Official Protocol Title:	Phase Ib Trial of Pembrolizumab (MK-3475) in Combination with Dinaciclib (MK-7965) in Subjects with Hematologic Malignancies (KEYNOTE-155)
NCT number:	NCT02684617
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TITLE:

Phase Ib Trial of Pembrolizumab (MK-3475) in Combination with Dinaciclib (MK-7965) in Subjects with Hematologic Malignancies (KEYNOTE-155)

IND NUMBER: Pembrolizumab 118,604; Dinaciclib 114,461

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-3475-155-05	12-MAR-2020	To include a limit to survival follow-up in order to end the study.
MK-3475-155-04	15-DEC-2017	To provide the most current information supporting a pembrolizumab 200 mg fixed dose, based on recent data generated in the pembrolizumab development program. To add/clarify language in alignment with pembrolizumab current label, including addition of myocarditis grade clarification and actions for dose modification evaluations. To introduce flexibility of survival status activities to ensure that current and complete survival data are available at the time of database locks.
MK-3475-155-03	24-OCT-2017	Addition of Arm B, combination treatment of pembrolizumab and MK-4280 in subjects with relapsed or refractory diffuse large B-cell lymphoma or relapsed or refractory indolent lymphomas. Each disease setting is an unmet medical need. Preclinical and clinical data for pembrolizumab have established antitumor activity in multiple tumor types, including hematologic malignancies. In preclinical trials, LAG-3 has been shown to be produced in elevated levels in hematologic malignancies, and blockage of LAG-3 and PD-L1 has demonstrated synergistic antitumor activity in solid tumors. An ongoing first-in-human trial investigating the combination of MK-4280 and pembrolizumab in advanced solid tumors, preliminary antitumor activity of this combination has been observed. Enrollment of subjects with rrDLBCL into Arm A or B cohorts will occur in parallel with treatment allocation accomplished by alternating assignment using an interactive voice response system/integrated web response system until

Document	Date of Issue	Overall Rationale
		enrollment into the Arm A rrDLBCL cohort is complete. Because initially both Arm A and B will be enrolling subjects with rrDLBCL concurrently, the enrollment into treatment cohorts will be automated to eliminate investigator selection bias and to initiate Arm B enrollment.
MK-3475-155-02	02-FEB-2017	To add inclusion criterion #7 for cardiac function suitable for hydration guidance and to update inclusion criteria #1, #11, #15, #16, #20 for clarification. To add exclusion criterion #17 to exclude subjects with known HIV infection, and exclusion criteria#20 and #24 to exclude subjects with CLL and DLBCL with Richter's Transformation; and to update exclusion criterion #18 for clarification.
MK-3475-155-01	20-MAY-2016	To add the exclusion criterion: "Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis," to clarify that patients who may have a history of pneumonitis are excluded from the study (when applicable).
MK-3475-155-00	11-DEC-2015	Original protocol

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
2.1 6.0 7.1.5.4	Trial Design Trial Flow Chart Follow-up Visits	Updated the follow-up duration after discontinuation to at least 12 months and/or until the end of the trial.	To allow for early closure of the trial.
1.0 2.1 5.1.2 5.2.1.3.1	Trial Summary Trial Design Subject Inclusion Criteria Premedication for Dinaciclib for rrCLL and rrDLBCL	Added a note to explain that the rrCLL cohort was closed due to lack of accrual.	To update status of the CLL arm
7.1.5.4.1	Follow-Up Post-Allogeneic Stem Cell Transplantation	Updated post-SCT follow-up to allow for completion of follow-up when the trial ends.	To allow for early closure of the trial.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
4.1.1.1	Pembrolizumab	Updated 2 reference citation DocIDs.	To allow proper linking at finalization.
4.2.3.5 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	Removed references to Future Biomedical Research "sub-trial."	Template update
7.1.5.4	Efficacy Follow-up Visits	Updated the heading name.	Template update for clarification.
7.1.5.4.2	Survival Follow-up	Added new template language on timing of survival follow-up	Template update for clarification.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase Ib trial of pembrolizumab (MK-3475) in combination with dinaciclib (MK-7965) in subjects with hematologic malignancies (KEYNOTE-155)
Trial Phase	Phase Ib
Clinical Indication	Treatment of subjects with relapsed or refractory chronic lymphocytic leukemia, multiple myeloma (rrMM), or diffuse large B-cell lymphoma (rrDLBCL). Note: The rrMM cohort was closed to enrollment on 07-AUG-2017 due to lack of efficacy, and all subjects with rrMM were discontinued from treatment. Remaining subjects with rrMM are in survival follow-up. Note: The rrCLL cohort was closed to enrollment on 30-APR-2019 due to lack of accrual, and all subjects with rrCLL have discontinued from treatment. Remaining subjects with rrCLL are in survival follow-up.
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous (IV)
Trial Blinding	Unblinded Open-label
Treatment Groups	Combination of pembrolizumab and dinaciclib
Number of trial subjects	Approximately 102 to a maximum of 138 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 36 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for up to approximately 26 months. Trial participation is defined as the period from the time the subject signs the Informed Consent Form through the final contact. After a screening phase of 28 days, each subject will receive combination treatment for a maximum of 35 cycles (approximately 2 years) or until documented disease progression by investigator assessment, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. After the end of treatment each subject will be followed for 30 days for a Safety Follow-Up Visit. Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-trial cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the trial.

A list of abbreviations used in this document can be found in Section 12.12.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a Phase Ib non-randomized, multi-site, open-label trial of dinaciclib (MK-7965) in combination with pembrolizumab (MK-3475) in subjects with relapsed or refractory chronic lymphocytic leukemia (rrCLL), multiple myeloma (rrMM) or diffuse large B-cell lymphoma (rrDLBCL) to be conducted in conformance with Good Clinical Practices. Subjects who meet the eligibility criteria will be enrolled to receive dinaciclib in combination with pembrolizumab.

> Note: The rrMM cohort was closed to enrollment on 07-AUG-2017 due to lack of efficacy, and all subjects with rrMM discontinued from treatment. Remaining subjects with rrMM are in survival follow-up.
>
> Note: The rrCLL cohort was closed to enrollment on 30-APR-2019 due to lack of accrual, and all subjects with rrCLL have discontinued from treatment. Remaining subjects with rrCLL are in survival follow-up.

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.

The trial will enroll an initial cohort of 12 subjects for Dose Evaluation. At least 3 subjects each with rrCLL, rrMM, or rrDLBCL will be enrolled in this cohort. During Dose Evaluation, subjects will receive dinaciclib and pembrolizumab as described in Table 2 and Table 3.

In Cycle 1, pembrolizumab 200 mg intravenous (IV) (30-minute infusion) will be administered on Day 1; dinaciclib 7 mg/m^2 IV (2-hr infusion) will be administered on Day 1, and 10 mg/m^2 IV on Day 8. Each cycle is 21 days (Q3W). In Cycle 2 and beyond, pembrolizumab will be administered on Day 1, and dinaciclib 14 mg/m^2 will be administered on Day 1 and Day 8. Disease response assessments will be performed every 3 cycles for rrCLL and rrDLBCL, and at the beginning of each cycle (except Cycle 1) for rrMM.

In the Dose Evaluation phase, safety data will be reviewed by the trial team. If 4 or fewer subjects experience dose-limiting toxicities (DLTs) (Section 5.2.1.4) in the first 2 cycles, 3 disease-specific expansion cohorts will be opened for Signal Detection. If 5 or more subjects experience DLTs within the first 12 subjects in the first 2 cycles, a lower dose of dinaciclib (Table 11) will be studied in up to 24 subjects (Section 5.2.1.3.4).

In the Signal Detection phase, approximately 30 subjects each with rrCLL, rrMM, or rrDLBCL will be enrolled in separate cohorts. The Dose Evaluation and Signal Detection phases will further evaluate safety and characterize preliminary efficacy.

In the Signal Detection phase, an interim analysis for safety and an efficacy interim analysis for futility will be conducted for each cohort after 12 subjects have been enrolled and the last subject has completed the first response assessment (ie, after Cycle 3 for CLL and rrDLBCL, and after Cycle 2 for rrMM), or otherwise discontinued trial treatment. Enrollment will be paused during the interim analysis (Section 8.7). The results will be reviewed by the trial

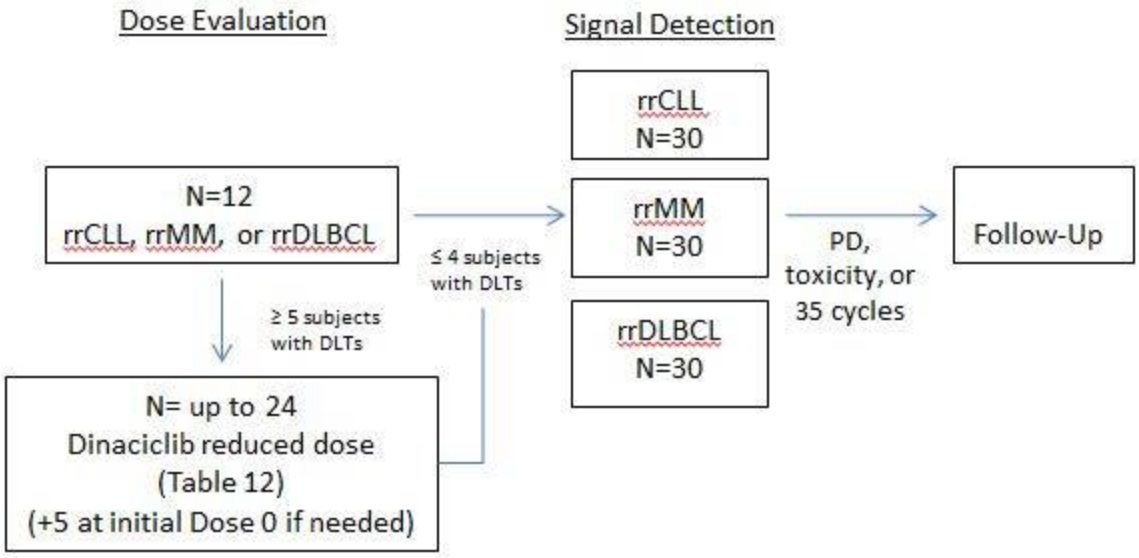
team. Enrollment may resume in that cohort if the results of the safety and efficacy analysis justify continuing.

Subjects will continue on treatment until disease progression (PD) (Section 7.1.2.7 and Section 7.1.2.8), unacceptable adverse event (AE), or treatment has been completed (ie, 35 cycles [approximately 2 years]). Subjects who discontinue treatment before PD, including subjects who discontinue treatment for bone marrow transplantation or to receive any other treatment, will be followed every 12 weeks for at least 12 months until PD is documented or until the end of the trial.

The primary objective of the trial is to evaluate the safety and tolerability of the combination of pembrolizumab and dinaciclib in subjects with hematologic malignancies. Secondary objectives by tumor type include the ORR, duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

2.2 Trial Diagram

The trial design is depicted in Figure 1.



All subjects will receive pembrolizumab and dinaciclib.

In Dose Evaluation, at least 3 subjects each with rrCLL, rrMM, or rrDLBCL will be enrolled in the initial cohort of 12. If there are ≥ 5 subjects with DLTs within the initial cohort of 12 subjects in Dose Evaluation, dinaciclib dosing will be evaluated according to Section 5.2.1.3.4 and Table 11.

A safety analysis will be performed after the 12 subjects in the Dose Evaluation cohort have had at least 2 cycles or have discontinued treatment or died due to study drug(s)-related toxicity.

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** In both the Dose Evaluation and Signal Detection phases, evaluate the safety and tolerability of dinaciclib in combination with pembrolizumab

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective:** Within each disease type of the Signal Detection phase, evaluate ORR according to investigator assessment using the disease-specific criteria (Section 7.1.2.7)
2) **Objective:** To evaluate the ORR (complete remission [CR] + partial response [PR]) of the combination of pembrolizumab and dinaciclib within each disease type, ie, CLL based on International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines [1], MM based on International Myeloma Working Group (IMWG) criteria for response assessment in multiple myeloma [2], and DLBCL based on the Revised Response Criteria for Malignant Lymphoma [3]
3) **Objective**: Within each disease type of the Signal Detection phase, evaluate DOR and PFS according to investigator assessment using the disease-specific criteria (Section 7.1.2.7); and OS

3.3 Other Objectives

1) **Objective:** To examine treatment effect on cluster of differentiation (CD)4, CD8, and quantitative immunoglobulins in subjects with rrCLL
2) **Objective:** To determine if known prognostic markers in rrCLL (immunoglobulin heavy chain [IgVH], CD38, and Beta-2 microglobulin) predict for response to treatment
3) **Objective**: To estimate dinaciclib exposure following a 2-hour IV infusion in the subject population
4) **Objective:** To compare the extent of pre-pembrolizumab programmed cell death ligand-1 (PD-L1) expression in tumor biopsies for pembrolizumab responders versus non-responders
5) **Objective:** To investigate the relationship between candidate efficacy biomarkers and antitumor activity of the treatments administered using pre- and post-treatment samples and local testing results
6) **Objective:** To explore the relationship between genomic variation and response to the treatment(s) administered. Variation across the human genome (germline and tumor) will be analyzed for association with clinical data collected in this trial

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death-1 (PD-1) receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of subjects across a number of indications. For more details on specific indications, refer to the Investigator's Brochure (IB). In this trial, pembrolizumab combination therapies will be tested for safety and preliminary efficacy in B-cell malignancies, with the intent of identifying combination that may broaden initial responses to treatment or re-sensitize treatment-resistant cancers.

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 Pembrolizumab

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [4]. 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 (Tregs) correlates with improved prognosis and long-term survival in many solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [5] [6].

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) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7] [8].

The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type domain responsible for ligand binding and a cytoplasmic tail that is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to ITSM within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta, and zeta-chain-associated protein kinase, which are involved in the CD3 T-cell signaling cascade [8] [10] [11] [12]. The mechanism by which PD 1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [13] [14].

As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in heme malgnancies.

4.1.1.2 Dinaciclib

Dinaciclib (MK-7965) is a novel, potent, small-molecule inhibitor of cyclin-dependent kinases (CDKs), which is being developed for the treatment of human malignancies. The aqueous solubility of dinaciclib drug substance is pH dependent, ranging from over 10 mg/mL at pH 3.5 to approximately 1 mg/mL at pH 7 or higher.

The mammalian cell cycle is a non-redundant process that integrates extracellular signaling, DNA synthesis, and mitosis [15] [16]. The CDKs are a family of serine/threonine kinases that function as critical regulators of the mammalian cell cycle [15] [17]. As their name suggests, CDKs are allosterically activated following association with a cyclin partner. CDK1 and CDK2 are closely related (90% identical) members of this family that play overlapping and essential roles during cell division [15] [17]. Aberrant regulation of CDK1 and CDK2 in cancer cells occurs through a variety of well-documented genetic mechanisms, including cyclin amplification and mutation of specific CDK inhibitor proteins [18] [19] [20] [21] [22].

Coordinated CDK2/CDK1 activity is required for appropriate regulation of S phase entry (DNA synthesis), suppression of apoptosis in late S phase, S phase exit, and entry into mitosis [15] [17]. Inhibition of CDK2/CDK1 in tumors is predicted to provoke cell-cycle arrest and apoptosis [23]. The lack of appropriate cell-cycle regulation in tumor cells predicts an increased tendency towards apoptosis in tumor cells, compared to normal tissue [23]. Hence, inhibition of the essential, rate-limiting activities of CDK2 and CDK1 represents an attractive therapeutic strategy for oncology indications.

CDK inhibitors that have entered clinical trials include flavopiridol and UCN 01. The development of both of these drugs has been complicated by significant binding to human serum proteins, which results in extremely long elimination half-lives (253 to 1660 hours for UCN 01) [24] and low free levels of drug leading to a lack of activity in early trials (flavopiridol) [25]. In contrast, in vitro discovery studies show that dinaciclib is approximately 87% protein bound in human plasma.

4.1.2 Pre-clinical and Clinical Trials

Refer to the current IBs for pembrolizumab and dinaciclib for information on pre-clinical and clinical trials.

4.1.2.1 Pembrolizumab

Ongoing clinical trials with pembrolizumab are being conducted in a wide variety of solid tumors and hematologic malignancies. Pembrolizumab has been administered to more than 9600 subjects in clinical trials. For trial details, refer to the pembrolizumab IB.

Preliminary results from an ongoing trial from cohorts of subjects with relapsed/refractory hematologic malignancies (Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, non-Hodgkin lymphoma) treated with pembrolizumab demonstrated high response rates and meaningful durations of response [26] [27] [28] (data on file, Merck Inc.).

