrow biopsy/aspirate, bone marrow morphology, IHC, and cytogenetics performed at baseline. Cytogenetics is done to evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If it is not a standard procedure in your region, this test does not need to be performed. See Section 7.1.2.7.8 for additional details.

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**						**End of Treatment**	**Post-treatment**		
		To be repeated beyond 3 cycles									
Treatment Cycle/Title: (28-day cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon	Post-Treatment Safety Follow-up Visit[b]	Efficacy Follow-up Visits[c]	Survival Follow-up[d]
Cycle Day (visit day) (± 3 days after Day 1 of Cycle 1 unless otherwise specified)	(-28 to -1 days)	**1**	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon (±3 days)	Every 12 weeks post Discon (±7 days)	Every 12 weeks (±7 days) or as directed by the Sponsor

cc. Tumor biopsies are required for subjects at Screening and Week 12 (± 7 days). If an archival biopsy is not available a new biopsy must be obtained. See Section 7.1.2.7.8 and the Procedures Manual for additional details.

dd. Correlative study samples should be collected at Screening, at the time of the Week 12 lymphoma disease response assessment, and upon progression. See Section 7.1.2.7.8 and the Procedures Manual for additional details.

ee. Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Day 1 of Cycle 1, Day 22 of Cycle 1, Day 15 of Cycle 2, Day 15 of Cycle 5, every 4th pembrolizumab infusion thereafter, and 30 days after discontinuation of study drug (or until the subject starts new anti-cancer therapy).

Note: Cohort 5 has been discontinued and there will be no further enrollment of subjects. All subjects in Cohort 5 must stop combination treatment immediately, complete the discontinuation visit and move into the long-term safety and survival follow-up per protocol. If clinically benefitting at time of stopping combination therapy, subjects may enter a transition period remaining on single agent lenalidomide or pembrolizumab for up to 90 days from 15-SEP-2017 and then must transition into long-term survival and safety follow-up. Cohort 5 subjects are no longer eligible for second course treatment phase.

6.12.1 Study Dose Chart L2: Cohort 5 Diffuse Large B-Cell Lymphoma (DLBCL) (Retreatment for Post-Complete Response Relapse Only) (Subjects allocated to pembrolizumab 200 mg administered intravenously once every 21 days in combination with lenalidomide taken orally once daily for 21 days + 7 days off. The cycle length is 28 days.)

	Each Cycle = 28 Days (To be repeated beyond 3 cycles)											
	Cycle 1				Cycle 2				Cycle 3			
Trial Treatment/ Cycle Day (± 3 days)	Days 1-7	Days 8-14	Days 15-21	Days 22-28	Days 1-7	Days 8-14	Days 15-21	Days 22-28	Days 1-7	Days 8-14	Days 15-21	Days 22-28
Pembrolizumab (Q3W)[a]	1			22			15			8		
Lenalidomide[b]	1 to 21				1 to 21				1 to 21			
Pill count for Lenalidomide[c]	1				1				1			
Pregnancy Prevention Counseling and Dispensing of Lenalidomide[d]	X											

Abbreviations: IV=intravenous; PO=per orem; Q3W=every 3 weeks; REMS=Risk Evaluation and Mitigation Strategy; RP2D=recommended Phase II dose.

a. Pembrolizumab will be administered as 200 mg every 21 days (3 weeks) as an IV infusion over 30 minutes.

b. Lenalidomide will be administered as RP2D PO, once daily on Days 1 to 21 of repeated 28-day cycles. Lenalidomide must be prescribed through and in compliance with the REVLIMID REMS™ program. Refer to local prescribing information.

c. Site should document drug accountability as per their institutional guidelines.

d. The Lenalidomide Education and Counseling Guidance Document must be completed for all subjects and signed by a trained counselor prior to each dispensing of lenalidomide (see Section 12.10). A copy of this document must be maintained in the subject's records for each dispense. Lenalidomide will be dispensed every 3-4 weeks as per local requirements.

Note: Cohort 5 has been discontinued and there will be no further enrollment of subjects. All subjects in Cohort 5 must stop combination treatment immediately, complete the discontinuation visit and move into the long-term safety and survival follow-up per protocol. If clinically benefitting at time of stopping combination therapy, subjects may enter a transition period remaining on single agent lenalidomide or pembrolizumab for up to 90 days from 15-SEP-2017 and then must transition into long-term survival and safety follow-up. Cohort 5 subjects are no longer eligible for second course treatment phase.

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 must obtain documented consent from each potential subject prior to participating in a clinical trial or Future Biomedical Research.

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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 study will be recorded separately and not listed as medical history.

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in the study will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Disease Details and Treatments

7.1.1.6.1 Disease Details

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

7.1.1.6.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation, and surgeries. For MDS subjects, transfusion history should be documented for 3 months prior to start of study and every 6 weeks during response assessment. Transfusion history should be obtained from patient medical records and/or blood bank records.

7.1.1.6.3 Subsequent Antineoplastic Therapy Status

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

7.1.1.7 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or 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.

7.1.1.8 Assignment of Randomization Number

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

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

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

Interruptions from the protocol specified treatment plan for > 12 weeks between doses of pembrolizumab or lenalidomide + pembrolizumab combination due to toxicity, require

consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of pembrolizumab will be witnessed by the investigator and/or trial staff. The total volume of pembrolizumab infused will be compared to the total volume prepared to determine compliance with each dose administered. Because subjects will self-administer lenalidomide, pill counts will be conducted on Day 1 of each cycle.

The instructions for preparing and administering pembrolizumab and for appropriate self-administration of lenalidomide will be provided in the Pharmacy Manual.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

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

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening and repeated as per the frequency defined in the Trial Flow Chart (Section 6.0). After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart (Section 6.0), the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs

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

rate, weight and blood pressure. Height will be measured at screening only and will not be repeated for second course treatment.

7.1.2.4 Electrocardiogram

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

7.1.2.5 Pulmonary Function Testing

Pulmonary function tests should include an assessment of forced vital capacity, forced expiratory flow between 25 and 75 percent of forced vital capacity, forced expiratory volume in 1 second, peak expiratory flow, and diffusion capacity. Additionally, oxygen saturation as assessed by pulse oximetry is required. These tests should be performed at baseline and subsequently at the discretion of the investigator. Hemoglobin must be obtained within 3 days of pulmonary function testing.

7.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.4) at screening, prior to the administration of each dose of pembrolizumab infusion and discontinuation of trial treatment as specified in the Trial Flow Chart (Section 6.0).

7.1.2.7 Assessment of Disease and Tumor Imaging

7.1.2.7.1 Criteria for Assessment of Disease

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

- MDS: Clinical application and proposal for modification of the IWG response criteria in myelodysplasia. [88]
- MM: International uniform response criteria for multiple myeloma [89]
- HL/NHL: Revised Response Criteria for Malignant Lymphoma. [87]

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

7.1.2.7.2 Hodgkin and Non-Hodgkin Lymphoma Disease Response Assessment

Lymphoma (HL/NHL) response assessment by CT/positron emission tomography (PET) is based on the Revised Response Criteria for Malignant Lymphoma [87]. Local reading (investigator assessment with site radiology reading) will be used to determine subject eligibility and for subject management. The Sponsor will also receive radiologic images for a retrospective analysis of subject eligibility and treatment response to be performed by a central

vendor if the primary efficacy endpoint is met. Assessment of lymphoma B symptoms should occur with each lymphoma disease response assessment.

7.1.2.7.3 Disease Assessment of Immunotherapeutic Agents

Immunotherapeutic agents, such as pembrolizumab, may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard lymphoma disease response assessment criteria may not provide a comprehensive response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, in the setting where a subject's lymphoma disease response assessment shows PD, trial treatment may be continued at the discretion of the principal investigator in a subject whose clinical condition is stable until repeat imaging performed to 6 weeks later confirms progression. However, imaging should occur at any time where there is clinical suspicion of progression. See Section 7.1.2.7.7 for additional information about the timing of the disease response assessment after PD.

NOTE: If a subject with confirmed progression according to response criteria for each cohort is clinically stable or clinically improved, an exception may be considered to continue treatment upon consultation with the Sponsor.

7.1.2.7.4 Timing of Disease Assessments

Uniform disease response assessments will occur at Week 12 for all indications (see Table 10 below). One additional disease assessment for MDS will occur after 6 weeks. Additional assessments for MM subjects will occur on therapy per the frequency in Table 10 to assess for kinetics of response. One additional disease assessment for FL and DLBCL subjects receiving 200 mg Q3W will occur at Week 6, with the exception of Cohort 5 (DLBCL). Treatment decisions will not be based on these additional assessments prior to Week 12.

Table 10 Disease Response Assessments

Indication	Assessment Frequency
MDS	Every 6 weeks
MM (Cohort 2 for subjects receiving 10 mg/kg Q2W)	Every 4 weeks
MM (Cohort 2 for subjects receiving 200 mg Q3W)	Every 3 weeks
HL/NHL (Cohort 3, 4A, 4B) for subjects receiving 10 mg/kg Q2W	Every 8 weeks following first assessment at Wk 12
NHL (Cohort 4A, 4C, 4D) for subjects receiving 200 mg Q3W	Wk 6, Wk 12, every 9 weeks following Wk 12
NHL (Cohort 5) for subjects receiving lenalidomide + pembrolizumab	Wk 12 and every 12 weeks following Wk 12.
Abbreviations: HL=Hodgkin lymphoma; MDS=myelodysplastic syndrome; MM=multiple myeloma; NHL=non-Hodgkin lymphoma; Q2W=every 2 weeks; Q3W=every 3 weeks.	

7.1.2.7.5 Initial Disease Assessment

Initial disease assessment or tumor imaging must be performed within 28 days prior to the first dose of trial treatment. For lymphoma the site study team must review pre-trial images to confirm the subject has measurable disease as defined in the inclusion criteria. The baseline imaging scan must be submitted to the central imaging vendor for a retrospective analysis of this eligibility criterion.

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. For lymphoma, CT and PET should be used throughout the study. For lymphomas that are not fludeoxyglucose-avid at screening, PET does not need to be repeated in follow-up assessments.

7.1.2.7.6 Disease Assessment During Trial

Disease assessments should be performed per the frequency defined in Table 10 above. There is a ± 7 day window for assessments performed after Day 1. Lymphoma tumor imaging should be performed by CT and PET throughout the trial (after Screening scan, PET is repeated to confirm response). Disease assessments or scans should not be delayed for delays in cycle starts.

Disease assessments and imaging should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. See Section 7.1.2.7.7 for confirmation assessment requirements when a subject's disease response assessment shows disease progression at the Week 12 assessment.

Assessment of Lymphoma B symptoms should occur at Screening (Visit 1) and with each lymphoma disease response assessment. These symptoms include the following:

- Unexplained weight loss of more than 10% of the body weight during the 6 months before initial staging investigation;
- Unexplained, persistent, or recurrent fever with temperatures above 38°C during the previous month; and
- Recurrent drenching night sweats during the previous month [90].

7.1.2.7.7 Confirmation Assessments

Because a subject treated with PD-1 inhibitors may have pseudoprogression of disease (there is progression per imaging, but the subject is clinically stable or improving), confirmation of progression should be conducted as follows:

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 a disease response assessment performed 4-6 weeks later confirms progression.

Clinical stability may be defined as:

1) Absence of symptoms and signs indicating clinically significant progression of disease (including worsening of laboratory values) with the exception of M-protein elevation for the multiple myeloma cohort.

2) No decline in ECOG performance status.

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

Subjects that are deemed clinically unstable are not required to have a repeat disease response assessment 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 no other anti-tumor therapy (e.g., chemotherapy, radiation, etc.) has been administered.

Subjects should have their next disease response assessment as detailed in the Trial Flow Chart (see Section 6.0). When feasible, subjects should not be discontinued until progression is confirmed.

For subjects who have SD, partial response, or CR following the disease response assessment at Week 12, a confirmation assessment is not required. Disease assessments and imaging should continue per the regular frequency.

Subjects who have a CR for at least 18 months, irrespective of continued or discontinued trial treatment, may have subsequent imaging done every 6 months according to institutional standards until confirmed progression.

NOTE: If a subject with confirmed progression according to response criteria for each cohort is clinically stable or clinically improved, an exception may be considered to continue treatment upon consultation with the Sponsor.