On 03-JUL-2017, the Food and Drug Administration (FDA) placed a clinical hold based on safety data in multiple myeloma trials involving the pembrolizumab plus IMiD combination (pomalidomide, lenalidomide, or thalidomide). The FDA determined that the risks of pembrolizumab plus pomalidomide or lenalidomide outweighed any potential benefit for subjects with MM. In those trials, the treatment phase was closed and subjects moved into the long-term safety and survival follow-up. Separate from this, on 07-AUG-2017, the rrMM cohort of this trial was stopped due solely to lack of efficacy. No safety concerns were seen. Subjects in this cohort were discontinued from treatment and moved to long-term follow-up.

4.1.2.2 Dinaciclib

Dinaciclib has been administered to more than 363 subjects enrolled in Phase 1 and Phase 2 clinical trials, using various doses and schedules, in various solid tumors and hematologic malignancies.

Preliminary results from dose-finding Phase 1 and Phase 2 trials of dinaciclib in subjects with various malignancies, including with relapsed/refractory CLL, MM, and lymphoma, demonstrated various rates of responses [29] [30] (data on file, Merck Inc.). For trial details, refer to the dinaciclib IB.

4.1.2.3 Pembrolizumab in Combination with Dinaciclib

Enhanced antitumor activity was observed with the combination of pembrolizumab and dinaciclib in a preclinical trial using a solid tumor syngeneic model (MC38). There were no significant safety findings with the combination (data on file, Merck Inc.).

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

This trial of the combination of pembrolizumab and dinaciclib, will be conducted in subjects with relapsed or refractory CLL, MM, or DLBCL. As defined by the eligibility criteria, each setting is an unmet medical need. Note: The rrMM cohort was closed to enrollment on 07-AUG-2017 due to lack of efficacy, and all subjects discontinued from treatment. Remaining subjects with rrMM are in survival follow-up.

Preclinical and clinical data for each of pembrolizumab and dinaciclib as monotherapies (or combined with other chemotherapeutics) have demonstrated antitumor activity in various tumor types, including hematologic malignancies.

This trial will evaluate the safety and tolerability of the combination of pembrolizumab and dinaciclib in subjects with relapsed or refractory CLL, MM, or DLBCL, as well as evaluate the efficacy of the combination.

4.2.2 Rationale for Dose Selection/Regimen

4.2.2.1 Pembrolizumab

The planned dose of pembrolizumab for this trial is 200 mg Q3W. Based on the totality of data generated in the Keytruda® development program, 200 mg Q3W is the appropriate dose

of pembrolizumab across all indications, regardless of tumor type. As outlined below, this dose is justified by:

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

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small cell lung cancer, covering different disease settings (treatment-naïve, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 B2, KN001 D, KN002, KN010 and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 B3, KN001 F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied, representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin lymphoma, confirming 200 mg Q3W as the appropriate dose, independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

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

4.2.2.2 Dinaciclib

Dinaciclib was rapidly eliminated from plasma; mean terminal phase half-life values ranged from 2 to 3 hours. There was a dose-related increase in exposure with doses from 0.33 to 58 mg/m^2. Dinaciclib did not accumulate in plasma upon weekly or Q3W multiple dosing. Coadministration of dinaciclib with aprepitant, an antiemetic agent, did not affect the pharmacokinetics of dinaciclib.

Phase 1 dose-escalation trials investigating two different IV dosing schedules of dinaciclib have determined the maximum administered dose and the RPTD for each schedule. Safety and PK data from these trials support the doses selected for further evaluation of dinaciclib. In the first Phase 1 trial (PN001), dinaciclib was administered as a 2-hour IV infusion on Days 1, 8, and 15 of a 28-day cycle to subjects with advanced malignancy refractory to conventional treatment. In subjects with solid tumors, a maximum administered dose of 14 mg/m^2 was reached in the PN001 trial, with an RPTD of 12 mg/m^2. The trial included an expansion cohort, at the RPTD of 12 mg/m^2, exploring safety and tolerability in subjects with MM or NHL. In Arm B of the PN001 trial, dose exploration to minimize the incidence of tumor lysis syndrome (TLS) in subjects with CLL revealed an RPTD of 7>10>14 mg/m^2 (Days 1, 8, and 15, respectively) in Cycle 1 and 14 mg/m^2 in Cycle 2 and thereafter (28-day cycles).

A Phase 1 trial examining dinaciclib administered as a 2-hour IV infusion given Q3W in a similar subject population (PN002) has determined an RPTD of 50 mg/m^2. In the acute leukemia trial (PN005), a planned safety analysis of intrasubject dose escalation from dinaciclib at 50 mg/m^2 to 70 mg/m^2, starting in Cycle 2, concluded that the 70 mg/m^2 dose is safe.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy objective for both arms of this trial is to evaluate the antitumor activity of pembrolizumab in combination with dinaciclib in subjects with rrCLL, rrMM, or rrDLBCL. The primary efficacy endpoint will be ORR as assessed by the investigator, according to tumor-specific response criteria. Objective response rate is an acceptable measure of clinical benefit to demonstrate a new antineoplastic combination therapy.

Other secondary efficacy endpoints will include DOR, PFS, and OS. These endpoints are commonly accepted endpoints by both regulatory authorities and the oncology community.

4.2.3.2 Safety Endpoints

The safety and tolerability of pembrolizumab in combination with dinaciclib in subjects with rrCLL, rrMM, or rrDLBCL will be characterized in this trial. The safety analysis will be based on subjects who experienced toxicities as defined by Common Toxicity Criteria for Adverse Events (CTCAE). Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab in combination with dinaciclib, including serious adverse events (SAEs) and events of clinical interest (ECIs).

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

4.2.3.3 Pharmacokinetic Endpoints

The PK endpoints of this trial are to define:

- the plasma concentration profile and estimate dinaciclib exposure following a 2-hour IV infusion, and
- the plasma concentration profile of pembrolizumab exposure following administration of combination therapy.

Plasma concentrations of dinaciclib and pembrolizumab will be determined using validated high performance liquid chromatography-tandem mass spectrometry methods.

Plasma drug concentration versus time data collected for PK purposes will be analyzed. Additionally, correlations between the model-estimated drug exposure and other subject characteristics, such as concomitant medication, available AEs, or pharmacodynamic data, may be explored.

4.2.3.4 Planned Exploratory Biomarker Research

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

Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab or dinaciclib 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:

<u>Multiplex Flow Cytometric Analysis</u>

Emerging data suggest that blockade of the PD-1/PD-L1 pathway results in enhanced T-cell mediated immune response. To test the hypothesis that T-cell activation mediated by pembrolizumab treatment correlates with clinical response, total T-cell count and T-cell subsets in peripheral blood, eg, naïve, activated, memory, and regulatory T cells, will be assessed pre- and post-dose and in both responders and non-responders. Natural killer cells enumeration will also be performed pre- and post-dose in both responders and non-responders.

Transcriptional Analyses

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

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

Gene Sequencing

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

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

Planned Genetic Analysis

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

Anti-Pembrolizumab Antibodies

Formation of antidrug antibodies (ADAs) can potentially confound drug exposures at therapeutic doses, and prime for subsequent infusion-related toxicities. Incidence of ADAs and neutralizing ADAs will be evaluated. Correlations between the presence/absence in subjects of ADAs with PK and pharmacodynamic markers, activity, and safety of pembrolizumab may be explored.

4.2.3.5 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific

understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of Future Biomedical Research are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

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

Preclinical and clinical data for pembrolizumab and dinaciclib have demonstrated antitumor activity in various tumor types, including hematologic malignancies. Enhanced antitumor activity was observed with the combination of pembrolizumab and dinaciclib in preclinical studies using a solid tumor syngeneic model (MC38). There were no significant safety findings with the combination. Based on the available preclinical and clinical information, the benefit/risk of the pembrolizumab plus dinaciclib combination appears reasonable to evaluate in a Phase Ib clinical trial.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IBs and informed consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of rrCLL, rrMM, or rrDLBCL 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:

All Subjects:

1. Be willing and able to provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Female subjects of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of trial medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

4. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.7.2 - Contraception, for the course of the trial through 120 days after the last dose of trial medication.

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

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

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

6. Must have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.

7. Cardiac function suitable for hydration guidelines outlined in Table 6 and Table 7 per investigator and/or cardiologist.

8. Be able to provide newly obtained (within 3 months) bone marrow biopsy material for biomarker analysis. If bone marrow biopsy was performed within 3 months before screening but subject had anticancer treatment after biopsy, the bone marrow biopsy and aspiration should be repeated.

9. Must demonstrate adequate organ function as defined below (Table 1):

Table 1 Subject Inclusion Criteria - Adequate Organ Function

System	Laboratory Value
Hematological	
ANC	> 1,500/µL (unless due to marrow involvement)
Platelets[a]	≥ 100,000/µL (≥30,000/µL for CLL)
Hemoglobin[a]	≥8.0 g/dL or ≥1.24 mmol/L[a]
Renal	
Creatinine **OR** Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or creatinine clearance)	≤ 1.5 X ULN **OR** ≥ 60.0 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 and ALT	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Coagulation	
INR or PT 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

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CLL = chronic lymphocytic leukemia; GFR=glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

CLL –Note: The rrCLL cohort was closed to enrollment on 30-APR-2019 due to lack of accrual, and all subjects with rrCLL have discontinued from treatment. Remaining subjects with rrCLL are in survival follow-up.

10. Confirmed diagnosis of CLL as defined by 2008 iwCLL criteria.

11. Subjects must have received at least one prior therapy.

12. Must meet one or more of the following consensus criteria for initiating treatment:

- Progressive disease or marked splenomegaly and/or lymphadenopathy,
- Anemia (hemoglobin < 11 g/dL) or thrombocytopenia (platelets < 100,000/mm3),
- Unexplained weight loss ≥ 10% of body weight over preceding 6 months
- National Cancer Institute CTCAE Grade 2 or 3 fatigue,

- Fevers >100°F/38°C or night sweats for greater than 2 weeks without evidence of infection,
- Progressive lymphocytosis, with an increase > 50% over a 2-month period or a doubling time < 6 months.

MM - Note: The rrMM cohort was closed to enrollment on 07-AUG-2017 due to lack of efficacy, and all subjects discontinued from treatment.

13. Has a confirmed diagnosis of active MM and measurable disease defined as:
    - Serum monoclonal protein (M-protein) levels ≥ 0.5 g/dL or
    - Urine monoclonal protein (M-protein) levels ≥ 200 mg/24-hrs or
    - For subjects without measurable serum and urine M-protein levels, an abnormal serum free light chain ratio (FLC k/l) with involved FLC level ≥ 100 mg/L. (Normal serum FLC k/l value: 0.26-1.65).
14. Must have undergone prior treatment with ≥ 2 treatment lines of anti-myeloma therapy and must have failed their last line of treatment defined as documented disease progression during or within 60 days of completing their last anti-myeloma therapy (refractory to last line of treatment)
15. Prior anti-myeloma treatments must have included an IMiD (pomalidomide, lenalidomide, or thalidomide) AND proteasome inhibitor (bortezomib, carfilzomib, or ixazomib) alone or in combination and subject must have failed therapy with an IMiD OR proteasome inhibitor defined as one of the following:
    - Refractory: Documented progressive disease on or within 60 days of completing treatment with an IMiD and/or proteasome inhibitor OR
    - Relapsed and refractory: In case of prior response (≥PR) to an IMiD or proteasome inhibitor, subjects must have relapsed within 6 months after stopping treatment with an IMiD and/or proteasome inhibitor-containing regimens.

DLBCL

16. Has a histologically confirmed diagnosis of DLBCL.
17. Subjects must have progressed following at least 2 lines of previous therapy, including progression after an autologous stem cell transplant (SCT), or are not a candidate (per institutional criteria) for an autologous stem cell transplant. Subjects who are ineligible for standard treatment or who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of that treatment and precluding retreatment with the same agent before progression of disease will also be eligible.
18. Have measurable disease, defined as at least one lesion that can be accurately measured in at least 2 dimensions with spiral computed tomography (CT) scan. Minimum measurement must be > 15 mm in the longest diameter or > 10 mm in the short axis.
19. Be able to provide newly obtained (within 3 months) core or excisional biopsy from lymph node or extranodal location for biomarker analysis. If bone marrow biopsy was performed 3 months before screening but subject had anti-cancer treatment after biopsy, the bone marrow biopsy and aspiration should be repeated.

5.1.3 Subject Exclusion Criteria

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

All Subjects:

1. Is currently participating and receiving trial therapy or has participated in a trial of an investigational agent and received trial therapy or used an investigational device within 28 days before trial Day 1.
2. Treatment with a cytochrome P450 3A4 (CYP3A4) strong inhibitor or inducer within 7 days prior to enrollment. See Section 12.6 for information about strong inhibitors/inducers of CYP3A4.
3. Treatment with anticancer therapy or thoracic radiation therapy within 14 days before the first dose of treatment.

   Exception: Subjects with CLL may receive ibrutinib (or similar for CLL) up to 7 days before trial Day 1.
4. Has known clinically active central nervous system involvement.
5. Has a known history of immunosuppression or is receiving systemic steroid therapy or any other form of systemic immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

   - The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
6. Has had a prior anticancer monoclonal antibody within 4 weeks prior to trial Day 1 or who has not recovered (ie, ≤ Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.
7. Grade 2 or higher nonhematological toxicities from prior therapy. Residual toxicity of Grade 1 from prior therapy or persistent treatment-related Grade 1 neurotoxicity will be allowed.

   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 for each tumor type.
8. Has undergone prior allogeneic hematopoetic 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.)
9. 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.
10. Has active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement

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

11. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
12. Has an active infection requiring intravenous systemic therapy.
13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
14. 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.
15. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or CAR-T cell therapy or with an agent directed to another stimulatory or co-inhibitory T-cell receptor.
16. Previously treated with a CDK inhibitor (eg, dinaciclib or flavopiridol).
17. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
18. Has a known history of or is positive for hepatitis B (hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (hepatitis C virus [HCV] RNA [qualitative] is detected).
19. Has received a live vaccine within 30 days prior to first dose.
20. Has known current symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

CLL

21. Subject with Richter's Transformation.

MM

22. Subjects with non-secretory or oligo-secretory myeloma, plasma cell leukemia, or Waldenström's macroglobulinemia.
23. History of primary amyloidosis, hyperviscosity or POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

DLBCL

24. Subjects with primary mediastinal B-cell lymphoma.
25. Subject with Richter's Transformation.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 2.

Table 2 Trial Treatments

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Treatment Period	Use
Pembrolizumab (MK-3475)	200 mg	Every 21 days	IV infusion	Until PD, or up to a maximum of 35 cycles (approximately 2 years)	Investigational
Dinaciclib (MK-7965)	14 mg/m^2 (Cycle 1 dosing per Table 3)	Table 3	IV infusion	Until PD, or up to a maximum of 35 cycles (approximately 2 years)	Investigational
Abbreviations: IV = intravenous; PD = progressive disease.					

Subjects will receive pembrolizumab and dinaciclib as described in Table 3. In Cycle 1, pembrolizumab 200 mg IV (30-minute infusion) will be administered on Day 1; dinaciclib 7 mg/m^2 IV (2-hour infusion) will be administered on Day 1, and 10 mg/m^2 IV on Day 8. Each cycle is 21 days. In Cycle 2 and beyond, pembrolizumab will be administered on Day 1, and dinaciclib 14 mg/m^2 will be administered on Day 1 and Day 8.

Table 3 Dosing Schedule of Pembrolizumab and Dinaciclib

Cycle	Day	Pembrolizumab	Dinaciclib
Cycle 1	1	200 mg	7 mg/m^2
	8	-	10 mg/m^2
	15	-	-
Cycle 2+	1	200 mg	14 mg/m^2
	8	-	14 mg/m^2
	15	-	-

If there are ≥ 5 subjects with DLTs within the initial cohort of 12 subjects in Dose Evaluation, dinaciclib dosing will be evaluated according to Section 5.2.1.3.4 and Table 13.

Trial treatment should begin on the day of treatment allocation or as close as possible to the date on which the subject is allocated/assigned. Treatment allocation by non-random assignment will be done using an IVRS/IWRS.

Dinaciclib and pembrolizumab will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

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

Pembrolizumab should be administered before dinaciclib. If one trial drug is held, the other trial drug should also be held. Details on the preparation and administration of trial treatments are provided in the Pharmacy Manual.

The investigator may attribute each toxicity event to dinaciclib alone, or pembrolizumab alone, or to the combination and use dose modification according to Table 4 (pembrolizumab), Table 8 (dinaciclib), and Table 9 (dinaciclib). If a subject experiences toxicities that are attributed to combination regimen as a whole and there are conflicting recommendations for the individual agents, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity) or consult with the Sponsor.

5.2.1.2 Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion Q3W on Day 1 of each cycle. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 min/+10 min).

5.2.1.2.1 Pembrolizumab Dose Modification

Dose Modification and Toxicity Management for Immune-Related Adverse Events Associated with Pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical 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 4.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events 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 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus).

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
	Grade 4	Permanently discontinue		• 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.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	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]		

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
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 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		

Immune-Related AEs	Toxicity Grade or Conditions (CTCAEv4.0)	Action Taken to Pembrolizumab	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
All other immune-related AEs	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		

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).

Abbreviations: AE = adverse event; ALT =alanine aminotransferase; AST =aspartate aminotransferase; irAE = immune-related adverse event; GI = gastrointestinal; IV = intravenous; T1DM = type 1 diabetes mellitus.

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 5.

Table 5 Pembrolizumab Infusion Reaction Dose Modification and 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 therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial drug treatment	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg po (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

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

Abbreviations: CTCAE = Common Toxicity Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAID = nonsteroidal anti-inflammatory drug; po = oral.

Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to trial therapy. Subjects should be placed back on trial therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's trial record.

5.2.1.3 Dinaciclib

Dinaciclib is administered as described in Table 2 and Table 3. IV infusion components (IV infusion bag and tubing) with contact surfaces made of polyvinyl chloride or non-polyvinyl chloride material are acceptable for use with dinaciclib. Under no circumstances will the dose be administered in less than a 2-hour period. A central venous catheter is not required

for infusion of dinaciclib; however, if the subject has a central venous catheter in place it is recommended that it be used for the infusion.

Body surface area will be calculated by the site using the weight obtained at each cycle and the height obtained at screening. Body surface area will be recalculated at the beginning of every cycle and the dinaciclib dosage adjusted if the calculated dose would change > 5% from previous.

5.2.1.3.1 Premedication for Dinaciclib for rrCLL and rrDLBCL

Note: The rrCLL cohort was closed to enrollment on 30-APR-2019 due to lack of accrual, and all subjects with rrCLL have discontinued from treatment. Remaining subjects with rrCLL are in survival follow-up.

Premedication and supportive care for dinaciclib is required for all subjects with rrCLL and rrDLBCL and is summarized in Table 6.

For subjects with rrCLL and rrDLBCL who will receive rasburicase as a premedication, glucose-6-phosphate dehydrogenase deficiency (G6PD) testing should be completed locally when required in subjects at higher risk of G6PD deficiency (eg, subjects of African or Mediterranean ancestry). These subjects should be tested and found to have adequate levels before treatment with rasburicase.

Subjects with rrCLL and rrDLBCL will be admitted to the inpatient service to begin Cycle 1 so as to facilitate aggressive hydration prior to and close monitoring during the first dose of dinaciclib on Cycle 1 Day 1 and Day 2.

Monitor the subject for laboratory TLS and cytokine release syndrome (CRS) during and after the first administration of dinaciclib as described in Section 12.5 for Supportive Care Guidelines for TLS Prevention and Management.

Absent severe TLS complicating dinaciclib administration, subsequent therapy will be delivered on an outpatient basis (Section 12.5).

Table 6 Premedication for Dinaciclib for rrCLL and rrDLBCL

	Agent/Drug	Dose	Route	Schedule
Premedication [a, b]	Rasburicase	0.2 mg/kg or per institutional standard	IV	2 hrs prior to C1D1 dose; thereafter at investigator discretion
	Antiemetic with a serotonin-receptor antagonist	Per drug label or institutional standard	Per drug label or institutional standard	Prior to each dose according to label or institutional standard
	Dexamethasone	12 mg	IV	30 min prior to each dose
	Kayexalate (or equivalent)	30 g	PO	At least 30 min prior, if serum potassium ≥ 4.0 mmol/L in Cycle 1 only
Supportive Care [a]	Oral phosphate binder, such as calcium acetate or equivalent	Calcium acetate 1334 mg	Calcium acetate PO	12 and 2 hrs prior to each dose
	IV hydration with 0.45% sodium chloride sterile solution, or other appropriate IV solution	Subjects with CLL and DLBCL: C1D1: 200 ml/hr for ≥ 10 hrs prior to initiation of, during and continuing for ≥ 10 hrs after completion of dinaciclib infusion. Subsequent infusions: 200 ml/hr for ≥ 1 hr prior to initiating, during and continuing for ≥ 2 hrs after completion of dinaciclib infusion.		
	Herpes zoster virus prophylaxis (valacyclovir 500 mg PO daily or acyclovir 400 mg PO BID or institutional standard			
	Pneumocystis pneumonia (previously known as P. carinii) prophylaxis (Bactrim DS 1 tablet PO BID Monday-Wednesday-Friday or dapsone 100 mg PO daily or institutional standard).			
	Subjects with documented evidence of current/previous hepatitis B should receive antiviral prophylaxis during and for 6 months beyond last treatment.			

[a] Institutional equivalents may be used for all premedications with the exception of rasburicase. Supportive care guidelines should be followed as above; however, if subject clinical condition requires modification to the dose, route, or schedule then institutional standards may be used only after consultation with the Sponsor.

[b] If TLS is not observed, these guidelines may be revised.

Abbreviations: BID = twice daily; C1D1 = Cycle 1 Day1; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; IV = intravenous; PO = oral; TLS = tumor lysis syndrome.

5.2.1.3.2 Premedication for Dinaciclib for rrMM

Note: The rrMM cohort was closed to enrollment on 07-AUG-2017 due to lack of efficacy and all subjects discontinued from treatment. Remaining subjects with rrMM are in survival follow-up.

Premedication and supportive care for dinaciclib is required for all subjects with rrMM and is summarized in Table 7.

Subjects with rrMM will receive Cycle 1 Day 1 dose and all subsequent doses of dinaciclib on an outpatient basis.

Table 7 Premedication for Dinaciclib for rrMM

	Agent/Drug	Dose	Route	Schedule
Premedication [a, b]	Antiemetic with a serotonin-receptor antagonist	Per drug label or institutional standard	Per drug label or institutional standard	Prior to each dose according to label or institutional standard
	Dexamethasone	12 mg	IV	30 min prior to each dose
Supportive Care [a]	Oral phosphate binder, such as calcium acetate or equivalent	Calcium acetate 1334 mg	Calcium acetate PO	12 and 2 hrs prior to each dose
	IV hydration with 0.45% NaCl sterile solution, or other appropriate IV solution	C1D1 and Subsequent infusions: 200 ml/hr for ≥ 1 hr prior to initiating, during, and continuing for ≥ 1 hrs after completion of dinaciclib infusion		
	Herpes zoster virus prophylaxis (valacyclovir 500 mg PO daily or acyclovir 400 mg PO BID or institutional standard			
	Pneumocystis jiroveci pneumonia (previously known as P. carinii) prophylaxis (Bactrim DS 1 tablet PO BID Monday-Wednesday-Friday or dapsone 100 mg PO daily or institutional standard).			
	Subjects with documented evidence of current/previous hepatitis B should receive antiviral prophylaxis during and for 6 months beyond last treatment.			

[a] Institutional equivalents may be used for all premedications with the exception of rasburicase. Supportive care guidelines should be followed as above; however, if subject clinical condition requires modification to the dose, route, or schedule then institutional standards may be used only after consultation with the Sponsor.

[b] If TLS is not observed, these guidelines may be revised.

Abbreviations: BID = twice daily; C1D1 = Cycle 1 Day1; NaCl = sodium chloride; IV = intravenous; PO = oral; TLS = tumor lysis syndrome.

5.2.1.3.3 Dinaciclib Dose Modifications

Dinaciclib dose modifications for hematologic toxicity will be based on laboratory and clinical assessment performed on Day 1 of each cycle. The dinaciclib dose will not be reduced for cytopenias that have resolved by Day 1 of the next cycle. Dose adjustments or delays due to hematologic toxicity apply to Day 1 of each cycle. There will be no adjustments for Day 8 hematologic results. Dose delays and modifications for dinaciclib due to hematologic toxicity are described in Table 8. Dose delays and modification for dinaciclib for nonhematologic toxicity are described in Table 9. Dose levels to be used for dinaciclib dose modification are described in Table 10. If dinaciclib is held on Day 1, pembrolizumab

should be held as well. If Day 8 toxicity causes dose delay, subject should be retested within visit window in order to identify earliest dosing opportunity. If dose cannot be given within visit window, then Day 8 dose should be skipped.

Table 8 Dinaciclib Dose Modification for Hematologic Toxicity

Criteria for Start of Each Cycle	Action[a]
If ANC≥1.0 x 10^9/L at C1D1 predose, then action[a] should be taken if ANC at subsequent Day 1 predose is <1.0 x 10^9/L If ANC<1.0 x 10^9/L at C1D1 predose, then action[a] should be taken if ANC at subsequent Day 1 predose is more than 20% lower than C1D1 predose level	Delay for up to 3 weeks until recovery. Reduce subsequent doses by 1 dose level. Discontinue subject if already at the lowest dose level or if the subject's ANC has not recovered in 3 weeks.
If platelet count≥50 x 10^9/L at C1D1 predose, then action[a] should be taken if platelet count at subsequent Day 1 predose is <50 x 10^9/L If platelet count <50 x 10^9/L at C1D1 predose, then action[a] should be taken if platelet count at subsequent Day 1 predose is more than 20% lower than C1D1 predose level	Delay for up to 3 weeks until recovery. Reduce subsequent doses by 1 dose level. Discontinue subject if already at the lowest dose level or if the subject's platelet count has not recovered in 3 weeks.
[a]Action is applied regardless of toxicity causality. If a subject's count recovers within the +/-3 day visit window, then no dose reduction is required. However, if subject's count recovers outside the +/-3 day visit window, then dose reduction guidance outlined above applies. Must hold both pembrolizumab and dinaciclib if a hold is required. Abbreviations: ANC = absolute neutrophil count; C1D1 = Cycle 1 Day 1.	

For any nonhematologic toxicity that results in dose delay, treatment may be delayed for up to 3 weeks until resolution of toxicity to ≤ Grade 1 (Table 9).

Table 9 Dinaciclib Dose Modification for Nonhematologic Toxicity

Criteria	Action
TLS requiring dialysis	Reduce subsequent doses by one dose level. Resume treatment, as an inpatient, only after complete recovery with return to baseline lactate dehydrogenase and electrolytes. If well tolerated, further treatment may continue as an outpatient. If TLS requiring dialysis occurs after dose reduction, the subject must be discontinued.
Post-treatment hyperkalemia with K+ rising above ULN, occurring during dose-escalation in Cycle 1	Manage hyperkalemia per standard of care. Continue with the current dose of dinaciclib and delay dose-escalation until dinaciclib can be administered without a rise in K+. For example, post-treatment hyperkalemia is noted on C1D1 following 7 mg/m^2 dose. C1D8 dose is not escalated and treatment continues at 7 mg/m^2 with no hyperkalemia. C2D1 dose is increased to 10 mg/m^2 and C2D8 dose is increased to 14 mg/m^2.
Any diarrhea	Diarrhea should be treated with oral loperamide 4 mg followed by loperamide 2 mg after each additional episode of diarrhea to a maximal dose of 16 mg per day, provided there is no clinical evidence of infectious diarrhea.
≥ Grade 3 diarrhea after loperamide	Reduce subsequent doses by one dose level. Discontinue subject who continues to experience ≥ Grade 3 diarrhea despite dose reduction and loperamide. Discontinue subject if already at the lowest dose level.
≥ Grade 3 nausea/vomiting	Add antiemetic agents as appropriate. Reduce subsequent doses by one dose level, only if subject continues to have ≥ Grade 3 toxicity despite maximum antiemetic therapy. Discontinue subject with persistent ≥ Grade 3 nausea/vomiting despite dose reduction and antiemetics. Discontinue subject if already at the lowest dose level.
Bilirubin ≥ 2 x ULN, serum creatinine ≥ 3 x ULN or calculated creatinine clearance < 50 mL/min	Delay for up to 3 weeks until recovery of bilirubin ≥ 2 x ULN or serum creatinine ≥ 3 x ULN. Reduce subsequent doses by one dose level. Discontinue subject if already at the lowest dose level or if subject has not recovered in 3 weeks.
All other clinically relevant toxicities ≥ Grade 3	Delay for up to 3 weeks until recovery to ≤ Grade 1 toxicity. Reduce subsequent doses by one dose level. Discontinue subject who continues to experience ≥ Grade 3 toxicity despite dose reduction. Discontinue subject if already at the lowest dose level or if subject has not recovered in 3 weeks.
Abbreviations: C = cycle; D = Day; K+ = potassium; TLS = tumor lysis syndrome; ULN = upper limit of normal.	

Table 10 Dinaciclib Dose

Dose of Dinaciclib at Time of Adverse Event Requiring Dose Reduction	Dose to use for Next Dose
14 mg/m^2	10 mg/m^2
10 mg/m^2	7 mg/m^2
7 mg/m^2	discontinue

For a subject who has had dose reductions, dose escalation of dinaciclib to the next dose level is permitted provided that the subject remains on trial after receiving 2 additional cycles of combination treatment without ≥ Grade 2 toxicity and upon consultation with sponsor.

Tumor Lysis Syndrome

The Cairo and Bishop criteria will be used to define TLS (Section 12.5) [31].

Using the Cairo-Bishop definition of laboratory TLS, K, calcium (Ca), phosphorus (P), and uric acid will be evaluated at 3 and 5 hours after the start of the first dinaciclib infusion (Cycle 1 Day 1) as part of a TLS work-up (Section 12.5). Subjects with a positive TLS work-up should remain in the hospital and follow-up should be initiated. If necessary, subjects must be admitted overnight for observation.

TLS is defined as any 2 of the following serum levels within 3 days before or 7 days after initiation of dinaciclib, assuming adequate hydration and administration of a hypo-uremic:

- Uric acid levels of > 476 µmol/L (8 mg/dL), or a 25% increase from Baseline
- Potassium (K+) levels of > 6 mmol/L (6 mEq/L), or a 25% increase from Baseline
- Phosphorus levels of > 1.45 mmol/L (4.5 mg/dL), or a 25% increase from Baseline
- Calcium levels of < 1.75 mmol/L (7 mg/dL), or a 25% decrease from Baseline

5.2.1.3.4 Dinaciclib Dose Evaluation

During Dose Evaluation, the first 12 subjects will receive pembrolizumab 200 mg on Day 1 of each cycle and Dose Level 0 of dinaciclib as described in Table 3 and Table 11.

Table 11 Dinaciclib Dose Levels

Dose Level	Dose of Dinaciclib
Level 0	C1D1: 7 mg/m^2; C1D8: 10 mg/m^2; C2D1+: 14 mg/m^2
Level -1	C1D1: 7 mg/m^2; C1D8: 10 mg/m^2; C2D1+: 10 mg/m^2
Level -2	C1D1: 7 mg/m^2; C1D8: 7 mg/m^2; C2D1+: 7 mg/m^2
C1D1: Cycle 1 Day 1 C1D8: Cycle 1 Day 8 C2D1+: Cycle 2 Day 1 and beyond.	

DLTs observed in Cycle 1 and Cycle 2 will be used to evaluate the dose level. If 4 or fewer subjects at Dose Level 0 have a DLT, the Signal Detection phase of the trial will be opened. Table 12 below summarizes the probabilities of observing the numbers and percentages of subjects under different assumptions of true DLT rate θ0, which can be interpreted as the one-sided p-values for testing the null hypothesis that the true DLT rate is less than θ0. These criteria are considered non-binding guidelines; recommendations would not be based solely on statistical grounds, as many other factors (ie, all aspects of the data from the trial) may be part of the decision process.

Table 12 Probability of Observing the Number (%) of Subjects with DLT

Observed Number (%) of Subjects	**Probabilities (p-values) Under Different Assumptions**				
	$\theta_0 = 0.20$	$\theta_0 = 0.25$	$\theta_0 = 0.30$	$\theta_0 = 0.35$	$\theta_0 = 0.40$
2 (16.7%)	0.442	0.609	0.747	0.849	0.917
3 (25.0%)	0.205	0.351	0.507	0.653	0.775
4 (33.3%)	0.073	0.158	0.276	0.417	0.562
5 (41.7%)	0.019	0.054	0.118	0.213	0.335
6 (50.0%)	0.004	0.014	0.039	0.085	0.158
The probabilities (p-values) for the monitoring of the first 12 subjects were calculated from Binomial distribution.					