7.1.2.7.8 Biopsy Collection and Correlative Studies Blood Collection

All subjects enrolled into this study must be able to provide an archived formalin-fixed paraffin-embedded biopsy sample or newly obtained core or excisional biopsy (fine needle aspiration not adequate) to be submitted for characterization at a central lab. FL and DLBCL subjects (Cohort 4C, 4D, and 5) are not required to have PD-L1 testing to determine eligibility; regardless, an archived formalin-fixed paraffin-embedded biopsy sample or newly obtained core or excisional biopsy needs to be submitted at screening.

Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous and the tissue sample should have proper size to enable multiple planned biomarker analyses, but not artificially decrease the longest diameter of the lesion. Biopsy sites should be selected so that subsequent biopsies can be performed at the same location. Tumors that are inaccessible or contraindicated due to subject safety concerns are exempt from this requirement.

Bone marrow and lymph node biopsies will be collected as per Table 11 below.

Table 11 Bone Marrow and Lymph Node Biopsy Assessments

Indication	Timing of Biopsy
MDS (Cohort 1) (Bone marrow biopsy/aspirate)	Screening, Wk 6 (± 7 days), Wk 12 (± 7 days), then every 12 weeks or as clinically indicated. If subject has PD at Wk 12, repeat bone marrow aspiration/biopsy at WK 16 to confirm PD.
MM (Cohort 2) subjects receiving 10 mg/kg Q2W (Bone marrow biopsy/aspirate)	Screening, Wk 4 (± 7 days), Wk 12 (± 7 days), to confirm CR, and sCR, and as clinically indicated. If subject has PD at Wk 12, repeat bone marrow/aspiration biopsy at WK 16 to confirm PD.
MM (Cohort 2) subjects receiving 200 mg Q3W (Bone marrow biopsy/aspirate)	Screening, Wk 6 (± 7 days), Wk 12 (± 7 days), to confirm CR, and sCR, and as clinically indicated. If subject has PD at Wk 12, repeat bone marrow/aspiration biopsy at WK 15 to confirm PD.
HL (Cohort 3) (Lymph node biopsy)	Screening and Wk 12 (± 7 days). [Screening biopsy may be archival (from recent relapse, if available) or newly obtained].
MLBCL (Cohort 4A) (Lymph node biopsy)	Screening and Wk 12 (± 7 days). [Screening biopsy may be archival (from recent relapse, if available) or newly obtained).
NHL (Cohort 4B) (Lymph node biopsy)	Screening (archival and newly obtained), and Wk 12 (± 7 days). (A newly obtained biopsy is required at Screening for all NHL subjects even if they have already been determined to be PD-L1 positive based on archival material.)
FL (Cohort 4C) and DLBCL (Cohort 4D) and (Cohort 5) (Lymph node biopsy)	Screening and Wk 12 (± 7 days). [Screening biopsy may be archival (from recent relapse, if available) or newly obtained.
HL/NHL (Cohort 3, 4A, 4B, 4C, 4D, and 5) (Bone marrow biopsy/aspirate) (All subjects will have bone marrow biopsy/aspirate performed at Screening. Subsequent bone marrow assessments will only be performed in subjects who have bone marrow involvement.)	Screening, to confirm CR (if subject has bone marrow involvement), and as clinically indicated.
Abbreviations: CR=complete response; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; HL=Hodgkin lymphoma; MDS=myelodysplastic syndrome; MLBCL=mediastinal large B-cell lymphoma; MM=multiple myeloma; NHL=non-Hodgkin lymphoma; PD=progressive disease; PD-L1=programmed cell death ligand 1; Q2W=every 2 weeks; Q3W=every 3 weeks; sCR=stringent complete response.	

Blood for correlative biomarker studies should be collected as per Table 12 below.

Table 12 Blood Collection for Correlative Biomarkers Studies

Indication	Timing of Correlative Blood Collection
MDS (Cohort 1)	Screening, Wk 6, Wk 12, and upon progression.
MM (Cohort 2) subjects receiving 10 mg/kg Q2W	Screening, Wk 4, Wk 12, and upon progression.
MM (Cohort 2) subjects receiving 200 mg Q3W	Screening Wk 6, Wk 12 and upon progression
HL (Cohort 3)/NHL (Cohort 4A, 4B, 4C, 4D, and 5)	Screening, Wk 12, and upon progression.
Abbreviations: HL=Hodgkin lymphoma; MDS=myelodysplastic syndrome; MM=multiple myeloma; NHL=non-Hodgkin lymphoma; Q2W=every 2 weeks; Q3W=every 3 weeks.	

7.1.3 Laboratory Procedures/Assessments

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

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

Laboratory tests for hematology, chemistry, and urinalysis are specified in Table 13.

Table 13 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
CBC with differential [a]	Alanine aminotransferase (ALT)	Protein	aPTT
Platelet count	Aspartate aminotransferase (AST)	Specific gravity	Total Triiodothyronine (T3) (or FT3) [b]
WBC (total and differential)	Lactate dehydrogenase (LDH)	Microscopic exam, if abnormal results are noted	Free thyroxine (T4)
Red Blood Cell Count	Carbon Dioxide (CO_2 or bicarbonate); if these evaluations are not performed as part of standard of care in your region, then these tests do not need to be performed	Urine pregnancy test [c]	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	Creatinine		Anti-pembrolizumab Antibodies
Absolute Lymphocyte Count	Uric Acid		PK
Reticulocyte Count (MDS cohort only)	Calcium		Blood for FBR
	Chloride		Blood for correlative studies
	Glucose		Viscosity (MM cohort only)
	Phosphorus		β2 microglobulin (MM, HL/NHL cohorts)
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct and Indirect Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		

Abbreviations: aPTT=activated partial thromboplastin time; CBC=complete blood cell count; FBR=Future Biomedical Research; HL=Hodgkin lymphoma; INR=International Normalized Ratio; MDS=myelodysplastic lymphoma; MM=multiple myeloma; NHL=non-Hodgkin lymphoma; PK=pharmacokinetics; PT=prothrombin time; WBC=white blood cell count.

[a] CBC differential should include blast percentage for MDS subjects.

[b] Free T3 may be performed instead of T3 per local standard of care.

[c] Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

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

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluation

7.1.3.2.1 Blood Collection for Serum MK-3475

Sample collection, storage and shipment instructions for serum samples will be provided in the operations/laboratory manual.

The time points for PK blood sampling are described in Section 6.0 – Trial Flow Chart.

7.1.3.2.2 Blood Collection for Anti-pembrolizumab Antibodies

Sample collection, storage, and shipment instructions for blood samples will be provided in the operations/laboratory manual.

The time points for anti-pembrolizumab antibodies are described in Section 6.0 – Trial Flow Chart.

7.1.3.3 Future Biomedical Research

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

- Blood for genomics use
- Leftover bone marrow biopsy/aspirate samples
- Leftover lymph node biopsies
- Leftover correlative blood samples

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, 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 or sCR (MM) may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1. After discontinuing treatment following assessment of CR or sCR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3.2).

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

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

7.1.4.2 Blinding/Unblinding

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

7.1.5 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 Period

Approximately 28 days prior to enrollment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

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).

- In females of childbearing potential, two negative pregnancy tests (sensitivity of at least 25 mIU/mL) must be obtained prior to initiating therapy in female subjects enrolled in Cohort 5 (DLBCL). The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing lenalidomide therapy.

- When an archival biopsy is being used for PD-L1 characterization, it is not required to be obtained within 28 days prior to the first dose of trial treatment.

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

7.1.5.1.1 Prospective Enrollment of PD-L1 Positive Subjects (Cohort 4B: Any-other NHL Only)

Subjects with a NHL subtype other than MLBCL require characterization of PD-L1 to determine eligibility. Subjects that have an archival lymph node biopsy sample available may sign a pre-screening consent to determine the PD-L1 status. After providing a pre-screening consent, subjects will be assigned a screening number.

Subjects that do not have an archival lymph node biopsy sample available must provide written consent for the main study before the lymph node biopsy or any other protocol-specified procedures can occur.

FL (Cohort 4C), DLBCL (Cohort 4D), and DLBCL (Cohort 5) subjects are not required to have PD-L1 testing to determine eligibility.

7.1.5.2 Treatment Period

Cohort 5 has been discontinued with no further enrollment of subjects. All subjects in Cohort 5 must stop combination treatment immediately, complete the discontinuation visit, and move into the long-term safety and survival follow-up per protocol. If clinically benefitting at time of stopping combination therapy, subjects may enter a transition period remaining on single agent lenalidomide or pembrolizumab for up to 90 days from 15-SEP-2017 and then must transition into long-term survival and safety follow-up. Additionally, enrollment in Cohort 2 has been completed; all subjects have previously discontinued study treatment and must transition into long-term safety and survival follow-up. There will be no further enrollment of subjects in this cohort.

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

Subjects may be eligible to receive pembrolizumab or lenalidomide + pembrolizumab combination in the Retreatment Period of this study if the study remains open and the subject meets the following conditions:

- Stopped initial treatment with pembrolizumab or lenalidomide + pembrolizumab combination after attaining an investigator-determined confirmed CR or sCR (MM) according to respective response criteria
- Was treated for at least 24 weeks with pembrolizumab or lenalidomide + pembrolizumab combination before discontinuing therapy
- Received at least 2 treatments with pembrolizumab or for subjects enrolled in Cohort 5 (DLBCL) an additional 21 consecutive daily doses of lenalidomide + 2 doses of pembrolizumab beyond the date when the initial CR or sCR was declared
- Experienced an investigator-determined confirmed disease progression after stopping their initial treatment with pembrolizumab or lenalidomide + pembrolizumab combination
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab or lenalidomide + pembrolizumab combination
- 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 subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have not been free from menses for > 2 years.
- 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.
- Subjects enrolled in Cohort 5 (DLBCL) must meet the criteria for eligibility related to pregnancy and contraception as described in Section 5.1.2, and must be willing to follow the requirements for contraception as described in Section 5.7.2 and Section 5.7.3. Subjects must be enrolled in the REVLIMID REMS program.

- 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 cycles for subjects receiving pembrolizumab Q3W or 26 cycles for subjects receiving pembrolizumab Q2W.

Subjects in Cohort 5 (DLBCL) will be retreated at the same dose frequency as when they last received lenalidomide + pembrolizumab combination for a treatment duration of a maximum of 13 cycles.

Note: Subjects in Cohort 2 and Cohort 5 are no longer eligible for second course treatment phase.

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 to 1 or until the beginning of a new antineoplastic therapy, whichever occurs first. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.

Subjects who are eligible for retreatment with pembrolizumab or lenalidomide + pembrolizumab combination (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.

7.1.5.3.2 Efficacy Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed to monitor disease status as follows:

- Every 6 weeks (±7 days) (MDS); every 12 weeks (±7 days) (MM); every 8 weeks (±7 days) (HL/NHL Cohorts 3, 4A, and 4B) and receiving pembrolizumab 10 mg/kg Q2W

- Every 9 weeks (±7 days) for NHL Cohorts 4A, 4C, and 4D and receiving pembrolizumab 200 mg Q3W

- Every 12 weeks (±7 days) for NHL Cohort 5 (DLBCL) and receiving pembrolizumab 200 mg administered intravenously once every 21 days in combination with lenalidomide taken orally once daily for 21 days + 7 days off

Every effort should be made to collect information regarding disease status until the start of new antineoplastic therapy, disease progression, death, end of the study, or if the subject begins retreatment with pembrolizumab or lenalidomide + pembrolizumab combination as detailed in Section 7.1.5.2.1. Information regarding post-study antineoplastic treatment will be collected if new treatment is initiated.

Note: For subjects who discontinue due to CR, modifications or extensions to the disease status assessment requirements during the Follow-Up Phase may be permitted following Sponsor Consultation.

Subjects who are eligible to receive retreatment with pembrolizumab or lenalidomide + pembrolizumab combination according to the criteria in Section 7.1.5.2.1 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.0 – Trial Flow Chart for Retreatment.

7.1.5.3.3 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 approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Survival follow-up information may be collected from a subject in-person if a non-study clinic visit falls within the survival follow-up window in lieu of contacting the subject by telephone.

Subjects who discontinue treatment to receive stem cell transplant are transitioned into survival follow-up. The conditioning regimen and the stem cell transplant procedure are collected as part of the survival follow-up. Additional parameters (see Section 7.2.3.2) are collected for subjects who receive allogeneic stem cell transplant. Subjects entering survival follow-up for other reasons (PD or starting new anti-cancer treatment) may also receive a stem cell transplant. The information for all stem cell transplants will be collected as described in this paragraph.