If there are ≥ 5 subjects with DLTs within the initial 12 subjects at Dose Level 0, up to 24 additional subjects may be enrolled using a design based on Ji et al. [32] (Table 13). If the monitoring guidance indicates escalation ("E") from Dose Level -1 to Dose Level 0, a maximum of 5 additional subjects will be evaluated at Dose Level 0, up to 17 subjects in all. Therefore, a minimum of 12 subjects (Dose Level 0), and although highly unlikely, a maximum of 41 subjects evaluable for DLT assessment (up to 17 at Dose Level 0 plus 12 each at Dose Levels -1 and -2), may be needed for Dose Evaluation. The pembrolizumab dose will not be changed.

If ≥ 5 subjects with DLTs are observed at Dose Level 0, the dose level of dinaciclib will be reduced (Table 11) to Level -1 ($7 > 10 > 10$ mg/m^2) to begin a new cohort of 3 subjects. Using Table 13, starting at the upper left corner, monitor the number of subjects and if the number of subjects/DLTs at Dose Level -1 reaches a "D" (de-escalate), then the dose level will be reduced to Level -2, and a cohort of 3 subjects will be enrolled at that dose level and monitored using Table 13 starting at the upper left corner (ie, the first 3 subjects at Dose Level -2).

At Dose Level -2, an "E" (escalate) would trigger an increase to Level -1, and enrollment and evaluation will continue at Level -1 from where it previously left off.

At Dose Level -1, an "E" (escalate) would trigger an increase to Level 0 and would resume at the number of subjects where it previously left off, or if it stopped at 12, would continue from subjects 13 up to 17. There is no dose escalation above Dose Level 0.

If the dinaciclib dose level is reduced to below Level 0, due to the potential complexity of trying to ensure balanced distribution of tumor types across the enrollment groups for dose evaluation, there are no restrictions regarding the minimum or maximum number of subjects

with CLL, MM, or DLBCL enrolled in these cohorts. This (no restriction) also applies if the dose is resumed back to Level 0.

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% is the target DLT rate used to generate the dose-adjustments in Table 13, the observed rate of DLTs at the maximum tolerated dose may vary slightly above or below 30%.

Table 13 Monitoring Guidance in Dose Evaluation (Target DLT Rate of 30%)

Number of Toxicities	Number of Subjects Treated at Current Dose Level [a]															
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**		**13[a]**	**14[a]**	**15[a]**	**16[a]**	**17[a]**
0	E	E	E	E	E	E	E	E	E	E		E	E	E	E	E
1	S	E	E	E	E	E	E	E	E	E		E	E	E	E	E
2	D	S	S	S	S	E	E	E	E	E		E	E	E	E	E
3	DU	DU	D	S	S	S	S	S	S	E		E	E	E	E	E
4		DU	DU	DU	D	D	S	S	S	S		S	S	S	E	E
5			DU	DU	DU	DU	D	D	S	S		S	S	S	S	S
6				DU	DU	DU	DU	DU	DU	D		D	S	S	S	S
7					DU	DU	DU	DU	DU	DU		DU	D	D	S	S
8						DU	DU	DU	DU	DU		DU	DU	DU	DU	D
9							DU	DU	DU	DU		DU	DU	DU	DU	DU
10								DU	DU	DU		DU	DU	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=.05, b=.05, k1=1.25; k2=0.5; pow=1.

Source: Ji et al. 2007) [32]

[a] A maximum of 12 subjects will be used to evaluate Dose Levels -1 and -2; subjects 13-17 are only used to evaluate Dose Level 0 if ≥ 5 subjects in initial group of 12 at Dose Level 0 experience DLT and Table 10 indicates escalation (E) from Dose Level -1 back to Dose Level 0.

5.2.1.4 Definition of Dose-Limiting Toxicity

DLTs will be defined from toxicities observed during Cycles 1 and 2. The occurrence of any of the following toxicities during these periods, if assessed by the investigator to be possibly, probably, or definitely related to pembrolizumab or dinaciclib will be considered a DLT:

1. Grade 4 nonhematologic toxicity (not laboratory)
2. Grade 4 hematologic toxicity lasting > 7 days, except thrombocytopenia
   a. Grade 4 thrombocytopenia of any duration
   b. Grade 3 thrombocytopenia is a DLT if associated with bleeding;
3. Any Grade 3 nonhematologic toxicity (not laboratory), 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.
4. Any Grade 3 or Grade 4 nonhematologic laboratory abnormality, if:
   - medical intervention is required, or
   - the abnormality leads to hospitalization, or
   - the abnormality persists for > 1 week
5. Febrile neutropenia Grade 3 or Grade 4
6. Any drug-related AE which caused subject to discontinue treatment during Cycles 1 or 2
7. Grade 5 toxicity
8. Any treatment-related toxicity which causes a > 2-week delay in initiation of Cycle 2 or Cycle 3

5.2.1.5 Replacement of Subjects in the Dose Evaluation Period

In order to determine safety, all subjects selected must meet the criteria for evaluability in Cycles 1 and 2. Subjects are considered non-evaluable for DLT assessment and will be replaced if:

- They are enrolled but not treated
- They discontinue from the trial prior to completing all the safety evaluations other than treatment-related AEs
- If they receive less than 90% of the total pembrolizumab or dinaciclib in Cycles 1 and 2 (eg, because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT.

Non-evaluable subjects will not be counted toward the total for Dose Evaluation. If a subject experiences a DLT in Cycles 1 or 2, trial treatment may be discontinued following discussion between the Sponsor and investigator. However, if the subject is deriving clinical benefit from the trial treatment, the subject may be allowed to continue after discussion between the Sponsor and the investigator.

5.2.2 Timing of Dose Administration

Pembrolizumab and dinaciclib dosing and schedules are described in Section 5.2.

Trial treatment may be administered up to 3 days before or after the scheduled dosing date for each infusion due to administrative reasons.

Missed doses (ie, Day 8) should be skipped, not delayed, if not given within the allowed window.

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

Details on the preparation and administration of dinaciclib and pembrolizumab are provided in the Pharmacy Manual.

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

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

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

All medication taken by the subject within 4 weeks prior to enrollment and all concomitant therapy taken by the subject during the trial up until 30 days after administration of the last dose of trial treatment are to be recorded on the electronic case report form. The identity of the therapy, the dose and the dates started and stopped (or notation of "continuing", as appropriate), and the reason for use must be recorded.

5.5.1 Acceptable Concomitant Medications

Medications required to treat AEs or concurrent illnesses, are allowed during the trial. Antiemetics, including serotonin-receptor antagonists, metoclopramide, prochlorperazine, or thietylperazine, are allowed throughout the trial.

Contraceptive medications, as per Section 5.7.2, are also allowed. Physiologic replacement doses of glucocorticoids are allowed.

Erythropoietin therapy and granulocyte colony-stimulating factor (G-CSF) are allowed at the discretion of the investigator. Erythropoietin therapy should be used in accordance with the American Society of Clinical Oncology/American Society of Hematology or the National Comprehensive Cancer Network guidelines [33].

G-CSF should be used in accordance with the American Society of Clinical Oncology guidelines [34]. Growth factors are not allowed to be used in order to boost a subject's hematology parameters if the subject is found to be ineligible based on the laboratory results performed at screening.

G-CSF for primary prophylaxis during Cycle 1 in Dose Evaluation is prohibited.

5.5.2 Prohibited Concomitant Medications and Therapies

The medications, supplement, and other substances prohibited prior to Screening are listed in Section 5.1.3 with the subject exclusion criteria.

Dinaciclib:

Dinaciclib is metabolized by the human hepatic enzyme CYP3A4. In vitro metabolism studies indicated that dinaciclib is a competitive inhibitor of CYP1A2, as well as an irreversible metabolism-dependent inhibitor of CYP3A4/5. Coadministration of dinaciclib with strong CYP3A4/5 inhibitors may increase the concentration of dinaciclib, and coadministration of dinaciclib with strong CYP3A4/5 inducers may decrease the concentration of dinaciclib.

Since dinaciclib is a substrate of CYP3A4, concomitant use of other drugs that are strong inhibitors or inducers of CYP3A4 is prohibited while the subject is enrolled in this trial except for required steroid premedication. See Section 12.6 for information about strong inhibitors/inducers of CYP3A4.

If the use of a medication that is a strong CYP3A4 inhibitor or inducer is medically necessary and an alternate therapeutic agent that is not a strong inhibitor or inducer of CYP3A4 is not available, then the subject must discontinue treatment with dinaciclib.

The investigator should be alerted if the subject is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

Additional information regarding drug interactions with cytochrome P450 isoenzymes can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/.

Pembrolizumab and dinaciclib: Subjects are prohibited from receiving the following therapies during the Screening and Treatment phase of this trial:

- Antineoplastic systemic chemotherapy, biological therapy, or immunotherapy
- G-CSF for primary prophylaxis during Cycle 1 in Dose Evaluation
- Granulate-macrophage colony-stimulating factor (GM-CSF)
- Investigational agents other than pembrolizumab and dinaciclib
- Radiation therapy
    - Note: Radiation therapy to a symptomatic soft tissue lesion, bone lesions, or to the brain may be allowed after consultation with Sponsor.
    - Thoracic radiation therapy is not allowed within 14 days before the first dose of treatment.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin, and oral typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than as a premedication for protocol treatments, and to modulate symptoms from an event of clinical interest of suspected immunologic etiology.
    - The use of physiologic doses of corticosteroids for use in subjects with conditions may be approved after consultation with the Sponsor.
- Grapefruit juice
- Strong inhibitors/inducers of CYP3A4 (except for required steroid premedication [Section 12.6]).

Subjects may receive other medications that the investigator deems to be medically necessary.

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

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

5.6 Rescue Medications & Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration

of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance.

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should refrain from grapefruit or grapefruit juice during the trial (Section 5.5.2).

5.7.2 Contraception

Pembrolizumab or dinaciclib may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab or dinaciclib 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 trial drug and for 120 days after the last dose of trial 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 Ethical Review Committees (ERCs) / Institutional Review Boards (IRBs). Periodic abstinence (eg, 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 trial medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the trial. In order to participate in the trial subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of trial medication initiation (or 14 days prior to the initiation of trial medication for oral contraception) throughout the trial period up to 120 days after the last dose of trial 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 trial.

5.7.3 Pregnancy

If a subject inadvertently becomes pregnant while on treatment, 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 SAE (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The trial investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner, the trial personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 7.2.2.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

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

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

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

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- Confirmed radiographic disease progression outlined in Section 7.1.2.7 (exception if the Sponsor approves treatment continuation).
- Unacceptable AEs as described in Section 7.2.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that 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.

- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.
- Recurrent Grade 2 pneumonitis.
- A confirmed positive serum pregnancy test.
- Noncompliance with trial treatment or procedure requirements.
- Investigator's decision to withdraw the subject.

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 6.0 – Trial Flow Chart, and Section 7.1.5.3 – Post Treatment Visits for those procedures to be completed at each specified visit.

5.8.2 Withdrawal from the Trial

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

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

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

5.9 Subject Replacement Strategy

Subjects in the Dose Evaluation period may be replaced as described in Section 5.2.1.5.

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).

5.11 Clinical Criteria for Early Trial Termination

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

6.0 TRIAL FLOW CHART

Trial Period:	**Screening Phase**	**Treatment Cycles (21-day cycles) To Be Repeated Beyond 3 Cycles**							**End of Treatment**		**Post-Treatment**	
Treatment Cycle (21 Day cycles)	Screening[b]	Cycle 1		Cycle 2		Cycle 3 +		Every 3 Cycles (ie, Cycle 4, 7, 10, etc)	Discon	Post-Treatment Safety Follow-up	Efficacy Follow-up Visits	Survival Follow-up
Cycle Day [a] (± 3 days unless otherwise specified)	-28 to -1	1	8	1	8	1	8	1 (± 7 d)	At time of Discon	30 days post Discon [v]	Every 12 weeks post Discon (± 14 d)	Every 12 weeks (± 14 d)
Administrative Procedures												
Informed Consent [c]	X											
Informed Consent for Future Biomedical Research [d]	X											
Inclusion/Exclusion Criteria	X											
Subject Identification Card	X											
Demographics and Medical History	X											
Prior Treatment Review	X											
Concomitant Medication Review [e]	X	X	X	X	X	X	X		X	X		
Post-trial Anticancer Therapy Status [f]										X	X	
Survival [g]		<----------										X
Pembrolizumab Administration		X		X		X						
Dinaciclib Administration		X	X	X	X	X	X					
Clinical Procedures/Assessments												
Full Physical Examination	X	X	X	X		X			X		X	
12-Lead Electrocardiogram	X											
Height [h]	X											
Vital Signs and Weight [h]	X	X	X	X	X	X	X		X		X	
ECOG Performance Status	X	X		X		X			X		X	
Adverse Event Review	X	X	X	X	X	X	X		X	X		
CLL: CT of Neck, Chest, Abdomen, and Pelvis	X							X	X		X	
CLL: Disease Response Assessment	X							X	X		X	
CLL: Constitutional Symptoms	X							X	X		X	
MM: Disease Response Assessment [i]	X			X		X			X		X	
MM: Skeletal Survey [j]	X							PRN				
MM: MRI or CT/PET for Extramedullary Soft Tissue Plasmacytoma [j]	X							PRN				

Trial Period:	**Screening Phase**	**Treatment Cycles (21-day cycles) To Be Repeated Beyond 3 Cycles**							**End of Treatment**		**Post-Treatment**	
Treatment Cycle (21 Day cycles)	Screening[b]	Cycle 1		Cycle 2		Cycle 3 +		Every 3 Cycles (ie, Cycle 4, 7, 10, etc)	Discon	Post-Treatment Safety Follow-up	Efficacy Follow-up Visits	Survival Follow-up
Cycle Day [a] (± 3 days unless otherwise specified)	-28 to -1	1	8	1	8	1	8	1 (± 7 d)	At time of Discon	30 days post Discon [v]	Every 12 weeks post Discon (± 14 d)	Every 12 weeks (± 14 d)
DLBCL: PET/CT Neck, Chest, Abdomen, and Pelvis [k]	X							X	X		X	
DLBCL: Lymphoma B Symptoms	X							X	X		X	
DLBCL: Disease Response Assessment [n]	X							X	X		X	
Laboratory Procedures/Assessments: Analysis Performed by Local Laboratory												
CBC with Differential	X	X	X	X	X	X	X		X	X		
Comprehensive Blood Chemistry Panel	X	X	X	X	X	X	X		X	X		
Urinalysis	X											
B2 Microglobulin	X											
hCG [l]	X	X		X		X		X		X		
PT (INR) and aPTT [y]	X											
Thyroid Tests (T3 [or FT3 per Local Standard]; FT4, and TSH)	X							X				
CLL:												
FISH, to Include Probes for del 17p, del 13q, del 11q, trisomy 12	X											
IgVH Mutational Status[u]	X											
CD38 Level	X								X			
CD4, CD8	X								X			
Quantitative Serum Immunoglobulins [x]	X							X		X		
G6PD Screening [m]	X											
Bone Marrow Biopsy and Aspiration [n]	X							PRN				
TLS labs: Potassium, Calcium, Phosphorus, Uric Acid (3 and 5 hrs After Start)		X										

Trial Period:	**Screening Phase**	**Treatment Cycles (21-day cycles) To Be Repeated Beyond 3 Cycles**							**End of Treatment**		**Post-Treatment**	
Treatment Cycle (21 Day cycles)	Screening[b]	Cycle 1		Cycle 2		Cycle 3 +		Every 3 Cycles (ie, Cycle 4, 7, 10, etc)	Discon	Post-Treatment Safety Follow-up	Efficacy Follow-up Visits	Survival Follow-up
Cycle Day [a] (± 3 days unless otherwise specified)	-28 to -1	1	8	1	8	1	8	1 (± 7 d)	At time of Discon	30 days post Discon [v]	Every 12 weeks post Discon (± 14 d)	Every 12 weeks (± 14 d)
Multiple Myeloma												
Serum Protein Electrophoresis ± Immunofixation [o]	X			X		X [i]			X			
24 hr Urine Protein Electrophoresis ± Immunofixation [o, p]	X			X		X [i]			X			
Serum Free Light Chain Assay [o, q]	X			X		X [i]			X			
Immunoglobulin quantification	X											
Bone Marrow Biopsy and Aspiration, with Morphology, IHC, Cytogenetics by Standard Karyotyping, FISH Panel [n]	X							PRN				
DLBCL:												
Lymph Node/Extranodal Lesion Biopsy[n]	X							PRN				
Bone Marrow Biopsy and Aspiration [n]	X							PRN				
G6PD Screening [m]	X											
TLS labs: Potassium, Calcium, Phosphorus, Uric Acid (3 and 5 hrs After Start)		X										
Laboratory Procedures/Assessments: Analysis Performed by Central Laboratory												
Whole Blood for Correlative Studies (RNA/DNA)		X		X					X			
Blood for Biomarker Studies (Plasma and Serum)		X		X					X			
Blood for Genetic Analysis [r]		X										
Saliva for Genetic Analysis [r]		X										
Pembrolizumab Pharmacokinetic Level and Anti-Pembrolizumab Antibodies [w]		X							X	X		
Pharmacokinetics (Dinaciclib) [s]		X				X [t]						