7.1.5.4 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an interim database lock, 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 unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

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

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

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

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

All adverse events that occur after the consent form is signed but before randomization/treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

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

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

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

For Cohort 1, 2, 3, 4A, 4B (in subjects receiving pembrolizumab 10 mg/kg Q2W): For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose.

For Cohort 2, 4A, 4C, 4D, and 5 (in subjects receiving pembrolizumab 200 mg Q3W): For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater.

For Cohort 5 (DLBCL), an overdose for lenalidomide will be defined as any dose exceeding the prescribed dose.

No specific information is available on the treatment of overdose of pembrolizumab or lenalidomide. In the event of overdose, 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

The following reporting requirements apply to Cohorts 1, 2, 3, and 4:

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).

The following reporting requirements apply to Cohort 5:

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), including the pregnancy of a male subject's female partner that occurs during the trial.

Pregnancies and lactations of subjects and female partners of male subjects from the time 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 of subjects and female partners of male subjects that occur from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, must be reported. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 14 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.

3. Follow-up Post-Allogeneic Stem Cell Transplantation

In the event a subject receives an allogeneic SCT within 24 months of the last dose of pembrolizumab, or before the end of the trial, the following events will be collected as ECIs through 18 months from the date of allogeneic SCT or until the end of the trial: GVHD, febrile syndrome treated with steroids, pulmonary complications, hepatic veno-occlusive disease and/or sinusoidal syndrome, immune-mediated AEs, critical illness, and transplant-related mortality. 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. Guidance on details to be collected and suggested events to be reported can be found in the procedure manual.

If available and relevant to an event post allo-SCT, concomitant medications and/or laboratory results may be reported. Additional medically important AEs may be submitted at the Investigator's discretion.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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

7.2.4 Evaluating Adverse Events

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

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

Table 14 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); 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 U.S. CLINICAL MONITOR 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

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

The primary purpose of this study is to investigate the safety, tolerability, and anti-tumor activity of pembrolizumab administered intravenously to subjects in the following disease cohorts:

- Intermediate-1, intermediate-2, or high risk MDS (Cohort 1)
- Relapse refractory or refractory MM (Cohort 2)
- Lymphoma, evaluated separately according to the following groups:
    - Relapsed / refractory nodular sclerosing or mixed cellularity HL (Cohort 3)
    - NHL – monotherapy (Cohort 4)
        - Relapsed / refractory MLBCL that have failed, are ineligible for, or refused a stem cell transplant (Cohort 4A)
        - Relapsed / refractory PD-L1 positive NHL (excluding MLBCL) that have failed, are ineligible for, or refused a stem cell transplant (Cohort 4B)
        - Irrespective of PD-L1 status, NHL subjects with relapsed / refractory FL that have failed, are ineligible for, or refused a stem cell transplant (Cohort 4C)
        - Irrespective of PD-L1 status, NHL subjects with relapsed / refractory DLBCL that have failed, are ineligible for, or refused a stem cell transplant (Cohort 4D)

    For the purposes of disease subtype analysis within Cohort 4, analyses for

    - “MLBCL” will consist of Cohort 4A subjects

- "FL" will consist of Cohort 4C subjects plus any PD-L1 positive FL subject in Cohort 4B
- "DLBCL" will consist of Cohort 4D subjects plus any PD-L1 positive DLBCL subjects in Cohort 4B
- "Other" will consist of Cohort 4B subjects excluding FL and DLBCL subjects

Cohort analyses, unless otherwise specified, will be conducted regardless of PD-L1 status or whether the subject received pembrolizumab given either as weight-based or fixed-dose.

- NHL – combination therapy (Cohort 5)
- Irrespective of PD-L1 status, NHL subjects with relapsed / refractory DLBCL that have failed, are ineligible for, or refused a stem cell transplant

Due to the current status of the study, statistical analyses of this section for Cohorts 2 and 5 may be modified and changes will be reported in the Clinical Study Report (CSR).

8.1.1 Efficacy Analyses

The FAS population (defined as all subjects with a baseline efficacy evaluation and at least one post-baseline efficacy evaluation) will serve as the primary population for the analyses of efficacy data in this trial. Supportive analyses of efficacy will be conducted in the intention to treat (ITT) population. An outline of the efficacy analysis strategy is presented in Table 15 below. For Cohorts 1 thru 4, a 90% CI (two-sided) along with a one-sided p-value for testing the null hypothesis based on the binomial distribution will be provided for the rate in each cohort. The respective cohort is considered to have reached the efficacy objective if the corresponding one-sided p-value for testing the respective null hypothesis is less than 5%. For Cohort 5 (DLBLC), a 90% CI (two-sided) will be presented.

Table 15 Primary Analysis Strategy for Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary 1. MDS (Cohort 1): ORR based on IWG (2006 criteria for MDS (investigator-assessed) 2. MM (Cohort 2): ORR based on IMWG criteria (investigator-assessed) 3. HL (Cohort 3): Complete Remission Rate (CRR) based IWG criteria (investigator-assessed) 4. NHL monotherapy (Cohort 4): ORR based on IWG criteria (investigator-assessed) 5. NHL combination therapy (Cohort 5): ORR based on IWG criteria (investigator-assessed)	Exact test of binomial parameter (Cohorts 1 thru 4); Descriptive statistics (Cohort 5)	FAS	Subjects with missing data are considered non-responders
Secondary binary endpoints • MDS (Cohort 1): a. Bone marrow response by IWG criteria (investigator assessed) b. Hematologic improvement by IWG criteria (investigator-assessed) c. Cytogenetic response by IWG criteria (investigator assessed) • MM (Cohort 2): a. CR + sCR by IMWG criteria (investigator assessed) • HL (Cohort 3): a. ORR • NHL monotherapy (Cohort 4): none • NHL combination therapy (Cohort 5): none	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Secondary time-to-event endpoints 1. MDS (Cohort 1): a. OS b. DOR 2. MM (Cohort 2): a. TTP b. DOR c. PFS d. OS 3. HL (Cohort 3): a. PFS b. OS c. DOR 4. NHL monotherapy (Cohort 4): a. PFS b. OS c. DOR 5. NHL combination therapy (Cohort 5): a. PFS b. OS c. DOR	Summary statistics using Kaplan-Meier method	OS, TTP, PFS: FAS DOR: all responders	Censored at last assessment
Secondary descriptive analyses Response by PD-L1 expression change before and after HMA treatment in each population separately: 1. MDS (Cohort 1) 2. MM (Cohort 2) 3. HL (Cohort 3) 4. NHL monotherapy (Cohort 4) 5. NHL combination therapy (Cohort 5)	Descriptive statistics	FAS	

8.1.2 Safety Analyses

The All-Subjects-as-Treated population will be employed for safety analyses.

8.1.3 Power and Sample Size

The calculation of power and sample size for each cohort does not account for an interim analysis.

MDS (Cohort 1)

With approximately 25 subjects with intermediate-1, intermediate-2, or high risk MDS, the study has ~80% power to detect a 20% difference in ORR under the null hypothesis of ORR=10% with a one-sided type I error rate of 5% if the true ORR is 30%. Success for this hypothesis requires at least 6/25 responses. The actual number of subjects enrolled may be larger than 25 to ensure that at least 25 subjects are evaluable for analysis.

MM (Cohort 2)

With approximately 28 subjects with relapse refractory or refractory Multiple Myeloma, the study has ~80% power to detect a 25% difference in ORR under the null hypothesis of ORR=25% with a one-sided type I error rate of 5% if the true ORR is 50%. Success for this hypothesis requires at least 12/28 responses. The actual number of subjects enrolled may be larger than 28 to ensure that at least 28 subjects are evaluable for analysis.

Lymphoma – HL (Cohort 3)

With approximately 25 subjects with HL, the study has ~80% power to detect a 20% difference in CRR under the null hypothesis of CRR=10% with a one-sided type I error rate of 5% if the true CRR is 30%. Success for this hypothesis requires at least 6/25 responses. The actual number of subjects enrolled may be larger than 25 to ensure that at least 25 subjects are evaluable for analysis.

Lymphoma –NHL monotherapy (Cohort 4)

With approximately 78 subjects with NHL, the study has ~80% power to detect a 14% difference in ORR under the null hypothesis of ORR=25% with a one-sided type I error rate of 5% if the true ORR is 39%. Success for this hypothesis requires at least 27/78 responses. The actual number of subjects enrolled may be larger than 78 to ensure that at least 78 subjects are evaluable for analysis.

The maximum half-width of the 2-sided 90% CI will be 16% for the DLBCL and FL subtypes with a targeted number of 30 subjects each, and wider CIs for the MLBCL and Other subtypes.

Lymphoma –NHL combination therapy (Cohort 5)

Approximately 30 to 66 subjects will be evaluated in this cohort, depending on the number of dose levels of lenalidomide assessed during safety run-in; subjects treated at the confirmed RP2D during safety run-in will be included among the 30 subjects assessed during dose expansion (see Section 5.2.1.3 for details).

The maximum half-width of the 2-sided 90% CI will be 16% with a targeted number of 30 subjects treated at the RP2D.

8.1.4 Interim Analysis

Unless otherwise indicated, an interim analysis will be performed if fewer than 10 subjects are enrolled in a cohort 6 months after the time that the first subject is treated in the respective cohort. The interim analysis will take place after 10 subjects have reached the Week 12 assessment. Results will be reviewed by the study team.

See Section 12.8 for further details regarding the decision rules for resuming enrollment following the interim analysis.

Table 16 summarizes the strategy and timing of the potential interim analysis for each cohort.

For the MDS and HL cohorts, if an interim analysis is conducted and 1 or fewer subjects out of the first 10 subjects with a post-baseline (Week 12) assessment/imaging scan have a confirmed or unconfirmed primary endpoint response (OR or CR respectively), then enrollment will be paused until response data for the subsequent (Week 24) assessment/imaging scan are reviewed for all subjects already enrolled in the trial (including those enrolled who have not reached the first post-baseline assessment/imaging scan). Enrollment will be resumed if the observed responses (confirmed or unconfirmed) for the primary endpoint in the respective cohort among subjects who are still enrolled in the trial indicates that the probability of the response for the primary endpoint >10% is at least 80% (e.g., ≥3/16 confirmed or unconfirmed responses). See Section 12.8 for further details regarding the decision rules for resuming enrollment following the interim analysis.

For the MM and NHL Cohorts 4A and 4B combined, if an interim analysis is conducted and 3 or fewer subjects out of the first 10 subjects with a post-baseline (Week 12) imaging scan have a confirmed or unconfirmed primary endpoint response, then enrollment will be paused until response data for the subsequent imaging scan (Week 24) are reviewed for all subjects already enrolled in the trial (including those enrolled who have not reached the first post-baseline scan). Enrollment will be resumed if the observed responses (confirmed or unconfirmed) for the primary endpoint in the respective cohort among subjects who are still enrolled in the trial indicates that the probability of the response for the primary endpoint >25% is at least 80% (e.g., ≥5/16 confirmed or unconfirmed responses). See Section 12.8 for further details regarding the decision rules for resuming enrollment following the interim analysis.

No interim analysis is planned for subjects with unselected PD-L1 status with relapsed / refractory FL, DLBCL receiving monotherapy (Cohort 4C and 4D, or DLBCL subjects receiving combination therapy (Cohort 5).

Table 16 Summary of Interim Analysis Strategy

Interim Analysis Number	Key Endpoints for Interim Analysis	Timing (Sample size) for analysis	Purpose of Analysis
Interim Analysis MDS (Cohort 1)	• ORR	• ≥10 subjects with 1st post-baseline (Week 12) disease assessment	• Pause enrollment until further evidence of efficacy
Interim Analysis MM (Cohort 2)	• ORR	• ≥10 subjects with 1st post-baseline (Week 12) disease assessment	• Pause enrollment until further evidence of efficacy
Interim Analysis Hodgkin Lymphoma (Cohort 3)	• CRR	• ≥10 subjects with 1st post-baseline (Week 12) imaging scan	• Pause enrollment until further evidence of efficacy
Interim Analysis NHL monotherapy (Cohorts 4A and 4B)	• ORR	• ≥10 subjects with 1st post-baseline (Week 12) imaging scan	• Pause enrollment until further evidence of efficacy

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses/In-House Blinding

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

This trial is being conducted as an open-label study, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

The Clinical Biostatistics department will generate the allocation schedule(s) for study treatment assignment.