Abbreviations: aPTT = activated partial thromboplastin time; β-hCG = beta human chorionic gonadotrophin; CBC = complete blood count; CLL = chronic lymphocytic leukemia; CR = complete remission; CT = computed tomography; Discon = discontinuation; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FDG = fluorodeoxyglucose; FISH = flourescence in situ hybridization; FT4 = thyroxinea; G6PD = glucose-6-phosphate dehydrogenase deficiency; IHC = immunohistochemistry; MM = multiple myeloma; MRI = magnetic resonance imaging; PET = positron-emission tomography; PRN = perform as needed; PT (INR) = prothrombin time (international normalized ratio);SAE = serious adverse events; T3 = triothyronine; TSH = thyroid stimulating hormone (thyrotropin); TSL = tumor lysis syndrome.

a. In general, assessments/procedures are to be performed prior to trial treatment on each cycle day unless otherwise specified. In general, the window for each visit is ±3 days unless otherwise noted. Trial treatment should begin on the day of treatment allocation or as close as possible to the date on which the subject is allocated/assigned.

b. Screening visit procedures must be performed within 28 days before Day 1 unless otherwise noted.

c. 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 (ie, within 28 days prior to the first dose of trial treatment). A screening number will be assigned when the trial informed consent is signed. Refer to Section 7.1.1.1.1 and Section 7.1.1.7.

d. Signing the informed consent for Future Biomedical Research samples is optional. Detailed instructions for the management of specimens for future biomedical research are provided in the Procedures Manual and Section 7.1.1.1.2.

e. Prior medications – Record all medications taken within 28 days of the screening visit. Concomitant medications – Enter new medications started during the trial through the 30-day Safety Follow-up visit. Record all medications taken for SAEs. Refer to Section 7.1.1.5 for additional details.

f. In subjects who discontinue trial therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging (or laboratory for MM) every 12 weeks (± 14 days) for at least 12 months or until (1) the start of new anticancer treatment, (2) documented disease progression, (3) death, or (4) the end of the trial, whichever occurs first.

g. After subjects who experience confirmed site-assessed PD or who start a new anti-cancer therapy, each subject will be contacted by telephone for survival approximately every 12 weeks (± 14 days) until the subject withdraws consent, is lost to follow-up, death, or the trial ends, whichever occurs first. In addition, upon Sponsor request, subjects may be contacted for survival status at any time during the course of the trial.

h. Vital signs are collected at all visits/cycles and include temperature, pulse, blood pressure, respiratory rate, and weight. Height will be measured at screening (Visit 1) only.

i. For subjects with MM, perform disease assessments at the beginning of every cycle (except Cycle 1). Imaging and disease assessments are not to be delayed for cycle delays

j. For subjects with MM, perform skeletal survey at screening to assess for bone disease. Imaging for plasmacytoma at screening is only done in subjects that have a plasmacytoma. After baseline, perform skeletal surveys or imaging for plasmacytoma if clinically indicated (Section 7.1.2.8.2).

k. For subjects with DLBCL, perform PET/CT during screening. On-trial perform disease assessments using PET/CT if PET-avid at baseline; otherwise CT may be used (Section 7.1.2.8.3).

l. 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 trial site laboratory will be required. Monthly pregnancy testing should be conducted as per local regulations where applicable. All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of each cycle of trial treatment and 30 days post-treatment.
m. For subjects with CLL and DLBCL who will receive rasburicase as a premedication, G6PD testing should be completed locally when required in subjects at higher risk of G6PD deficiency (eg, subjects of African or Mediterranean ancestry). These subjects should be tested and found to have adequate levels before treatment with rasburicase (Section 5.2.1.3.1).
n. All subjects must provide newly obtained (within 3 months) bone marrow biopsy material for biomarker analysis at screening. If bone marrow biopsy was performed within 3 months before screening but subject had anticancer treatment after biopsy, the bone marrow biopsy and aspiration should be repeated. If bone marrow biopsy was performed within 3 months before screening but subject has not had anticancer treatment after biopsy, the bone marrow biopsy and aspiration does not need to be repeated. Subjects with rrDLBCL must provide core or excision biopsy of a lymph node or extranodal lesion (performed within 3 months) at screening. For MM, bone marrow analysis will include bone marrow morphology, IHC, Cytogenetics by standard karyotyping, FISH panel. Post-baseline bone marrow or lymph node (DLBCL) assessments should be performed to confirm response as defined by disease-specific criteria, or as clinically indicated. For DLBCL, subsequent bone marrow assessment will only be performed in subjects who have bone marrow involvement at screening. A bone marrow biopsy assessment should be performed to confirm CR (if subject had bone marrow involvement at screening) and as clinically indicated.
o. Baseline serum and urine M protein (24 hr) levels will be assessed by electrophoresis and immunofixation. Free light chain (FLC) levels and ratio will also be assessed. If serum M protein by electrophoresis (SPEP) is ≥ 1g/dL at baseline, SPEP will be assessed after each cycle. Post-baseline serum: immunofixation needed only in absence of M-spike. Post-baseline: perform all serum, urine, and FLC analyses as needed to confirm response per criteria.
p. If baseline urine M protein (24 hr) by electrophoresis (UPEP) ≥ 200 mg, collect urine (24 hr) after each cycle. Otherwise, assess urine protein (24 hr) as needed to confirm response per criteria.
q. FLC post-baseline: for subjects with non-secretory myeloma (SPEP < 1 g/dL and UPEP < 200 mg/24 hr) at baseline, but serum light chain ≥ 10 mg/dL, serum FLC will be assessed after each cycle. Otherwise, assess FLC as needed to confirm response per criteria.
r. Refer to Section 7.1.3 Laboratory Procedures/Assessments and the Procedures Manual for additional details. For CLL cohort only: Saliva for genetic analysis for CLL subjects is to be sent to the Central Lab and not performed locally.
s. Blood samples for dinaciclib PK will be collected on Cycle 3 Day 1 (14 mg/m^2) at the following times: pre-dose, and 1 hour, 2 hours (end of infusion), 3 hours and 5 hours after the start of the infusion. Refer to Section 7.1.3.5 and the Procedures Manual for additional details.
t. NOT to be repeated at every cycle thereafter.
u. A historical IgVH mutational status result is to be permitted for CLL subjects.
v. 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.
w. Blood samples for pembrolizumab PK levels and anti-pembrolizumab antibodies will be collected within 24 hours before infusion at Cycle 1 Day 1, at the time of discontinuation and post treatment safety follow up (30 days after the last dose of trial treatment or before the initiation of a new antineoplastic treatment, whichever comes first).
x. Quantitative immunoglobulins will be collected predose on Cycle 1 Day 1, every 3 cycles while subject is on trial drug, and post-treatment safety follow-up (30 days after the last dose of trial treatment or before the initiation of a new antineoplastic treatment, whichever comes first).
y. PT (INR) and aPTT are required at screening only and to be performed more frequently if clinically indicated for subject on anticoagulants.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before

performing any procedure related to Future Biomedical Research. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

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

Prior acute and/or chronic Graft versus Host Disease, 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 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 trial will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial through the Safety Follow-up visit.

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

7.1.1.5.3 Prior Cancer Treatment Details

The investigator or qualified designee will review all prior cancer treatments including but not limited to systemic treatments, prior transplantation, radiation, and surgeries and record in the trial database.

7.1.1.5.4 Subsequent Antineoplastic Therapy

The investigator or qualified designee will review all new antineoplastic therapy initiated after the last dose of trial treatment.

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

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.

7.1.1.6 Assignment of Screening Number

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

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

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.

7.1.1.7 Assignment of Treatment/Randomization Number

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

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

7.1.1.8 Trial Compliance

Interruptions from the protocol specified treatment plan for ≥ 3 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of dinaciclib and pembrolizumab will be done 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.

The instructions for preparing and administering dinaciclib and pembrolizumab will be provided in the Pharmacy Manuals.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Oncologic Disease Details

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

DLBCL subtypes, including germinal center B-cell–like (GCB), activated B-cell–like (ABC), and unclassified (not fitting the criteria for either ABC or GCB DLBCL subtypes), are requested. Other known pathology and biology parameters, such as T-cell/histiocyte-rich B-cell lymphoma, Epstein-Barr virus positive lymphoma, MYC, B-cell lymphoma 2 (BCL2) gene rearrangement, expression and MYC gene alterations, should be recorded if data are available.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. At this visit, 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.

7.1.2.3 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.

7.1.2.4 Vital Signs

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

7.1.2.5 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG status (Section 12.4) at screening, on Day 1 of Q3W cycle and discontinuation of trial treatment as specified in the Trial Flow Chart (Section 6.0).

7.1.2.6 Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. AEs will be graded and recorded throughout the trial and during the follow-up period according to National Cancer Institute's CTCAE Version 4.0 (Section 12.11). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

7.1.2.7 Criteria for Assessment of Disease

Antitumor activity of dinaciclib and pembrolizumab will be evaluated locally using the following criteria:

- CLL: iwCLL guidelines [1]
- MM: International uniform response criteria for multiple myeloma [2]
- DLBCL: Revised Response Criteria for Malignant Lymphoma [3]

7.1.2.7.1 Disease Assessment During Trial

Disease assessments should be performed locally per the frequency defined in the Trial Flow Chart (Section 6.0). There is a ± 7-day window for assessments performed after Day 1.

Disease assessments or scans should not be delayed for delays in cycle starts.

Images and/or laboratory assessments may be requested by the Sponsor for independent review.

7.1.2.7.2 Disease Assessment of Immunotherapeutic Agents

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

Refer to Section 7.1.2.7.3 for confirmation assessment requirements when a subject's disease response assessment shows PD.

7.1.2.7.3 Disease Progression Assessments

A subject with progression of disease documented at a disease response assessment may continue trial treatment until the next response assessment, provided the subject's clinical condition is stable. However, a response assessment should occur at any time where there is clinical suspicion of progression.

Subjects may only receive treatment while waiting for confirmation of PD if the following criteria are met:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status

- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites

After the first disease response assessment, it is at the discretion of the investigator to keep a clinically stable subject on trial treatment or to stop trial treatment until a repeat assessment is performed. Subjects who are deemed clinically unstable after first disease response assessment should not continue trial treatment and must be discontinued from the trial. Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation.

For subjects noted to have progression of disease at a time point beyond the disease response assessment, the investigator, upon consultation with the Sponsor, may keep a clinically stable subject on trial treatment as long as the subject is deriving clinical benefit.

Sponsor recommendation is that the subject should be on trial treatment for at least 8 weeks in order to confirm disease progression and at least 2 consecutive assessments with minimum of 2 weeks of time between assessments are required unless there is a clinical compromise in which case the subject may be discontinued after consultation with the Sponsor.

7.1.2.8 Assessment of Disease and Tumor Response

7.1.2.8.1 CLL Response Assessments

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 Cycle 1 Day 1.

CT scans of the neck, chest, abdomen, and pelvis will be obtained at screening within 28 days of Cycle 1 Day 1. Follow-up CT scans of the neck should be performed if enlarged lymph nodes (defined as ≥ 1.5 cm) are detected on the screening CT neck scan or if medically indicated by the discretion of the treating physician.

CT scans will be repeated every 3 cycles (approximately 9 weeks) despite any delays in treatment. CT scans will be read locally.

Response will be determined locally according to the iwCLL criteria, using results of the subject's CT scan, hematology laboratory results (complete blood counts), and presence of CLL symptoms as described in Section 12.7. Response assessments should be completed in conjunction with the subject's CT scan schedule.

If medically appropriate, a confirmatory assessment of the initial progression event should be performed within 9 weeks. A CT scan of the neck (if indicated), chest, abdomen and pelvis and hematology laboratory (complete blood counts) will be obtained, and the presence of CLL symptoms will be determined at each response assessment time point.

7.1.2.8.2 Multiple Myeloma Response Assessments:

7.1.2.8.2.1 Myeloma Laboratory Testing Disease Measurements

Baseline

For subjects with MM, collect serum and urine samples within 28 days of Cycle 1 Day 1 for baseline disease assessment. Baseline serum and urine (24 hr) M protein levels will be assessed by electrophoresis and immunofixation. Free light chain (FLC) levels and ratio will also be assessed.

Serum electrophoresis (SPEP)

If serum M protein by electrophoresis (SPEP) ≥ 1 g/dL at baseline, SPEP will be assessed after each cycle.

Urine electrophoresis (UPEP)

If urine M protein (24 hr) by electrophoresis (UPEP) ≥ 200 mg, UPEP (24 hr) will be assessed after each cycle.

FLC

For subjects with non-secretory myeloma (SPEP < 1 g/dL and UPEP < 200 mg/24 hr) at baseline, but serum light chain ≥ 10 mg/dl, serum FLC will be assessed after each cycle.

Best Response

Laboratory assessments should be repeated to confirm best response, including SPEP and UPEP, serum and urine immunofixation, and FLC. Bone marrow biopsy is recommended to confirm CR.

Response will be determined locally according to IMWG criteria [2] described in Section 12.8.

7.1.2.8.2.2 Imaging for Subjects with Myeloma Bone Disease

Skeletal survey by conventional radiography must be performed at screening within 28 days of Cycle 1 Day 1 to determine the extent of the subject's myeloma bone disease. The use of conventional or low dose CT scan or magnetic resonance imaging (MRI) bone survey is acceptable. A skeletal survey performed as standard of care prior to signing consent can be used for screening if performed within 28 days of Cycle 1 Day 1.

During the course of the trial, skeletal surveys should be performed as clinically indicated. If suspected disease progression, the same modality of imaging used at screening should be performed for assessment of progression. The development of a compression fracture does not necessarily exclude antitumor response if not related to disease progression. Bone lesions should be considered as non-measurable disease and recorded as such.

For subjects with extramedullary soft tissue plasmacytomas, an MRI, CT, or positron emissions tomography (PET)/CT should be performed at baseline within 28 days of Cycle 1 Day 1. An MRI, CT, or PET/CT performed as standard of care prior to signing consent can be used for screening if performed within 28 days of Cycle 1 Day 1. During the course of the trial, subsequent imaging should be performed as clinically indicated (whether or not an

extramedullary soft tissue plasmacytoma was present at baseline) and at the time of a CR or stringent CR (sCR) assessment. The same modality of imaging used at screening should be performed for subsequent assessments.

At any time a subject develops bone pain or there is a suspicion of new bone disease or extramedullary soft tissue plasmacytoma indicative of disease progression, appropriate imaging according to clinical practice should be performed to confirm disease progression.

7.1.2.8.3 DLBCL Disease Response Assessment

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 Cycle 1 Day 1. CT and PET should be used throughout the trial. For lymphomas that are not PET-avid at screening, PET does not need to be repeated in follow-up assessments.

The site trial team must review pre-trial images to confirm the subject has measurable disease as defined in the inclusion criteria.

PET/CT scans of the chest, abdomen, and pelvis will be repeated every 3 cycles (9 weeks) or when medically indicated despite any delays in treatment.

PET/CT scans of the neck should be performed if enlarged lymph nodes are detected during the PE exam or if otherwise medically indicated by the discretion of the treating physician.

PET/CT scans will be read locally.

Response assessment by CT or PET/CT is based on the Revised Response Criteria for Malignant Lymphoma [3] described in Section 12.9. If complete remission is documented by both CT and FDG-PET, subsequent assessments may be by CT only, with PET used only if relapse or recurrence is suspected. Local reading (investigator assessment with site radiology reading) will be used to determine subject eligibility and for subject management.

Assessment of lymphoma B symptoms should occur with each lymphoma disease response assessment (Section 12.10). If a subject has radiographically progressive disease but is clinically stable and suspicious for pseudo-progression, the subject can continue trial treatment after consultation with the Sponsor. Additionally, the subject should be rescanned within 4 to 6 weeks for confirmation. The subject should discontinue trial treatment if they meet discontinuation criteria described in Sections 5.8.1, 7.1.2.7.2, and 7.1.2.7.3.

7.1.2.9 Biopsy Collection and Correlative Studies Blood Collection

All subjects enrolled into this trial must be able to provide a bone marrow biopsy sample or newly obtained core or excisional biopsy (fine needle aspirate not adequate) to be submitted for characterization. Subjects with rrDLBCL must also provide a core or excisional biopsy add of lymph node or extranodal lesion at Screening. If the investigator deems that a biopsy is unsafe or not indicated for other reasons, a Sponsor consultation is required.

Biopsies done previously within 3 months before screening are permitted to be used for this trial. If bone marrow biopsy was performed within 3 months before screening but the subject had anticancer treatment after biopsy, the bone marrow biopsy and aspirate should be repeated.

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. DLBCL subtypes, GCB, ABC, and unclassified (not fitting the criteria for either ABC or GCB DLBCL subtypes), need to be classified and recorded. Other known pathology and biology parameters, such as T-cell/histiocyte-rich B-cell lymphoma, Epstein-Barr virus positive lymphoma, MYC, BCL2 gene rearrangement, expression and MYC gene alterations, should be recorded if data is available.

Bone marrow and lymph node biopsies will be collected as per Table 14.

Table 14 Bone Marrow or Lymph Node Biopsy Assessments

Tumor type	Timing of Biopsy
CLL: Bone marrow biopsy and aspiration	Screening; to confirm CR, or as clinically indicated
MM: Bone marrow biopsy and aspiration	Screening; to confirm CR, sCR, or as clinically indicated
DLBCL: Lymph node or extranodal lesion biopsy, bone marrow biopsy (aspiration only at screening if bone marrow biopsy was performed >3 months before screening and the subject had a subsequent anticancer treatment).	Screening; to confirm CR (if subject had bone marrow involvement at screening), or as clinically indicated All subjects will have lymph node or extranodal lesion biopsy performed during screening. Bone marrow biopsy/aspirate may be performed during screening or an archived bone marrow will be collected at Screening. Subsequent bone marrow assessments will only be performed in subjects who have bone marrow involvement at screening.

Abbreviations: CLL = chronic lymphocytic leukemia; CR = complete response; DLBCL = diffuse large B-cell lymphoma; MM = multiple myeloma; sCR = stringent complete response.

Tissue for correlative biomarker studies should be collected as per Table 15.

Table 15 Tissue Collection for Correlative Biomarkers Studies

Indication	Timing of Correlative Blood Collection
Whole Blood for RNA/DNA:	Pre-dose on C1DI, pre-dose on C2D1, Discontinuation
Blood for biomarker studies (plasma and serum)	Pre-dose on C1D1, pre-dose on C2D1, Discontinuation
Blood for genetic analysis	Pre-dose on C1D1
CLL: Saliva for genetic analysis	Pre-dose on C1D1

Abbreviations: C1D1 = Cycle 1 Day 1; C2D1 = Cycle 2 Day 1; CLL = chronic lymphocytic leukemia.

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 Trial Procedures Manual. Refer to the Trial Flow Chart (Section 6) for the timing of laboratory assessments.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Table 16. Except for analyses of biomarkers or other prognostic indicators (proteomics, genetics, transcriptional analysis, pharmacokinetics, antibodies), all tests will be analyzed locally.

Table 16 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (serum or urine)[a]
Hemoglobin	Alkaline phosphatase	Glucose	PT/INR
Platelet count	Alanine aminotransferase	Protein	aPTT
WBC (total and differential)[d]	Aspartate aminotransferase	Specific gravity	Total T3 or free T3, FT4, and TSH[b]
RBC	Bicarbonate[c]	Microscopic exam, if abnormal results are noted	B2 microglobulin G6PD (as necessary)
Absolute lymphocyte count[d]	Calcium		
	Chloride		
Absolute neutrophil count[d]	Creatinine		
	Glucose LDH		
	Phosphorus		
	Potassium		
	Sodium		
	Total bilirubin		
	Direct bilirubin		
	Total protein		
	Uric Acid		
	Blood urea nitrogen		

[a] Perform on women of childbearing potential only 72 hours prior to Day 1 of Cycle 1. All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of each cycle of trial treatment and 30 days post-treatment.

[b] T3 is preferred; if not available free T3 may be tested.

[c] If this test is not done as part of local standard of care, this test does not need to be performed.

[d] Report % or absolute results per standard of practice. Report the results in the same manner throughout the trial.

Abbreviations: aPTT = activated partial thromboplastin time; G6PD = glucose-6-phosphate dehydrogenase deficiency; INR = international normalized ratio; LDH = lactic dehydrogenase; PT = prothrombin time; RBC = red blood cells; WBC = white blood cells.

7.1.3.2 Pregnancy Test

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

7.1.3.3 Evaluations for Subjects with CLL

For subjects with CLL, at baseline assess for constitutional symptoms and analyze blood or serum as appropriate for the following (all analyses local). Repeat at post-baseline as needed (Section 6).

- Fluorescence in situ hybridization (FISH) or cytogenetics for del17p, del13q, del11q, trisomy 12,
- IgVH mutational status (mutated is ≥ 2% difference from germline)
- CD38 (percentage of CLL cells expressing CD38)
- CD4, CD8
- Quantitative serum immunoglobulins (IgA, IgG, IgM)

7.1.3.4 Evaluations for Subjects with MM

For subjects with MM, baseline bone marrow analysis (local) will include morphology, immunohistochemistry, cytogenetics by standard karyotyping, and FISH panel. Additionally, baseline quantitative serum immunoglobulins (IgA, IgG, IgM) are required. Repeat these studies if post-baseline bone marrow is done (Section 6).

7.1.3.5 Pharmacokinetic/Pharmacodynamic Evaluations

Blood samples will be obtained to measure pharmacokinetics of serum dinaciclib on Cycle 3 Day 1 and of serum pembrolizumab as per the Trial Flow Charts (Section 6). If the infusion is being given through a central venous catheter, either arm may be used to obtain pharmacokinetic samples.

7.1.3.6 Blood Collection for Anti-pembrolizumab Antibodies

Sample collection, storage, and shipment instructions for serum samples will be provided in the procedure manual. Anti-pembrolizumab antibody samples should be drawn according to the collection schedule (Section 6). Every effort should be taken to collect samples at 30 days after end of treatment (or **before** the subject starts new anticancer therapy, **whichever comes first**) for pembrolizumab pharmacokinetic level and anti-pembrolizumab antibodies.

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

7.1.3.7 Blood Collection for Correlative and Biomarker Studies

Any leftover samples from the correlative and biomarker blood studies will be stored for future biomedical research if the subject signs the Future Biomedical Research consent. Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

7.1.3.8 Planned Genetic Analysis Sample Collection

Sample collection, storage, and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedures Manual. Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/Independent Ethics Committee [IEC] does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Leftover DNA extracted from planned genetic analysis samples will be stored for future biomedical research only if subject signs the Future Biomedical Research consent.

7.1.3.9 Future Biomedical Research

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

- DNA for future research
- Leftover bone marrow biopsy samples
- Leftover lymph node biopsies
- Leftover DNA and RNA from correlative studies
- Leftover plasma and serum from biomarker studies

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to

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

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

7.1.4.1.2 Lost to Follow-up

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

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

- The investigator or designee must make every effort to regain contact with the subject at each missed visit (eg, phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.

- Note: A subject is not considered lost to follow-up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines.

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Domiciling

Subjects with CLL or DLBCL will report to the clinical research unit on Day -1 prior to the scheduled day of trial drug administration on Cycle 1 Day 1 and remain in the unit until approximately 10 hours post-dose on Day 1. At the discretion of the investigator, subjects may be requested to remain in the clinical research unit longer.

7.1.4.4 Calibration of Critical Equipment

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

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

Critical Equipment for this trial includes:

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

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

7.1.5 Visit Requirements

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

7.1.5.1 Screening

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

Written consent for the main trial 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:

- 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 trial site laboratory).

Subjects may be rescreened 1 time after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

7.1.5.2 Treatment Period

Visit requirements are outlined in Section 6– Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures.

7.1.5.3 Post-Treatment Visits

Antineoplastic treatments started after trial treatment completion are collected during Follow-up and Survival Follow-up.

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment **or before the initiation of a new antineoplastic treatment, whichever comes first**. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new antineoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded.

7.1.5.4 Efficacy Follow-up Visits

Subjects who complete the protocol-required cycles of treatment or who discontinue trial treatment for a reason other than confirmed PD will move into the Follow-Up Phase and should be assessed every 12 weeks (± 14 days) for at least 12 months to monitor disease status (Section 6). Every effort should be made to collect information regarding disease response status until the start of new antineoplastic therapy, documented PD by investigator assessment, death, or end of the trial. Information regarding post-trial antineoplastic treatment will be collected if new treatment is initiated.

7.1.5.4.1 Follow-Up Post-Allogeneic Stem Cell Transplantation

For subjects who have an allogeneic SCT within 24 months of last dose of pembrolizumab or before the end of the trial, transplant parameters will be collected, and specific events will be collected as ECIs for 18 months from the date of the allogeneic transplant or until the end of the trial, to include graft-versus-host-disease, hepatic veno-occlusive disease and/or sinusoidal syndrome, febrile syndrome (a steroid-requiring febrile illness without an infectious cause), pulmonary complications, immune-mediated AEs, critical illness, and transplant-related mortality, for all grades, and regardless of relationship to trial drug. Additional medically important AEs post-allogeneic SCT may be submitted at the investigator's discretion (Section 7.2.3.2.1). If available and relevant to an event post-allogeneic SCT, concomitant medications and/or laboratory results may also be reported.

Post-allogenic-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.

7.1.5.4.2 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new antineoplastic therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks (± 14 days) to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first. The first survival follow-up assessment should be scheduled as described below:

For participants who discontinue treatment intervention and who will not enter the efficacy follow-up phase, the first survival follow-up assessment will be scheduled 12 weeks after the discontinuation visit and/or safety follow-up visit (whichever is last).

For participants who completed assessments in the efficacy follow-up phase, the first survival follow-up assessment will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

7.1.5.4.3 Survival Status

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

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab defined as any dose of ≥ 1000 mg (5 times the protocol-defined dose), and for dinaciclib defined as any dose > 70 mg/m^2. No specific information is available on the treatment of overdose of pembrolizumab or dinaciclib. In the event of overdose, pembrolizumab or dinaciclib should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be

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

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

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 14 days following cessation of Sponsor's product 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 17 for additional details regarding each of the above criteria.

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

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

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

7.2.3.2.1 Follow-Up Post-Allogeneic Stem Cell Transplantation

For subjects who have an allogeneic SCT within 24 months of last dose of pembrolizumab or before the end of the trial, transplant parameters will be collected, and specific ECIs will be collected for 18 months from the date of the allogeneic transplant, to include graft-versus-host-disease, hepatic veno-occlusive disease and/or sinusoidal syndrome, febrile syndrome (a steroid-requiring febrile illness without an infectious cause), pulmonary complications, immune-mediated AEs, critical illness, and transplant-related mortality for all grades, and regardless of relationship to trial drug. Additional medically important AEs post-allogeneic SCT may be submitted at the investigator’s discretion.

Post-allogenic SCT events of ECIs that occur after the normal safety follow-up period and before the end of the trial 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.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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 trial will be forwarded to global safety as a SAE within 24 hours of determination that the event is not progression of the cancer under trial.

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.

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

Table 17 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	

Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		

Record one of the following	Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the trial. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental statistical analysis plan and referenced in the Clinical Trial Report (CSR) for the trial. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized in the Statistical Analysis Plan Summary below; the comprehensive plan is provided in Sections 8.2 to 8.12.

Unless indicated otherwise, statistical analyses will be performed separately for Dose Evaluation and Signal Detection of this trial. For Signal Detection, statistical analyses will be performed separately by cohort.

Statistical Analysis Plan Summary

Trial Design Overview	This trial, entitled "Phase Ib Trial of Pembrolizumab (MK-3475) in Combination with Dinaciclib (MK-7965) in Subjects with Hematologic Malignancies (KEYNOTE-155)" is a multicenter, multiple-cohort, non-randomized trial of dinaciclib (MK-7965) in combination with pembrolizumab (MK-3475) in subjects with relapsed or refractory CLL, MM, or DLBCL. After a Dose Evaluation phase, the cohorts (CLL, MM, DLBCL) will be enrolled for Signal Detection.
Treatment Assignment	In Dose Evaluation, 12 subjects (at least 3 subjects each with rrCLL, rrMM, or rrDLBCL) meeting inclusion/exclusion criteria will receive pembrolizumab and dinaciclib at the initial dose (Dose Level 0) as described in Table 3 and Table 11; Dose Levels -1 and -2 will be evaluated with no restriction on the distribution of disease types rrCLL, rrMM, and rrDLBCL. If and when the safety criteria for Dose Evaluation are met, Signal Detection will use the same doses of pembrolizumab and dinaciclib.
Analysis Populations	In Signal Detection, the primary analysis population for both efficacy and safety assessments is the "All Subjects as Treated" (ASaT) population, defined as all subjects who receive at least one dose of trial medication (pembrolizumab or dinaciclib).
Primary Endpoint(s)	The primary endpoint is DLT (as defined in Section 5.2.1.4).
Key Secondary Endpoints	1. ORR according to investigator assessment using the overall population and for disease-specific criteria (as applicable) 2. DOR 3. PFS 4. OS
Statistical Methods for	In Signal Detection, the point estimate of the ORR will be calculated as well as

Key Efficacy Analyses	a 95% 2-sided exact confidence interval.
Statistical Methods for Key Safety Analyses	In Dose Evaluation, descriptive statistics will be used to evaluate the DLT rate. Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate.
Interim Analyses	In Signal Detection, both safety and efficacy will be assessed prior to full enrollment within each cohort. In terms of efficacy, a cohort may terminate if inadequate efficacy is observed (0 responses out of first 12 evaluable subjects in the MM and DLBCL cohorts; 2 or fewer out of 12 for the CLL cohort); refer to Section 8.7 for details.
Multiplicity	No adjustment for multiplicity is planned.
Sample Size and Power	The minimum and maximum overall sample size for this trial is 102 and 131 subjects, respectively (ie, 12 to 41 from Dose Evaluation plus 90 from Signal Detection). Assuming a 5% non-evaluable rate (ie, not evaluable for DLT in Dose Evaluation or not treated in Signal Detection), a maximum of 138 subjects would be enrolled in this trial. In Signal Detection, with 30 subjects in the experimental arm (pembrolizumab + dinaciclib), the maximum half-width of the two-sided 95% confidence interval for ORR within each cohort is 19%.

8.2 Responsibility for Analyses/In-House Blinding

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

This trial is being conducted as an open-label trial; therefore, subjects, investigators, and Sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

8.3 Hypotheses/Estimation

No formal hypotheses are to be tested in this trial; objectives of the trial are stated in Section 3.

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

Efficacy endpoints will be based on investigator assessment using the disease-specific criteria outlined in Section 7.1.2.8.

Primary

Objective Response Rate

ORR is defined as the proportion of subjects in the analysis population who achieved at least a partial response according to the disease-specific criteria (CR+PR for CLL and DLBCL; sCR+CR+VGPR (very good partial remission)+PR for MM).

Secondary

Duration of Response

For subjects who demonstrated a response (PR or better), DOR is defined as the time from first documented evidence of response until first documented evidence of disease progression or death due to any cause, whichever occurs first.

Progression-Free Survival

PFS is defined as the time from first dose of trial treatment to the first documented evidence of disease progression or death due to any cause, whichever occurs first.

Overall Survival

OS is defined as the time from first dose of trial treatment to death due to any cause.

8.4.2 Safety Endpoints

Safety measurements are described in Section 7.2.

8.5 Analysis Populations

In Dose Evaluation, subjects are considered to be evaluable for DLT assessment if the subjects meet all the following criteria:

- Subjects enrolled and received at least one dose of trial medication.
- Subject did not discontinue within the first 2 cycles, or subject experienced a DLT prior to completing the first 2 cycles of treatment

In Signal Detection, the analyses of efficacy and safety endpoints are based on the ASaT population. Subjects will be included if they receive at least 1 dose of trial medication.

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

8.6 Statistical Methods

This section provides the statistical details for analyses of efficacy and safety endpoints.