8.2.2 Hypotheses/Estimation

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

8.2.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

8.2.3.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

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

MDS (Cohort 1)

The primary efficacy endpoint for the MDS cohort is ORR, defined as the proportion of subjects in the analysis population who have response according to the IWG 2006 criteria at any time during the study. Response for the primary analysis will be determined by the investigator.

Key secondary efficacy endpoints for the MDS cohort include:

- OS
- Bone Marrow Response based on IWG criteria for MDS (investigator-assessed)
- Hematologic improvement based on IWG criteria for MDS (investigator-assessed)
- Cytogenetic response based on IWG criteria for MDS (investigator-assessed)
- DOR
- Response by PD-L1 expression change before and after HMA treatment

Additional analyses of efficacy endpoints in MDS based on central review of bone marrow assessment may be conducted at the end of the trial and will be considered exploratory.

MM (Cohort 2)

The primary efficacy endpoint for the MM cohort is ORR, defined as the proportion of subjects in the analysis population who have response according to the IMWG criteria at any time during the study. Response for the primary analysis will be determined by the investigator.

Key secondary efficacy endpoints for the MM cohort include:

- CR + sCR rate based on IMWG criteria (investigator-assessed)
- TTP
- DOR
- PFS
- OS
- PD-L1 expression at baseline among responders/non-responders

Lymphoma – HL (Cohort 3)

The primary efficacy endpoint for the HL cohort is CRR, defined as the proportion of subjects meeting the Revised Response Criteria for Malignant Lymphoma for a CR at any time during the study. Response for the primary analysis will be assessed by the investigator.

Key secondary endpoints in the HL cohort include:

- PFS
- OS
- ORR
- DOR
- PD-L1 expression at baseline among responders/non-responders

Additional analyses of HL efficacy endpoints based on central imaging assessment may be conducted at the end of the trial and will be considered exploratory.

Lymphoma –NHL monotherapy (Cohort 4)

The primary efficacy endpoint for the NHL monotherapy cohort is ORR, defined as the proportion of subjects meeting the IWG criteria for an OR at any time during the study. Response for the primary analysis will be assessed by the investigator.

Key secondary endpoints in the NHL cohort include:

- PFS
- OS
- DOR
- PD-L1 expression at baseline among responders/non-responders

These endpoints will also be assessed separately for subjects with relapsed / refractory MLBCL (Cohort 4A), FL (Cohort 4C + FL subjects in Cohort 4B), DLBCL (Cohort 4D + DLBCL subjects in Cohort 4B), DLBCL combo (Cohort 5) and Other (non-FL and non-DLBCL Cohort 4B subjects).

Additional analyses of NHL monotherapy efficacy endpoints based on central imaging assessment may be conducted at the end of the trial and will be considered exploratory.

Lymphoma –NHL combination therapy (Cohort 5)

The primary efficacy endpoint for the NHL combination therapy cohort is ORR, defined as the proportion of subjects meeting the IWG criteria for an OR at any time during the study. Response for the primary analysis will be assessed by the investigator.

Key secondary endpoints in the NHL cohort include:

- PFS
- OS
- DOR
- PD-L1 expression at baseline among responders/non-responders

Additional analyses of NHL combination therapy efficacy endpoints based on central imaging assessment may be conducted at the end of the trial and will be considered exploratory.

8.2.3.2 Safety Endpoints

A description of safety measures is provided in Section 4.2.3.1.

The primary safety endpoints are AEs graded using CTCAE (Version 4.0) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab (Cohorts 1 thru 4) or lenalidomide + pembrolizumab (Cohort 5), including SAEs and ECIs. Other safety endpoints include laboratory safety assessments, ECOG performance status, vital signs and physical examinations.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized subjects in each disease cohort who:

- Receive at least one dose of study treatment,
- Have a baseline disease assessment, and
- Have a post baseline disease assessment OR discontinue the trial due to PD/drug related AE

Supportive analyses will be conducted in the ITT population, defined as all randomized subjects.

For MDS cohort only, two additional subpopulations FAS/WHO-Classification and ITT/WHO-Classification will be used. These two populations have the same definition as above except for requiring the baseline disease assessment to satisfy WHO criteria.

Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data. Details on the approach to handling missing data are provided in Section 8.2.5 Statistical Methods.

8.2.4.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

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

Details on the approach to handling missing data for safety analyses are provided in Section 8.2.5 Statistical Methods.

8.2.5 Statistical Methods

Statistical testing and inference for safety analyses are described in 8.2.5.2. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 8.2.6, Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses.

8.2.5.1 Statistical Methods for Efficacy Analyses

Efficacy will be evaluated separately in each disease cohort. For the primary efficacy endpoint, the point estimate, 90% CI, and p-value for testing primary endpoint rate is greater than the historical control for each cohort will be provided using exact binomial distribution. Subjects in the primary analysis population (FAS) without response data will be counted as non-responder.

Table 17 summarizes the key efficacy analyses.

Table 17 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary 1. MDS (Cohort 1): ORR based on IWG (2006) criteria for MDS (investigator-assessed) 2. MM (Cohort 2): ORR based on IMWG criteria (investigator-assessed) 3. HL (Cohort 3): Complete Remission Rate (CRR) based IWG criteria (investigator-assessed) 4. NHL monotherapy (Cohort 4): ORR based on IWG criteria (investigator-assessed) 5. NHL combination therapy (Cohort 5): ORR based on IWG criteria (investigator-assessed)	Exact test of binomial parameter (Cohorts 1 thru 4); Descriptive statistics (Cohort 5)	FAS (P) ITT (S)	Subjects with missing data are considered non-responders
Secondary binary endpoints 1. MDS (Cohort 1): a. ORR based on IWG (2006) criteria for MDS (investigator-assessed) b. Bone marrow response by IWG criteria (investigator assessed) c. Hematologic improvement by IWG criteria (investigator-assessed) d. Cytogenetic response by IWG criteria (investigator assessed) 2. MM (Cohort 2): a. CR + sCR by IMWG criteria (investigator assessed) 3. HL (Cohort 3): a. ORR 4. NHL monotherapy (Cohort 4): none 5. NHL combination therapy (Cohort 5): none	Exact test of binomial parameter	MDS ORR: FAS/WHO-Classification (P) ITT/WHO-Classification (S) All Others: FAS (P) ITT (S)	Subjects with missing data are considered non-responders

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Secondary time-to-event endpoints 1. MDS (Cohort 1): a. OS b. DOR 2. MM (Cohort 2): a. TTP b. DOR c. PFS d. OS 3. HL (Cohort 3): a. PFS b. OS c. DOR 4. NHL monotherapy (Cohort 4): a. PFS b. OS c. DOR 5. NHL combination therapy (Cohort 5): a. PFS b. OS c. DOR	Summary statistics using Kaplan-Meier method	OS, TTP, PFS: FAS (P) ITT (S) DOR: all responders	Censored at last assessment
Secondary descriptive analyses Response by PD-L1 expression change before and after HMA treatment in each population separately: 1. MDS (Cohort 1) 2. MM (Cohort 2) 3. HL (Cohort 3) 4. NHL monotherapy (Cohort 4) 5. NHL combination therapy (Cohort 5)	Descriptive statistics	FAS (P) ITT (S)	
P=Primary approach; S=Supportive approach; FAS=Full Analysis Set; ITT=Intention to treat			

In addition to the analyses specified above for overall cohort 4, separate efficacy analyses, descriptive in nature, will be performed with subjects with relapsed / refractory MLBCL (Cohort 4A), FL (Cohort 4C + FL subjects in Cohort 4B), DLBCL (Cohort 4D + DLBCL subjects in Cohort 4B), and Other (Cohort 4B excluding FL and DLBCL subjects).

The strategy to address multiplicity issues with regard to multiple efficacy endpoints is described in Section 8.2.6, Multiplicity and Section 8.2.9, Interim Analyses.

Exploratory objectives in each cohort will be evaluated using descriptive statistics.

8.2.5.2 Statistical Methods for Safety Analyses

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

Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate. The 95% CI for the incidence rate of Grade 2 or higher adverse events with an immune etiology and the incidence rate of Grade 4/5 AEs will be provided as appropriate.

Safety analysis will be performed separately for Cohorts 1 through 5 as well as the subtypes within Cohort 4.

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.2.5.3.1 Demographic and Baseline Characteristics

Baseline characteristics will be assessed by the use of tables and/or graphs for each cohort. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, 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 treatment either by descriptive statistics or categorical tables.

8.2.6 Multiplicity

The false positive rate for testing the primary efficacy endpoint in each disease cohort (MDS, MM, HL, and NHL monotherapy is controlled at 0.05 (1-sided) for each cohort. No additional multiplicity adjustment is required because each disease cohort will be evaluated independently. No statistical testing will be performed for Cohort 5 (NHL combination therapy).

8.2.7 Sample Size and Power Calculations

The calculation of power and sample size for each cohort does not account for an interim analysis.

MDS (Cohort 1)

With approximately 25 subjects with intermediate-1, intermediate-2, or high risk MDS, the study has ~80% power to detect a 20% difference in ORR under the null hypothesis of ORR=10% with a one-sided type I error rate of 5% if the true ORR is 30%. Success for this hypothesis requires at least 6/25 responses. The null hypothesis ORR of 10% is based on the historic response rate in phase I/II trials of chemotherapy in MDS (Table 18). The actual number of subjects enrolled may be larger than 25 to ensure that at least 25 subjects are evaluable for analysis.

MM (Cohort 2)

With approximately 28 subjects with MM, the study has ~80% power to detect a 25% difference in ORR under the null hypothesis of ORR=25% with a one-sided type I error rate of 5% if the true ORR is 50%. Success for this hypothesis requires at least 12/28 responses. The null hypothesis ORR of 25% is based on the historic OR rate for MM (Table 18). The actual number of subjects enrolled may be larger than 28 to ensure that at least 28 subjects are evaluable for analysis.

Lymphoma – HL (Cohort 3)

With approximately 25 subjects with HL, the study has ~80% power to detect a 20% difference in CRR under the null hypothesis of CRR=10% with a one-sided type I error rate of 5% if the true CRR is 30%. Success for this hypothesis requires at least 6/25 responses. The null hypothesis CRR of no greater than 10% is estimated based on CR rate observed in prior studies of single agents in relapsed / refractory HL combined with the assumption that the HL population enrolled in the current trial would have failed prior brentuximab vedotin treatment (Table 18). The actual number of subjects enrolled may be larger than 25 to ensure that at least 25 subjects are evaluable for analysis.

Table 18 Historic Response Rates for Hematologic Malignancies

Disease	Reference	Agents	N	Response rate	Timing of Response Assessment
MDS	Bhatnagor [91]	Decitabine	13	0% ORR	Best objective response
	Silverman [92]	5-Aza	191	23% ORR	Best objective response
MM	Siegel [93]	Carfilzomib	257	23.7%	Best objective response
	Richardson [94]	Pomalidomide w/ low-dose Dexamethasone	113	33%	Best objective response
HL	Devizzi [95]	Vinorelbine	22	14% CR	Best objective response
	Savage [96]	Gemcitabine	29	0% CR	Best objective response
	Younes [39]	Brentuximab	102	34% CR	Best objective response
NHL	Churpek [97]	Epothilone	51	27% ORR	Best objective response
	Goy [98]	Bortezomib	27	19%	Best objective response
	Wiernik [54]	Lenalidomide	49	35%	Best objective response

Lymphoma –NHL monotherapy (Cohort 4)

With approximately 78 subjects with NHL, the study has ~80% power to detect a 14% difference in ORR under the null hypothesis of ORR=25% with a one-sided type I error rate of 5% if the true ORR is 39%. Success for this hypothesis requires at least 27/78 responses. The null hypothesis ORR of 25% is based on the historic OR rate from chemotherapy trials in NHL and MLBCL (Table 18). The actual number of subjects enrolled may be larger than 78 to ensure that at least 78 subjects are evaluable for analysis.

The maximum half-width of the 2-sided 90% exact CI will be 16% for the DLBCL and FL subtypes with a targeted number of 30 subjects each, and wider CIs for the MLBCL and Other subtypes.

Lymphoma –NHL combination therapy (Cohort 5)

Approximately 30-66 subjects will be evaluated in this cohort, depending on the number of dose levels of lenalidomide assessed during safety run-in. Subjects in the safety run-in treated at the RP2D will be included in the dose expansion evaluation of 30 subjects for efficacy (see Section 5.2.1.3 for details).

The maximum half-width of the 2-sided 90% exact CI will be 16% with a targeted number of 30 subjects. Table 19 describes examples of 90% CIs across a possible range of ORRs.