A summary of the primary analysis strategy for the primary and secondary efficacy endpoints is provided in Table 19.

The analyses will be performed for Signal Detection only, separately within each cohort. In Dose Evaluation, subject listings for these endpoints (ORR, DOR, PFS, and OS) will be provided.

8.6.1 Objective Response Rate

The analysis of ORR will consist of the point estimate and 95% 2-sided exact confidence interval using the Clopper-Pearson method, which will have at least 95% coverage of the true rate.

8.6.2 Duration of Response

The analysis of DOR will consist of Kaplan-Meier estimates. DOR data will be censored on the date of the last disease assessment documenting absence of progressive disease for subjects who do not have tumor progression and are still on trial at the time of an analysis, are given antitumor treatment other than the trial treatment, or are removed from trial prior to documentation of tumor progression.

8.6.3 Progression-Free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve. Additional details, including censoring rules for those subjects without PD, are summarized in Table 18.

Table 18 Censoring Rules for PFS

Situation	Analysis
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death
PD or death documented after ≥ 2 missed disease assessments	Progressed at date of documented PD or death
No PD and no death and lost to follow-up after ≥ 2 missed disease assessments	Censored at last disease assessment

Abbreviation: PD = progressive disease.

8.6.4 Overall Survival

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

Table 19 Analysis Methods for Efficacy Endpoints (Signal Detection)

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
ORR – by investigator assessment using disease-specific criteria[a]	2-sided 95% exact confidence interval	ASaT	Subjects with missing data are considered non-responders.
Secondary:			
DOR – by investigator assessment using disease-specific criteria[a]	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis.
PFS – by investigator assessment using disease-specific criteria[a]	Summary statistics using Kaplan-Meier method	ASaT	Censored at last assessment (see Table 18 for additional details)
OS	Summary statistics using Kaplan-Meier method	ASaT	Censored at last assessment

[a] CLL based on iwCLL guidelines [1]; MM based on IMWG criteria [2]; DLBCL based on the Revised Response Criteria for Malignant Lymphoma [3].

Abbreviations: ASaT = all subjects as treated; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

8.6.5 Statistical Methods for Safety Analyses

In both Dose Evaluation and Signal Detection, safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, ECIs, laboratory tests, and vital signs. Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate.

See Section 8.8 for statistical details on the dose evaluation of pembrolizumab plus dinaciclib conducted in Dose Evaluation.

8.6.6 Other Analyses

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

Additional exploratory analyses will be described in the supplemental statistical analysis plan.

8.7 Interim Analysis

In Signal Detection, a futility analysis will be conducted separately within each cohort. After the first 12 subjects are evaluable for efficacy (treated and with at least one post-baseline

disease assessment), the ORR will be evaluated according to the disease-specific criteria. Enrollment would not be paused within a cohort during the futility evaluation. For the MM and DLBCL cohorts, if 0 responses are observed among the 12 subjects, which would rule out an ORR of 17% with 90% confidence (1-sided), the cohort may be terminated; for the CLL cohort, if 2 or fewer responses are observed among the 12 subjects, which would rule out an ORR of 39% with 90% confidence (1-sided), the totality of the data including both safety and efficacy will be evaluated to decide whether or not to continue enrollment in that cohort.

8.8 Sample Size and Power Calculation

In the Dose Evaluation phase, a minimum of 12 subjects will be evaluated at Dose Level 0.

A potential maximum of 41 subjects may be evaluated across dose levels for DLTs as described in Section 5.2.1.3.4. Twelve subjects evaluated at Dose Level 0 is not entirely based on statistical grounds but would allow for at least 3 evaluated per disease (rrCLL, rrMM, and rrDLBCL) with an overall statistical assessment of the DLT rate as described in Table 12.

In Signal Detection phase, the proposed sample size is 30 subjects for the primary analysis population (ASaT) for each cohort (CLL, MM, DLBCL), 90 in all. With 30 subjects in each cohort, the maximum half-width of the two-sided 95% exact confidence interval for ORR within each cohort is 19%. Table 20 describes examples of 95% confidence intervals per cohort across a possible range of ORRs.

Table 20 Precision (95% Confidence Intervals) for Range of Observed ORR (33% - 83%)

Number of responses/Number of treated subjects (ORR)	95% 2-sided Confidence Interval[a]
10/30 (33%)	(17, 53)
15/30 (50%)	(31, 69)
20/30 (67%)	(47, 83)
25/30 (83%)	(65, 94)

[a] exact (Clopper-Pearson) confidence limit for the binomial proportion.
Abbreviation: ORR = objective response rate.

Thus, the minimum and maximum overall sample size for this trial is 102 and 131 subjects, respectively, 12 to 41 subjects from Dose Evaluation plus 90 from Signal Detection. Assuming a 5% non-evaluable rate (ie, not evaluable for DLT in Dose Evaluation or not treated in Signal Detection), a maximum of 138 subjects would be enrolled in this trial.

8.9 Multiplicity

No multiplicity adjustment is planned in this trial.

8.10 Subgroup Analyses and Effect of Baseline Factors

Point estimate of the ORR (with an exact two-sided 95% confidence interval) will be provided within each disease cohort. For subgroups such as age (≤ 65 vs > 65 years), sex (female vs male), race (white vs non-white) and region (US, ex-US), ORR 95% confidence interval will be provided if the subgroup sample size is adequate.

8.11 Compliance (Medication Adherence)

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

8.12 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

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

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

Table 21 Product Descriptions

Product Name & Potency	Dosage Form	Source / Additional Information
Pembrolizumab (MK-3475) 50 mg	Lyophilized powder for IV injection	Provided centrally by the Sponsor
Pembrolizumab (MK-3475) 100 mg/4mL	Solution for infusion	Provided centrally by the Sponsor. However, solution will not be supplied at the initiation of the trial. It is considered a back-up formulation.
Dinaciclib (MK-7965) 5 mg/mL	Solution for infusion	Provided centrally by the Sponsor

9.2 Packaging and Labeling Information

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

Open-label vials will be provided for subject dosing.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the

Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will

allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*

Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.9 – Future Biomedical Research will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

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.

d. Future Biomedical Research Specimen Collections

[insert: 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. **OR** Buccal swab specimens for DNA isolation will be obtained at a time when the subject is having other trial procedures conducted.] 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 the contract. 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 contacting 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 future biomedical research, risks to the subject have been minimized. (No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research [ie, only leftover samples are being retained].)

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.

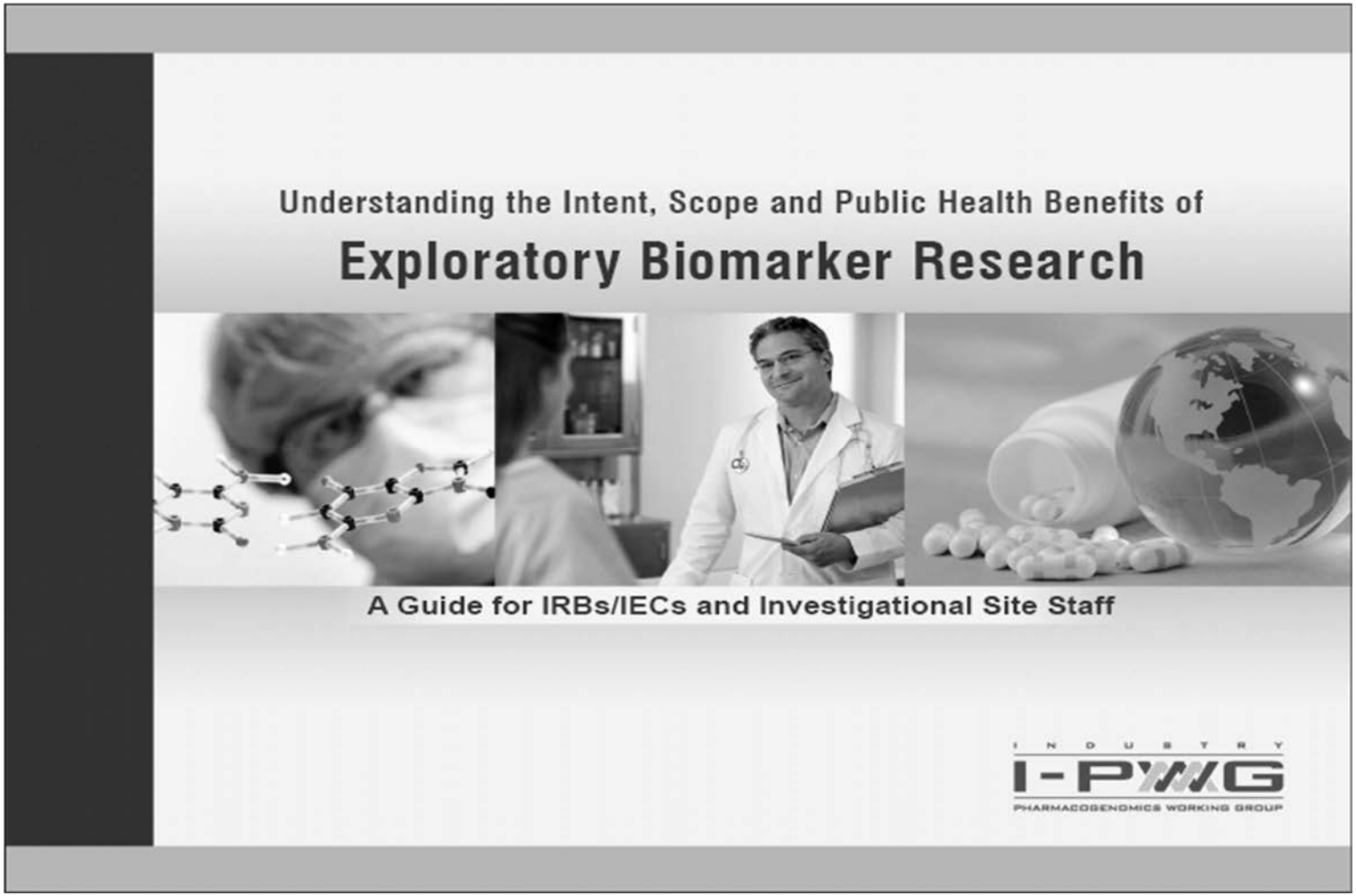
13. Questions

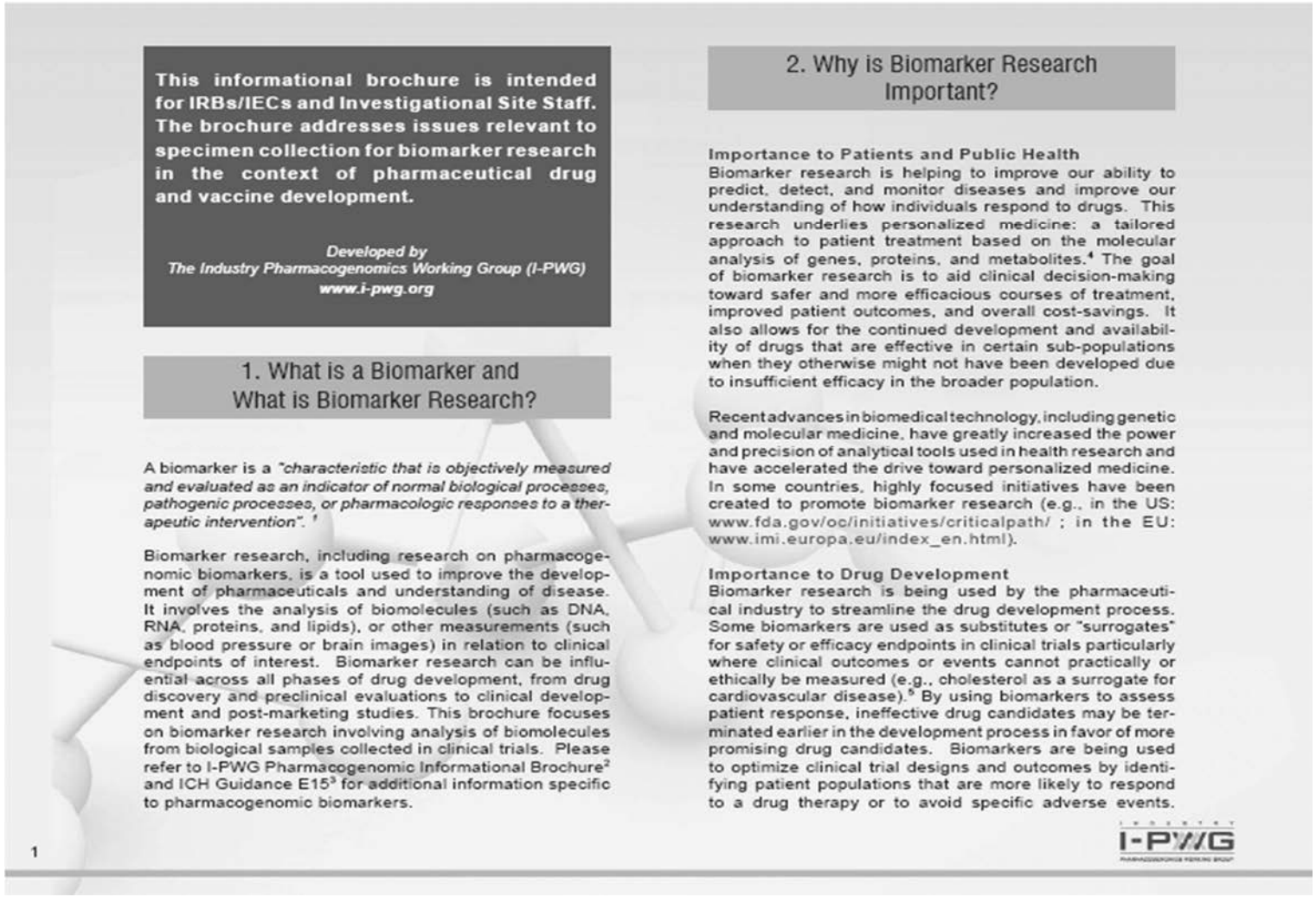
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

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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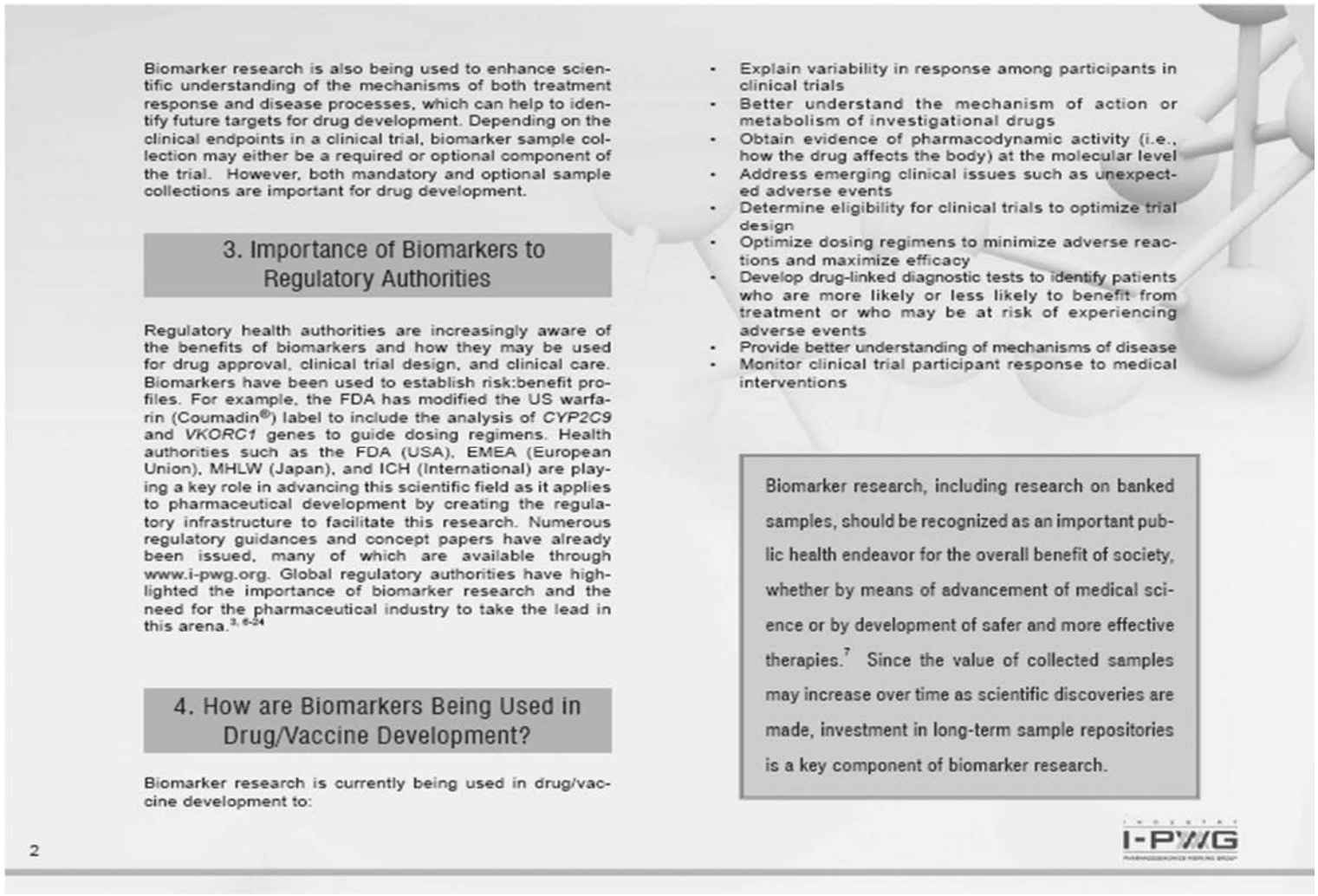