Table 19 Precision (90% Confidence Intervals) for range of observed ORR (33% - 83%)

Number of responses/Number of treated subjects (ORR)	90% 2-sided Confidence Interval*
10/30 (33%)	(19, 50)
15/30 (50%)	(34, 66)
20/30 (67%)	(50, 81)
25/30 (83%)	(68, 93)
*exact (Clopper-Pearson) confidence limit for the binomial proportion	

8.2.8 Subgroup Analyses and Effect of Baseline Factors

No other subgroup analysis is planned.

8.2.9 Interim Analyses

Unless otherwise indicated, an interim analysis will be performed if fewer than 10 subjects are enrolled in a cohort 6 months after the time that the first subject is treated in the respective cohort. The interim analysis will take place after 10 subjects have reached the Week 12 assessment. Results will be reviewed by the study team.

MDS/HL (Cohorts 1 and 3)

For the MDS and HL cohorts, if an interim analysis is conducted and 1 or fewer subjects out of the first 10 subjects with a post-baseline (Week 12) assessment/imaging scan have a confirmed or unconfirmed primary endpoint response (OR or CR respectively), then enrollment will be paused until response data for the subsequent (Week 24) assessment/imaging scan are reviewed for all subjects already enrolled in the trial (including those enrolled who have not reached the first post-baseline assessment/imaging scan). Enrollment will be resumed if the observed responses (confirmed or unconfirmed) for the primary endpoint in the respective cohort among subjects who are still enrolled in the trial indicates that the probability of the response for the primary endpoint >10% is at least 80%

(e.g., ≥3/16 confirmed or unconfirmed responses). See Section 12.8 for further details regarding the decision rules for resuming enrollment following the interim analysis. If the required number of responses is observed, enrollment will be resumed in the respective cohort regardless of whether all subjects have had disease assessments through Week 24. Table 20 provides the operating characteristics for the interim analysis rule in MDS and HL.

Table 20 Operating Characteristics of Interim Analysis Rule for MDS and HL – Pause Enrollment if ≤1/10 Subjects Achieve an Overall Response (MDS) or a Complete Response (HL); Final Analysis with 25 Subjects

True ORR	Probability of Pausing Enrollment	Probability of Passing the IA and Achieving Study Success
10%	0.73	0.03
15%	0.54	0.14
20%	0.37	0.34
25%	0.25	0.55
30%	0.15	0.74
35%	0.09	0.87
40%	0.05	0.93

MM (Cohort 2) and NHL (Cohorts 4A and 4B)

For the MM (Cohort 2) and combined MLBCL and PD-L1 positive NHL Cohorts 4A and 4B, respectively), if an interim analysis is conducted and 3 or fewer subjects out of the first 10 subjects with a post-baseline (Week 12) imaging scan have a confirmed or unconfirmed primary endpoint response, then enrollment will be paused until response data for the subsequent imaging scan (Week 24) are reviewed for all subjects already enrolled in the trial (including those enrolled who have not reached the first post-baseline scan). Enrollment will be resumed if the observed responses (confirmed or unconfirmed) for the primary endpoint in the respective cohort among subjects who are still enrolled in the trial indicates that the probability of the response for the primary endpoint >25% is at least 80% (e.g., ≥5/16 confirmed or unconfirmed responses). See Section 12.8 for further details regarding the decision rules for resuming enrollment following the interim analysis. If the required number of responses is observed, enrollment will be resumed in the respective cohort regardless of whether all subjects have had disease assessments through Week 24. Table 21 provides the operating characteristics for this interim analysis rule in MM and MLBCL and PD-L1 Positive NHL Cohorts, respectively.

No interim analysis is planned for subjects with unselected PD-L1 status with relapsed / refractory FL (Cohort 4C) or DLBCL (Cohort 4D).

Table 21 Operating Characteristics of Interim Analysis Rule for MLBCL and PD-L1 Positive NHL subjects (Cohorts 4A and 4B) and MM (Cohort 1)– Pause Enrollment if ≤3/10 Subjects Achieve an Overall Response (PR or better); Final Analysis with 28 Subjects

True ORR	Probability of Pausing Enrollment	Probability of Passing the IA and Achieving Study Success
25%	0.78	0.02
30%	0.65	0.08
35%	0.51	0.20
40%	0.38	0.37
45%	0.27	0.57
50%	0.17	0.74
55%	0.10	0.86
60%	0.05	0.93

8.2.10 Compliance (Medication Adherence)

A day within the study will be considered an On-Therapy day if the subject receives any dose of study medication. The number of Days Should be on Therapy is the total number of days from the first day of study medication to the date of the last dose of study medication. For each subject, percent compliance will then be calculated (separately for pembrolizumab and lenalidomide for Cohort 5) using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100.$$

Summary statistics will be provided on percent compliance for the FAS population.

8.2.11 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 22.

Table 22 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
pembrolizumab (MK-3475) 50 mg	Lyophilized Powder for Injection	Provided centrally by the Sponsor (non-US).
pembrolizumab (MK-3475) 100 mg/ 4mL	Solution for Injection	Provided centrally by the Sponsor (US only).
lenalidomide 5, 10, 15, 20, and 25 mg	Capsules for Oral Administration	Provided centrally by the Sponsor except in regions that can source locally. Not all dose strengths will be made available centrally from the Sponsor. Reference the study Pharmacy Manual.

9.2 Packaging and Labeling Information

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

Vials will be provided in an open label fashion for subject dosing.

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 to treatment. Drug identity (name, strength) 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.

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:

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a

Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control

procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The sponsor 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 discarding 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 Amendments Act (FDAAA) of 2007, and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor

of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialregister.eu or other local registries. 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 FDAAA or the EMA clinical trials directive 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 FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

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 by the Sponsor.

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.

11.0 LIST OF REFERENCES

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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

i. 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.

ii. 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.

iii. 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

bb. 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.

cc. 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.

dd. 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.

ee. 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

ff. 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.

gg. 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.

hh. 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 DNA, blood, lymph node and bone marrow specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug. The DNA, blood, lymph node and bone marrow specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug 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, 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 Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

Subjects are not required to participate in Future Biomedical Research in order to participate in the main trial. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main trial.

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

a. Future Biomedical Research Specimen Collections

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

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

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

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

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

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

5. Biorepository Specimen Usage

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

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens.

Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in FBR protocol and consent. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

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 writing to the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact Merck using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided by Merck 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 Merck to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

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

8. Data Security

Separate databases for specimen information and for results from Future Biomedical Research will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using

network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only and will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Gender, Ethnicity and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

For FBR, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

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

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

12. Self-Reported Ethnicity

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

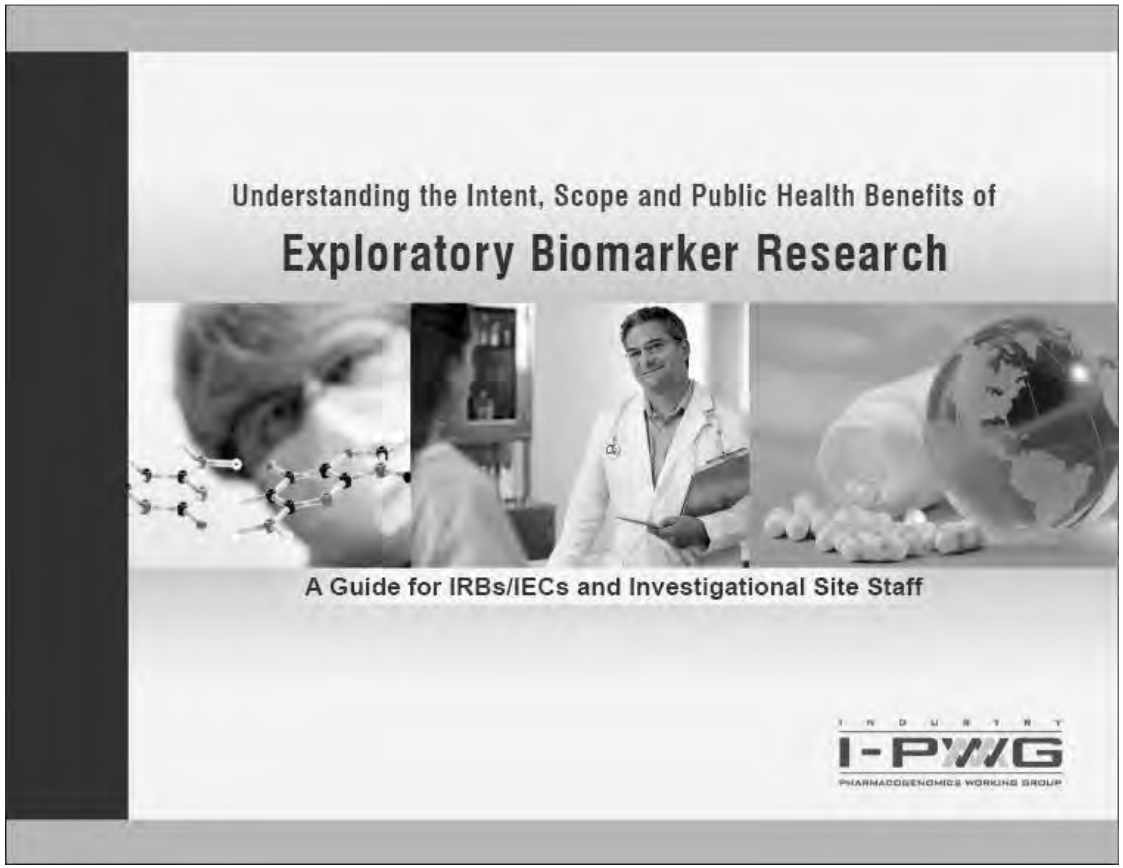
13. Questions

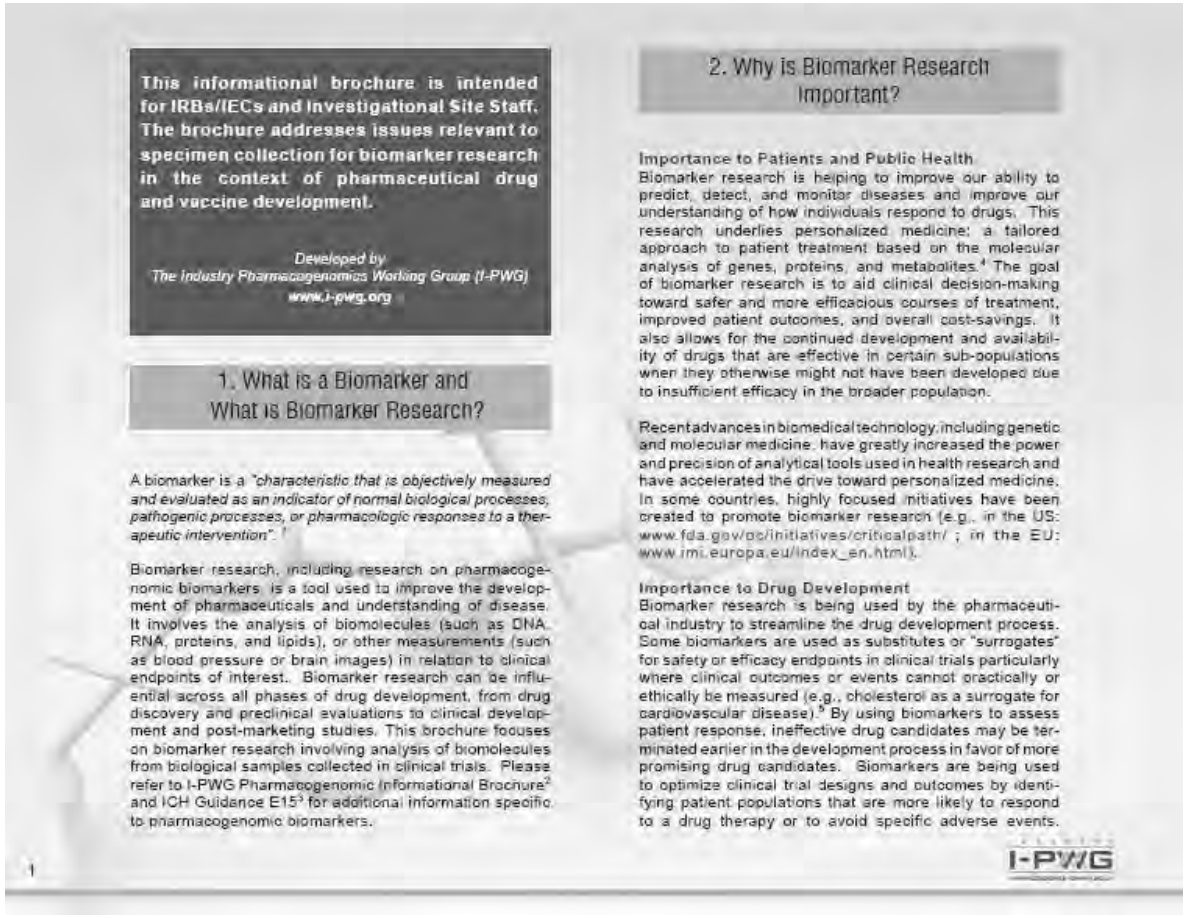
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. References

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

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





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

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

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

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

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

2. Why is Biomarker Research Important?

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

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

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

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

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3,5-24]

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

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

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

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

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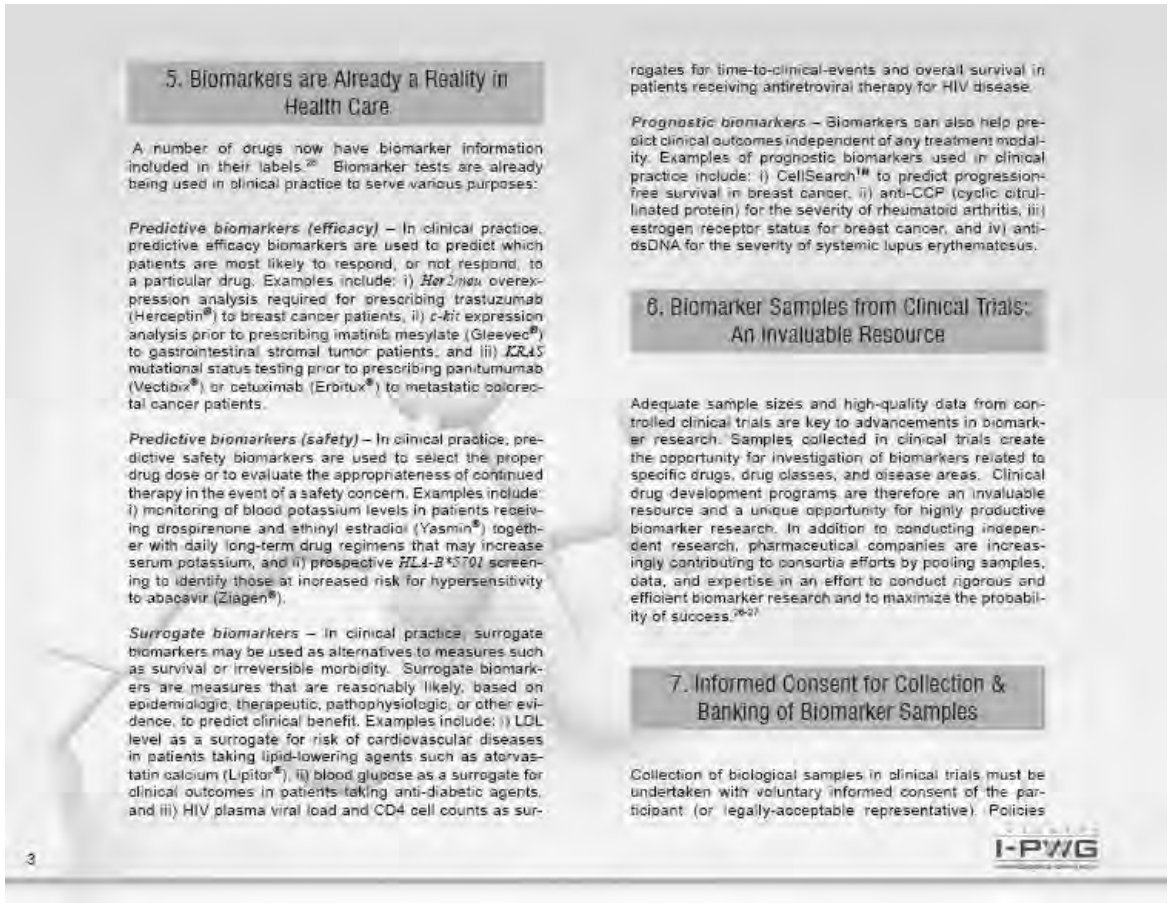


5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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.[29-31]

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

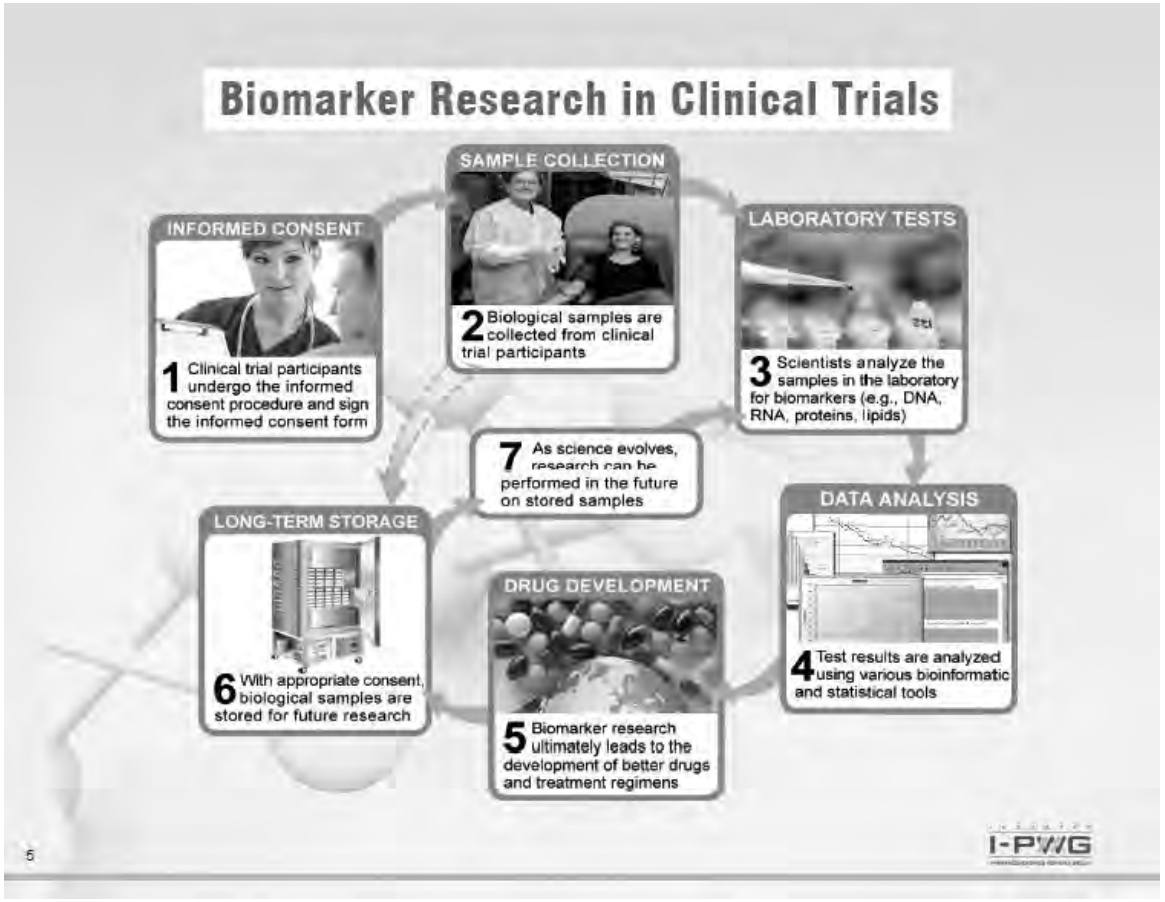
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants 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.[9, 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:[29]

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.[9] 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.[35]

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


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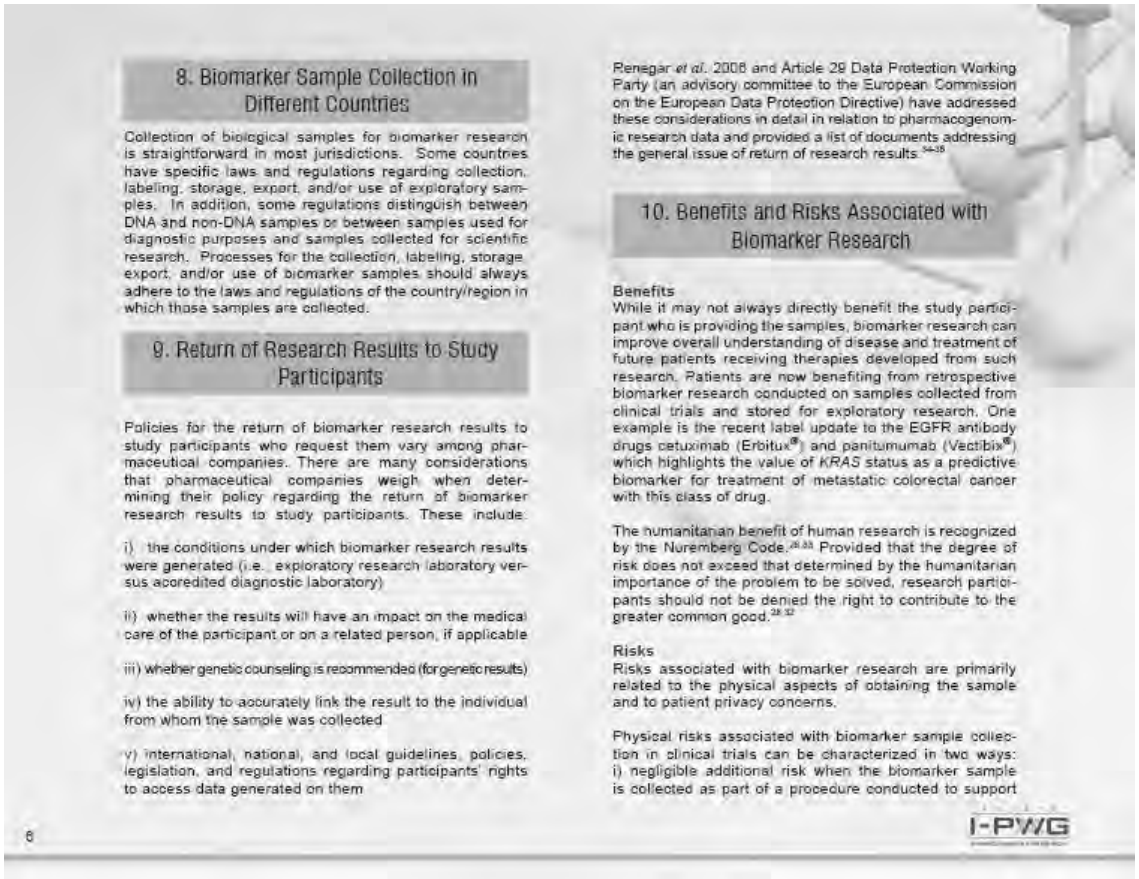

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

Renegar *et al*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-38]

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [21]

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).[18-20]

12. Where to Get More Information?

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

13. What is I-PWG?

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

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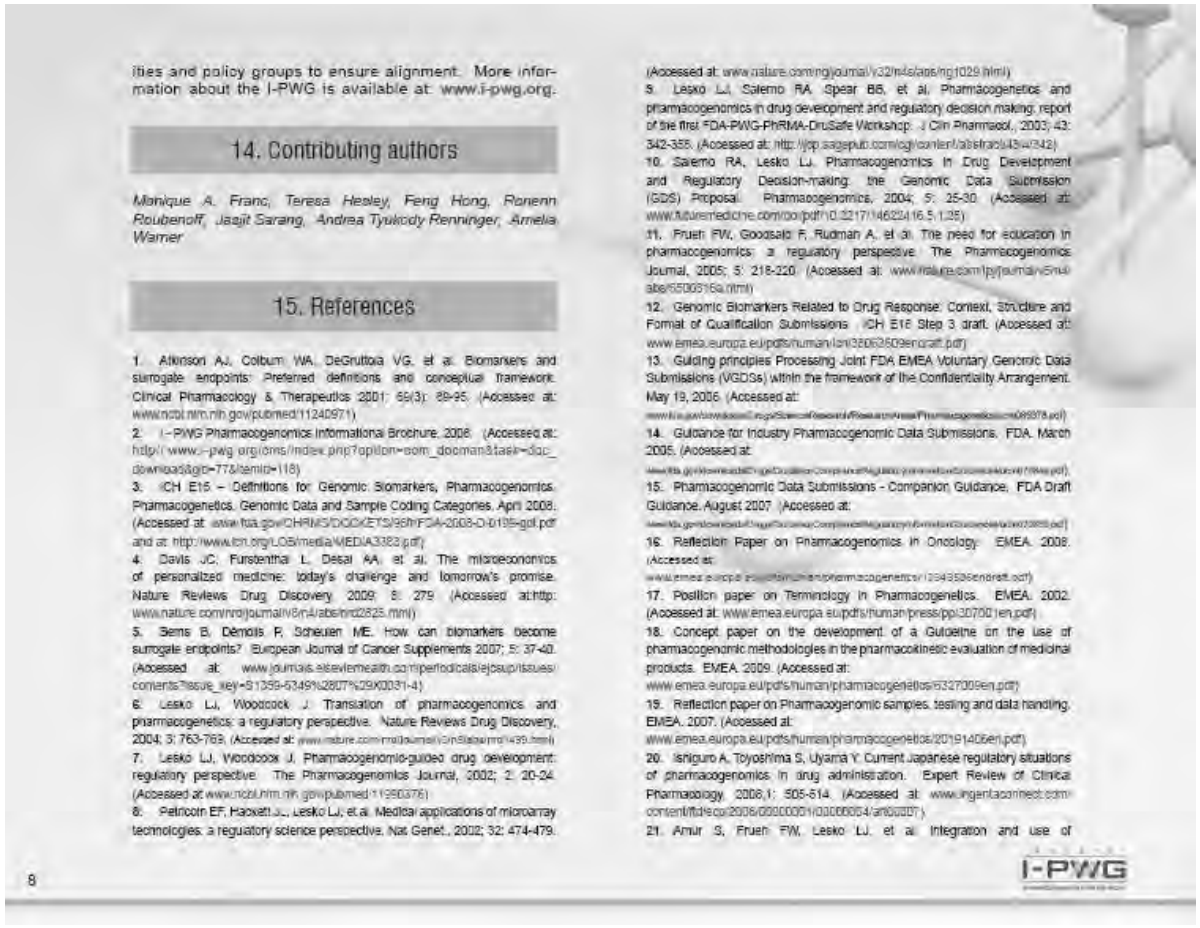

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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

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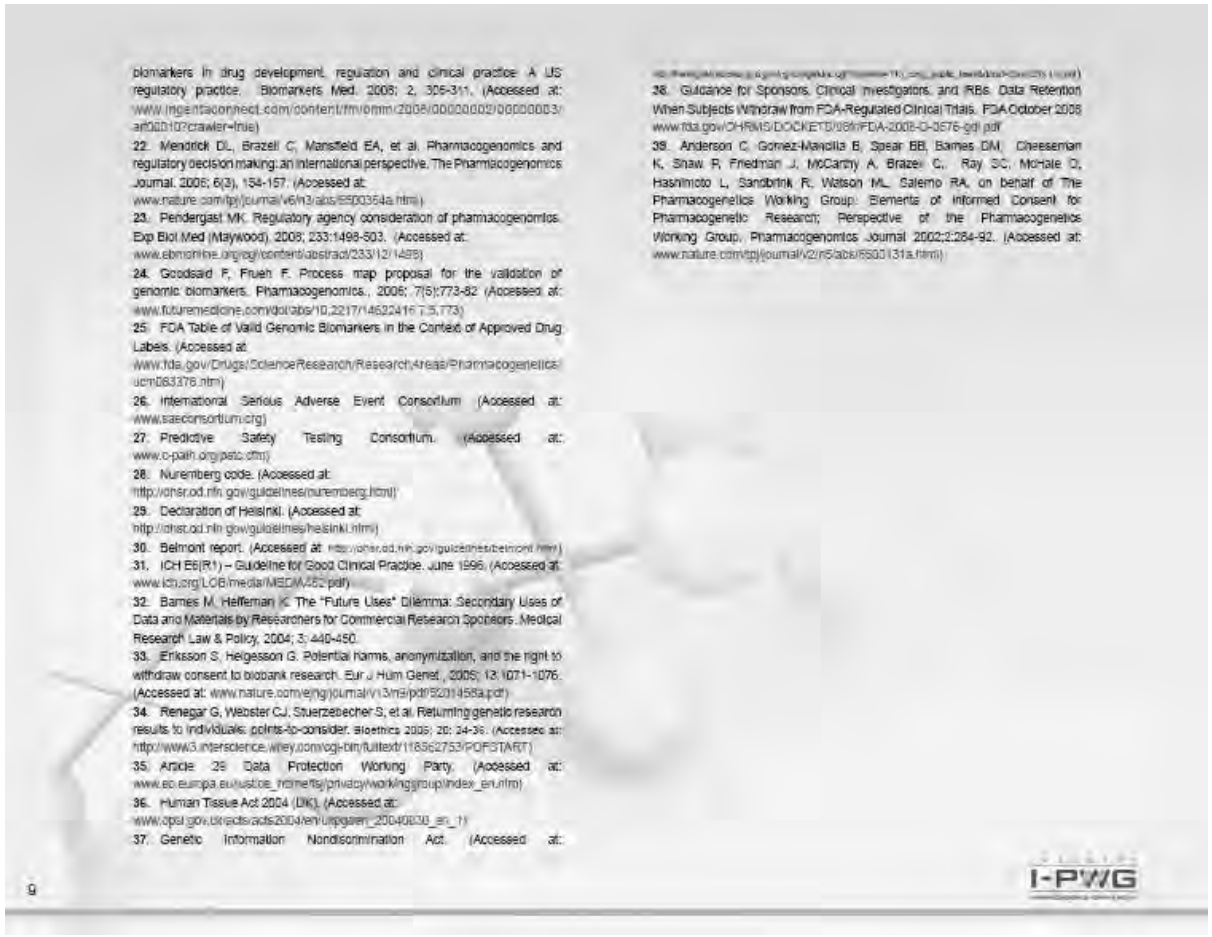

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12.4 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	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	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead.

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

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

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

12.6 Multiple Myeloma Diagnostic Criteria

Durie, Seminars in Oncology, Vol 13, No 3 (September), 1986:pp300-309:

Table 1. Diagnostic Criteria[1,4,6,7]

1. Criteria for Diagnosis of Multiple Myeloma

   Major criteria

   I. Plasmacytoma on tissue biopsy.

   II. Bone marrow plasmacytosis with >30% plasma cells.

   III. Monoclonal globulin spike on serum electrophoresis exceeding 3.5 g/dL for IgG peaks or 2.0 g for IgA peaks, ≥1.0 g/24 h of κ or λ light chain excretion on urine electrophoresis in the absence of amyloidosis.

   Minor criteria

   a. Bone marrow plasmacytosis with 10% to 30% plasma cells.

   b. Monoclonal globulin spike present, but less than the levels defined above.

   c. Lytic bone lesions.

   d. Normal IgM <50 mg, IgA <100 mg, or IgG <600 mg/dL.

Diagnosis will be confirmed when any of the following features are documented in symptomatic patients with clearly progressive disease. The diagnosis of myeloma requires a minimum of one major + one minor criterion or three minor criteria that must include a + b

1. I + b, I + c, I + d (I + a not sufficient)
2. II + b, II + c, II + d.
3. III + a, III + c, III + d.
4. a + b + c, a + b + d.

12.7 Disease Response Criteria

12.7.1 MDS Disease Response Criteria

Cheson et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006; 108:419-425.

Criteria for MDS disease assessment:

Table 3. Proposed modified International Working Group response criteria for altering natural history of MDS[7]

Category	Response criteria (responses must last at least 4 wk)
Complete remission	Bone marrow: < 5% myeloblasts with normal maturation of all cell lines*
	Persistent dysplasia will be noted*†
	Peripheral blood‡
	Hgb > 11 g/dL
	Platelets > 100 × 10^9/L
	Neutrophils > 1.0 × 10^9/L†
	Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except:
	Bone marrow blasts decreased by > 50% over pretreatment but still > 5%
	Cellularity and morphology not relevant
Marrow CR†	Bone marrow: < 5% myeloblasts and decrease by > 50% over pretreatment†
	Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following:
	Return to pretreatment bone marrow blast percentage
	Decrement of > 50% from maximum remission/response levels in granulocytes or platelets
	Reduction in Hgb concentration by > 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete
	Disappearance of the chromosomal abnormality without appearance of new ones
	Partial
	At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with:
	Less than 5% blasts: > 50% increase in blasts to > 5% blasts
	5%-10% blasts: > 50% increase to > 10% blasts
	10%-20% blasts: > 50% increase to > 20% blasts
	20%-30% blasts: > 50% increase to > 30% blasts
	Any of the following:
	At least 50% decrement from maximum remission/response in granulocytes or platelets
	Reduction in Hgb by > 2 g/dL
	Transfusion dependence
Survival	Endpoints:
	Overall: death from any cause
	Event free: failure or death from any cause
	PFS: disease progression or death from MDS
	DFS: time to relapse
	Cause-specific death: death related to MDS

Deletions to IWG response criteria are not shown.
To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.
*Dysplastic changes should consider the normal range of dysplastic changes (modification).[41]
†Modification to IWG response criteria.
‡In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Criteria for MDS hematologic improvement assessment:

Table 4. Proposed modified International Working Group response criteria for hematologic improvement[7]

Hematologic improvement*	Response criteria (responses must last at least 8 wk)†
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, $< 100 \times 10^9$/L)	Absolute increase of $\geq 30 \times 10^9$/L for patients starting with $> 20 \times 10^9$/L platelets Increase from $< 20 \times 10^9$/L to $> 20 \times 10^9$/L and by at least 100%†
Neutrophil response (pretreatment, $< 1.0 \times 10^9$/L)	At least 100% increase and an absolute increase $> 0.5 \times 10^9$/L†
Progression or relapse after HI‡	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by ≥ 1.5 g/dL Transfusion dependence

Deletions to the IWG response criteria are not shown.
To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement.
*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart (modification).
†Modification to IWG response criteria.
‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

12.7.2 Multiple Myeloma Disease Response Criteria

Durie et al. International uniform response criteria for multiple myeloma. *Leukemia.* 2006; 20:1467-1473.

Criteria for multiple myeloma disease assessment:

Table 5 International Myeloma Working Group uniform response criteria: CR and other response categories

Response subcategory	*Response criteria*[a]
sCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h If the serum and urine M-protein are unmeasurable,[d] a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.
[a]All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.
[b]Confirmation with repeat bone marrow biopsy not needed.
[c]Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of >4:1 or <1:2.
[d]Refer to Table 4 for definitions of measurable disease.

Table 6 International Myeloma Working Group uniform response criteria: disease progression and relapse

Relapse subcategory	*Relapse criteria*
Progressive disease[a] To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive Disease: requires any one or more of the following: Increase of ⩾25% from baseline in Serum M-component and/or (the absolute increase must be ⩾0.5 g/dl)[b] Urine M-component and/or (the absolute increase must be ⩾200 mg/24 h Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dl. Bone marrow plasma cell percentage: the absolute % must be ⩾10%[c] Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[b] It is not used in calculation of time to progression or progression-free survival but is listed here as as something that can be reported optionally or for use in clinical practice 1 Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.5 mg/dl) [2.65 mmol/l] 4. Decrease in hemoglobin of ⩾2 g/dl [1.25 mmol/l] (see Table 3 for further details) 5. Rise in serum creatinine by 2 mg/dl or more [177 μmol/l or more]
Relapse from CR[a](To be used only if the end point studied is DFS)[d]	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ⩾5% plasma cells in the bone marrow[c] Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see below)

Abbreviations: CR, complete response; DFS, disease-free survival.
[a]All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.
[b]For progressive disease, serum M-component increases of ⩾1 gm/dl are sufficient to define relapse if starting M-component is ⩾5 g/dl.
[c]Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.
[d]For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

12.7.3 Lymphoma Disease Response Criteria

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

Criteria for lymphoma disease assessment:

Table 2. Response Definitions for Clinical Trials

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

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

12.8 Interim Analysis Decision Rules

The table below describes the detailed Go/No-Go decision rules for resuming enrollment (GO = Resume enrollment; NG = do not resume enrollment) based on the number of subjects enrolled and number of responses following the interim analysis.

MDS/HL	Number of subjects enrolled at IA	
Number of Responses	10 to 14	15 to 20
0	NG	NG
1	NG	NG
2	GO	NG
3+	GO	GO

MM and MLBCL/PD-L1+ NHL	Number of subjects enrolled at IA			
Number of Responses	10 to 11	12 to 15	16 to 18	19 to 20
0 to 3	NG	NG	NG	NG
4	GO	NG	NG	NG
5	GO	GO	NG	NG
6	GO	GO	GO	NG
7	GO	GO	GO	GO

GO = Resume enrollment; NG = do not resume enrollment

12.9 Dose Timing Table for Lenalidomide + Pembrolizumab Combination Treatment

Cycle	Weeks	Day	Pembrolizumab 200 mg	Lenalidomide RP2D
Cycle 1	1-4	1	Dose 1	Days 1-21 + 7 days off
		8		
		15		
		22	Dose 2	
Cycle 2	5-8	1		Days 1-21 + 7 days off
		8		
		15	Dose 3	
		22		
Cycle 3	9-12	1		Days 1-21 + 7 days off
		8	Dose 4	
		15		
		22		
Cycle 4	13-16	1	Dose 5	Days 1-21 + 7 days off
		8		
		15		
		22	Dose 6	
Cycle 5	17-20	1		Days 1-21 + 7 days off
		8		
		15	Dose 7	
		22		
Cycle 6	21-24	1		Days 1-21 + 7 days off
		8	Dose 8	
		15		
		22		
Cycle 7	25-28	1	Dose 9	Days 1-21 + 7 days off
		8		
		15		
		22	Dose 10	
Cycle 8	29-32	1		Days 1-21 + 7 days off
		8		
		15	Dose 11	
		22		
Cycle 9	33-36	1		Days 1-21 + 7 days off
		8	Dose 12	
		15		
		22		
Cycle 10	37-40	1	Dose 13	Days 1-21 + 7 days off
		8		
		15		
		22	Dose 14	
Cycle 11	41-44	1		Days 1-21 + 7 days off
		8		
		15	Dose 15	
		22		

Cycle	Weeks	Day	Pembrolizumab 200 mg	Lenalidomide RP2D
Cycle 12	45-48	1		Days 1-21 + 7 days off
		8	Dose 16	
		15		
		22		
Cycle 13	49-52	1	Dose 17	Days 1-21 + 7 days off
		8		
		15		
		22	Dose 18	
Cycle 14	53-56	1		Days 1-21 + 7 days off
		8		
		15	Dose 19	
		22		
Cycle 15	57-60	1		Days 1-21 + 7 days off
		8	Dose 20	
		15		
		22		
Cycle 16	61-64	1	Dose 21	Days 1-22 + 7 days off
		8		
		15		
		22	Dose 22	
Cycle 17	65-68	1		Days 1-21 + 7 days off
		8		
		15	Dose 23	
		22		
Cycle 18	69-72	1		Days 1-21 + 7 days off
		8	Dose 24	
		15		
		22		
Cycle 19	73-76	1	Dose 25	Days 1-21 + 7 days off
		8		
		15		
		22	Dose 26	
Cycle 20	77-80	1		Days 1-21 + 7 days off
		8		
		15	Dose 27	
		22		
Cycle 21	81-84	1		Days 1-21 + 7 days off
		8	Dose 28	
		15		
		22		
Cycle 22	85-88	1	Dose 29	Days 1-21 + 7 days off
		8		
		15		
		22	Dose 30	

Cycle	Weeks	Day	Pembrolizumab 200 mg	Lenalidomide RP2D
Cycle 23	89-92	1		Days 1-21 + 7 days off
		8		
		15	Dose 31	
		22		
Cycle 24	93-96	1		Days 1-21 + 7 days off
		8	Dose 32	
		15		
		22		
Cycle 25	97-100	1	Dose 33	Days 1-21 + 7 days off
		8		
		15		
		22	Dose 34	
Cycle 26	101-104	1		Days 1-21 + 7 days off
		8		
		15	Dose 35	
		22		

12.10 Lenalidomide Pregnancy Prevention Plan for Subjects in Clinical Trials

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving lenalidomide within a clinical trial. The following PPP documents are included:

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 12.10.1) provides the following information:
   - Potential risks to the fetus associated with lenalidomide exposure
   - Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
   - Requirements for counseling of all subjects receiving lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
   - Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving lenalidomide in the study
   - Pregnancy testing requirements for subjects receiving lenalidomide who are FCBP
2. The Lenalidomide Education and Counseling Guidance Document for each gender (female and male; Sections 12.10.6 and Section 12.10.7, respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of lenalidomide. A copy of this document must be maintained in the subject's records for each dispense.
3. The Lenalidomide Information Sheet (Section 12.10.8) will be given to each subject receiving lenalidomide. The subject must read this document prior to starting lenalidomide and each time the subject receives a new supply of lenalidomide.

12.10.1 Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

12.10.1.1 Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. A teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

12.10.1.2 Definition of Females of Childbearing Potential

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least

24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

12.10.1.3 Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

12.10.2 Counseling

12.10.2.1 Females of Childbearing Potential

For a FCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting lenalidomide, throughout the entire duration of lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence lenalidomide as soon as it is dispensed following a negative pregnancy test
- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 12.10.4) and in the Informed Consent
- She acknowledges that she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

12.10.2.2 Females Not of Childbearing Potential

For a FNCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

12.10.2.3 Males

Traces of lenalidomide have been found in semen. Male subjects taking lenalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.

12.10.3 Contraception

12.10.3.1 Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while taking lenalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of lenalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - IUD
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - Tubal ligation
  - Partner’s vasectomy
- Examples of additional effective methods:
  - Male condom

- Diaphragm
- Cervical Cap

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

12.10.3.2 Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

12.10.4 Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.

12.10.5 Pregnancy Precautions for Lenalidomide Use

12.10.5.1 Before Starting Lenalidomide

12.10.5.1.1 Female Subjects of Childbearing Potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting lenalidomide.

12.10.5.1.2 Male Subjects

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

12.10.5.2 During and After Study Participation

12.10.5.2.1 Female Subjects

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.

- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a subject, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

12.10.5.2.2 Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving lenalidomide, during dose interruptions or for at least 28 days after the last dose of lenalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking lenalidomide, the Investigator must be notified immediately.

12.10.6 Lenalidomide Education and Counseling Guidance Document for Female Subjects

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- ☐ NOT FCBP

12.10.6.1 Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. Females of childbearing potential must agree not to become pregnant while taking lenalidomide.
   - ☐ That the required pregnancy tests performed are negative.
   - ☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving lenalidomide, while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide).

     One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

     – Examples of highly effective methods:
       - o IUD

- Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
- Tubal ligation
- Partner's vasectomy

– Examples of additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of lenalidomide and at the last dose of lenalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

– Two pregnancy tests will be performed prior to receiving lenalidomide, one within 10 to 14 days, and a second within 24 hours of the start of lenalidomide.

– Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking lenalidomide if menstrual cycles are regular.

– Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking lenalidomide if menstrual cycles are irregular.

– If the subject missed a period or has unusual menstrual bleeding.

– When the subject is discontinued from the study and at Day 28 after the last dose of lenalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of lenalidomide.

☐ The subject confirmed that she will stop taking lenalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will never share lenalidomide with anyone else.

☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

- ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
- ☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

12.10.6.2 Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject has not and will never share lenalidomide with anyone else.
   - ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
   - ☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.
2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving lenalidomide, while receiving lenalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date:
_____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

12.10.7 Lenalidomide Education and Counseling Guidance Document for Male Subjects

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject confirmed that he has not impregnated his female partner while in the study.
   - ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking lenalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The subject has not and will never share lenalidomide with anyone else.
   - ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking lenalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
   - ☐ The subject confirmed that he will return unused lenalidomide capsules to the study doctor.
2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

12.10.8 Lenalidomide Information Sheet

For subjects enrolled in clinical research studies

Please read this Lenalidomide Information Sheet before you start taking lenalidomide and each time you get a new supply. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

1. **Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects.

   If you are a female who is able to become pregnant:

   - **Do not take lenalidomide if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting lenalidomide
     - while taking lenalidomide
     - during breaks (dose interruptions) of lenalidomide
     - for at least 28 days after the last dose of lenalidomide
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days prior to the first dose of lenalidomide
     - 24 hours prior to the first dose of lenalidomide
     - weekly for the first 28 days
     - if you have regular menstrual periods: every 28 days after the first month
     - if you have irregular menstrual periods: every 14 days after the first month
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking lenalidomide if you become pregnant while taking lenalidomide**
     - If you suspect you are pregnant at any time during the study, you must stop lenalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation.

- **Do not breastfeed while taking lenalidomide and for at least 28 days after the last dose of lenalidomide**
- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not able to become pregnant:

In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

A small amount of lenalidomide is found in human semen. The risk to an unborn baby in females whose male partner is receiving lenalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking lenalidomide
  - During breaks (dose interruptions) of lenalidomide
  - For at least 28 days after the last dose of lenalidomide
- **Male subjects should not donate sperm or semen** while taking lenalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of lenalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

2. **All subjects:**

- **Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
- **Do not donate blood** while you take lenalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of lenalidomide.
- **Do not break, chew, or open lenalidomide capsules at any point.**
- You will get no more than a 28-day supply of lenalidomide at one time.
- Return unused lenalidomide capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

12.11 List of Abbreviations

Abbreviation/Term	Definition
5-Aza	5-Azacytidine
ABC	Activated B-cell-like
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
Allo-SCT	Allogeneic stem cell transplantation
ALT	Alanine transferase
AML	Acute myeloid leukemia
aPTT	Activated partial thromboplastin time
ASaT	All Subjects as Treated
AST	Aspartate transferase
auto-SCT	Autologous stem-cell transplantation
β-HCG	Beta human chorionic gonadotropin
CBC	Complete blood cell 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
CRAB	Hypercalcemia, renal failure, anemia, or bone destruction
CrCl	Creatinine clearance
CRF	Case report form
CRR	Complete response rate
CSR	Clinical Study Report
CSR CI	Clinical Study Report Coordinating Investigator
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocytes
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
D	De-escalate
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DU	Current dose level is considered unacceptably toxic
E	Escalate
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ERC	Ethics Review Committee
EU	European Union
FAB	French-American-British
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration

Abbreviation/Term	Definition
FDAAA	Food and Drug Administration Amendments Act
FEF	Forced expiratory flow
FL	Follicular lymphoma
FLC	Free light chain
FT3	Free triiodothyronine
FVC	Forced vital capacity
GCB	Germinal center B-cell-like
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GFR	Glomerular filtration rate
GM-CSF	Granulocyte/macrophage colony stimulating factor
GVHD	Graft-versus-host-disease
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HMA	Hypomethylating agent
IB	Investigator's Brochure
ICH	International Council for Harmonization
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMiD	Immunomodulatory imide drug
IMWG	International Myeloma Working Group
INR	International Normalized Ratio
IPSS	International Prognostic Scoring System
IPSS-R	Revised International Prognostic Scoring System
irAE	Immune-related adverse event
IRB	Institutional Review Board
IRF	Interferon regulatory factor
ITSM	Immunoreceptor tyrosine-based switch motif
ITT	Intention to Treat
IUD	Intrauterine device
IV	Intravenous
IWG	International Working Group
LDH	Lactate dehydrogenase
MDS	Myelodysplastic syndrome
MLBCL	Mediastinal large B-cell lymphoma
MM	Multiple myeloma
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival

Abbreviation/Term	Definition
OTC	Over-the-counter
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
PEF	Peak expiratory flow
PFS	Progression-free survival
PGt	Pharmacogenetic
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/pharmacodynamic
PMLBCL	Primary mediastinal large B-cell lymphoma
POEMS	Polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes
PR	Partial response
Protocol CI	Protocol Coordinating Investigator
PT	Prothrombin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
R-CHOP-21	Rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone every 3 weeks
REMS	Risk Evaluation and Mitigation Strategy
RNA	Ribonucleic acid
RP2D	Recommended Phase II dose
S	Stay
SAE	Serious adverse events
SAP	Statistical Analysis Plan
sCR	Stringent complete response
SCT	stem cell transplant
SD	Stable disease
SFU	Survival follow-up
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard Operating Procedures
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid stimulating hormone
TTP	Time to progression
ULN	Upper limit of normal
US	United States
WBC	White blood cell count
WHO	World Health Organization

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	SIGNATURE	DATE
_____	_____	_____

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	SIGNATURE	DATE
_____	_____	_____