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either 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, 6-24]

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

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

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

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

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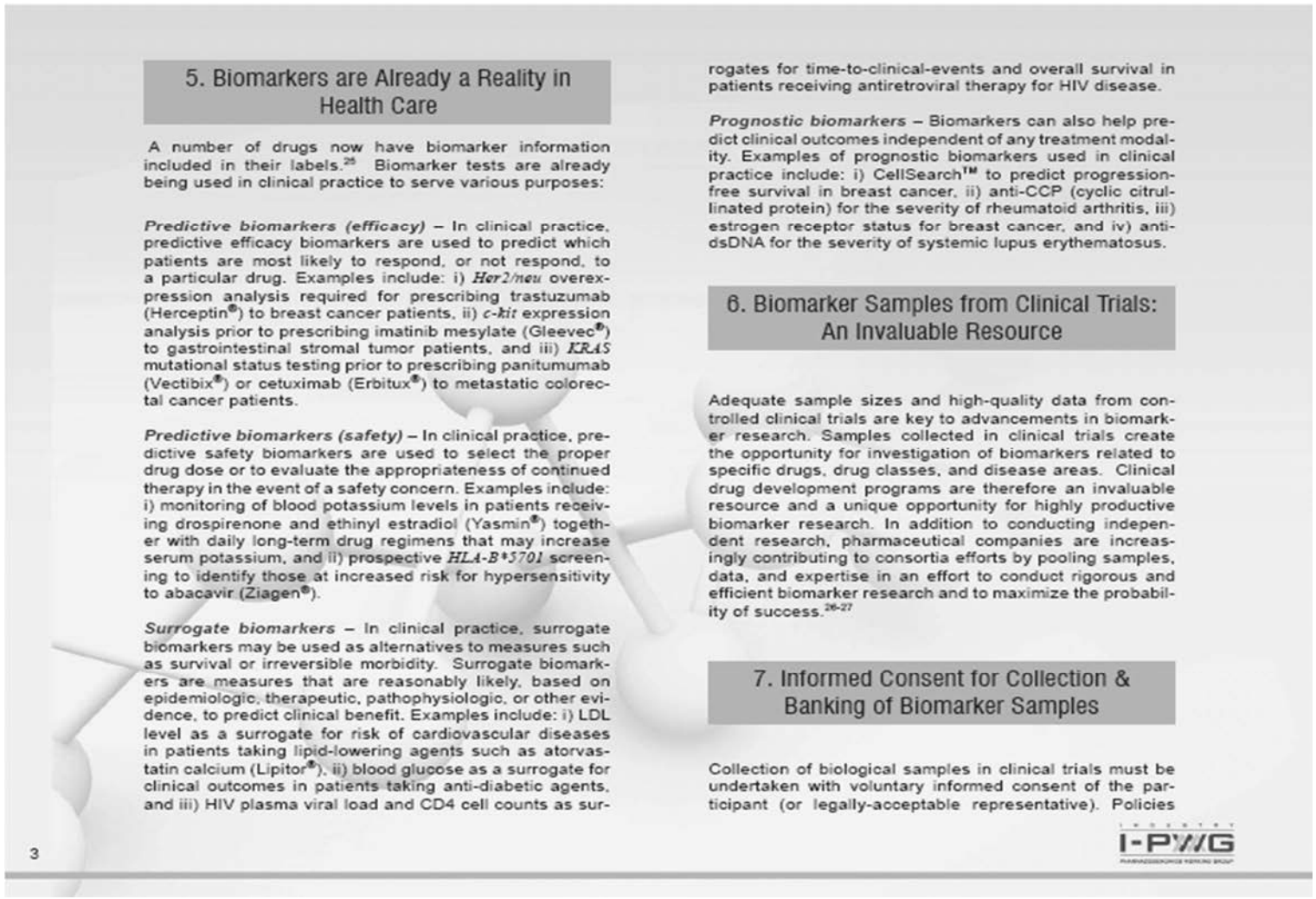

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[26-31]

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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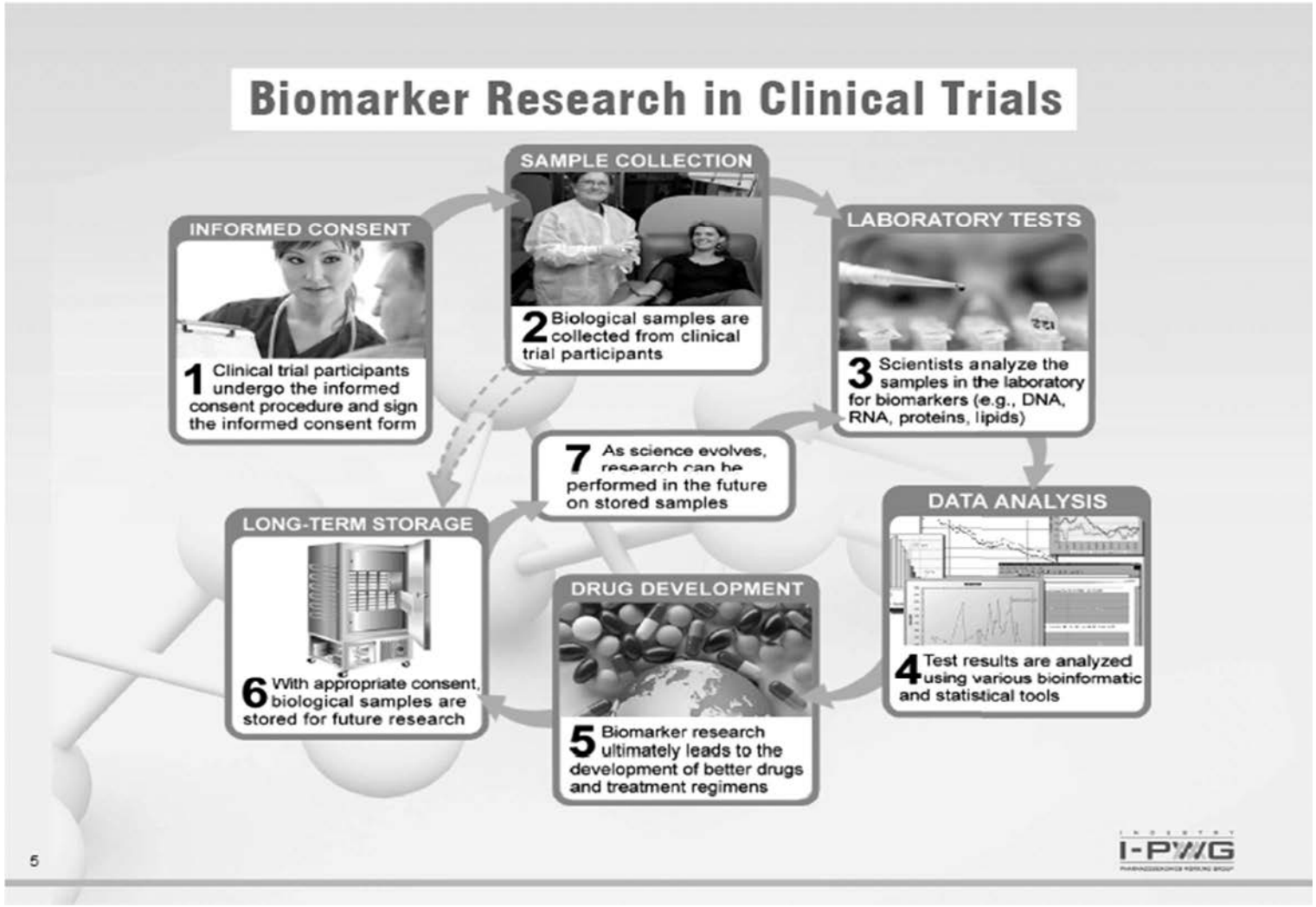
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the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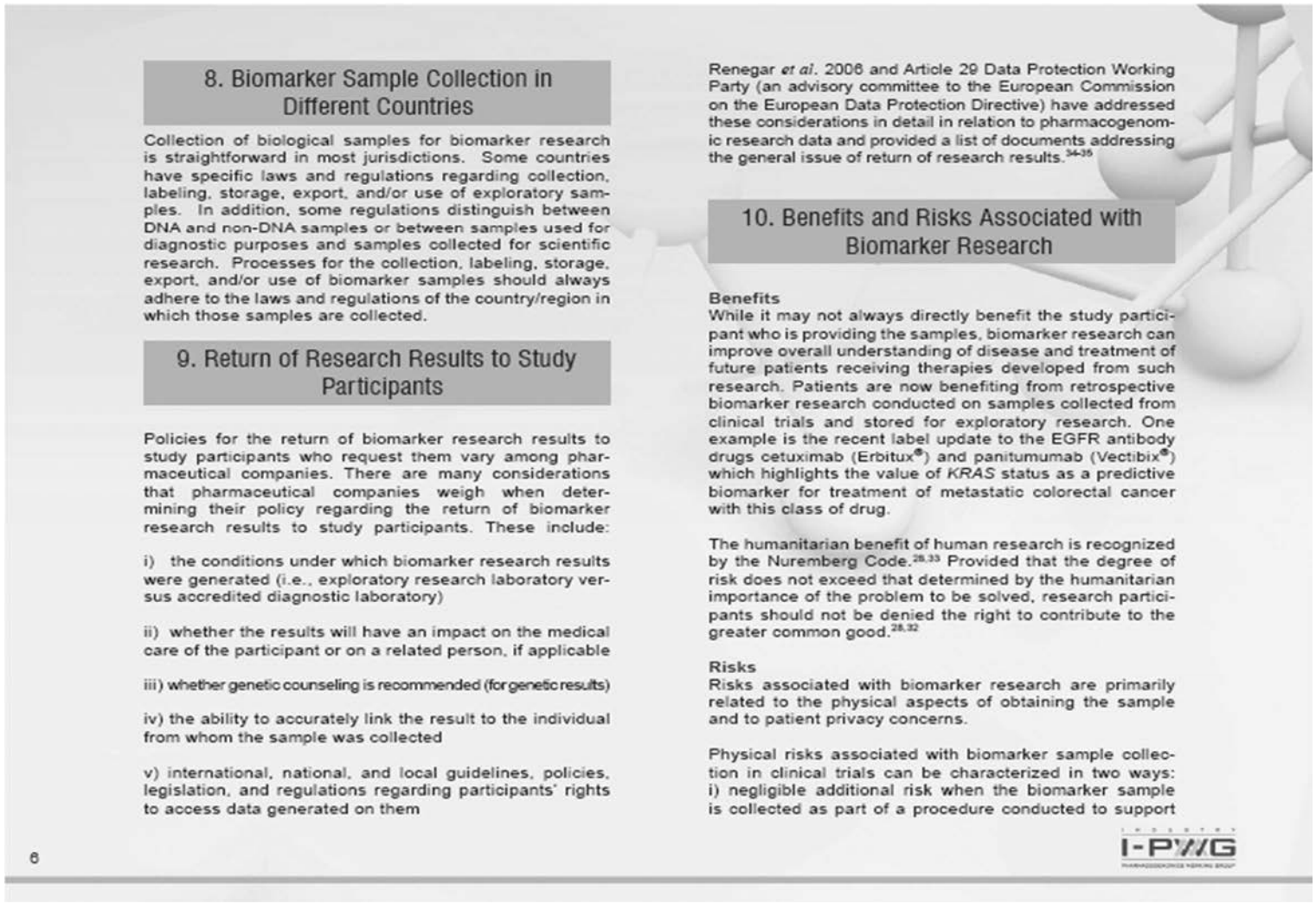

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

Renegar *et al*. 2006 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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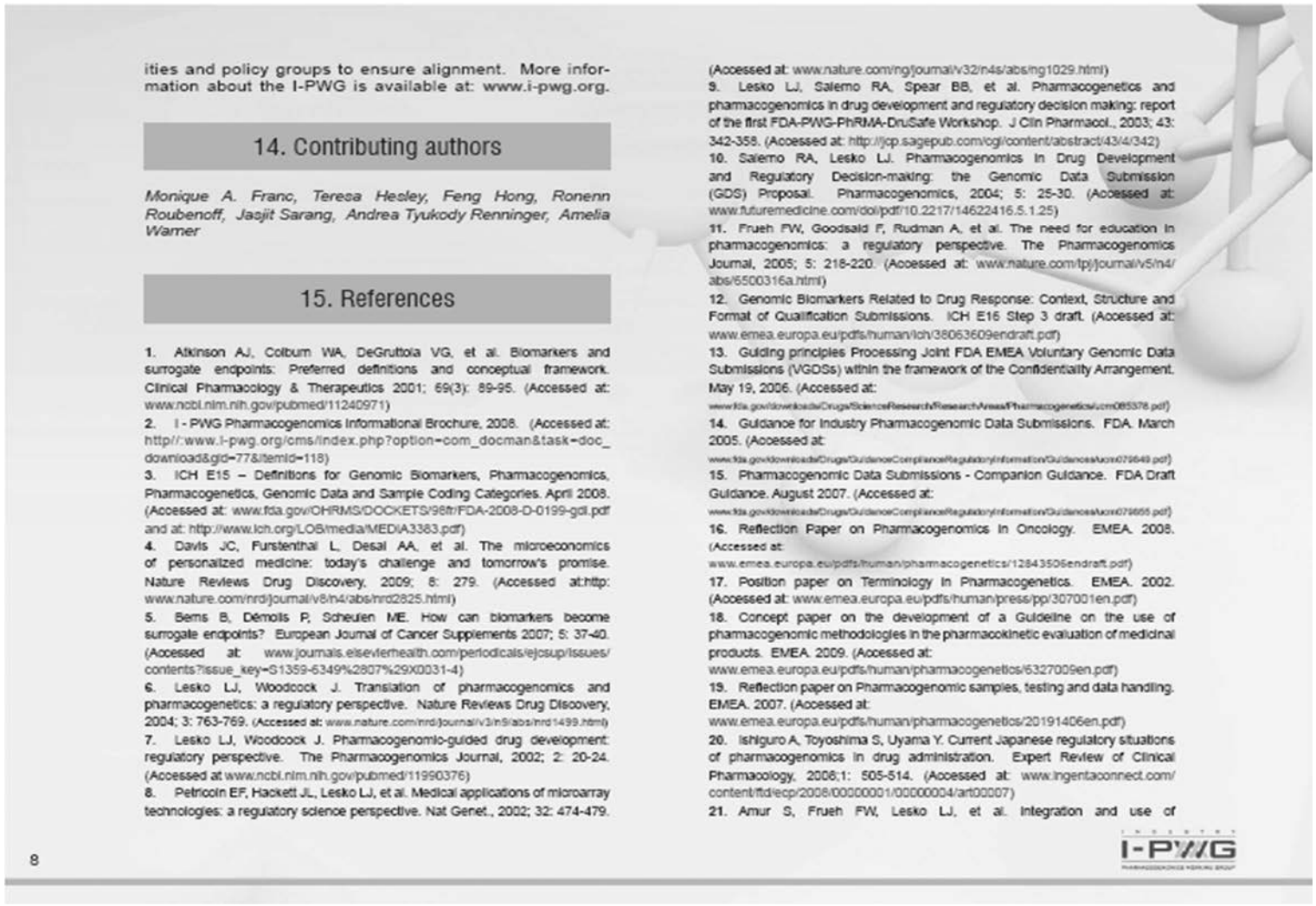

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jasjit Sarang, Andrea Tyukody Renninger, Amelia Warner

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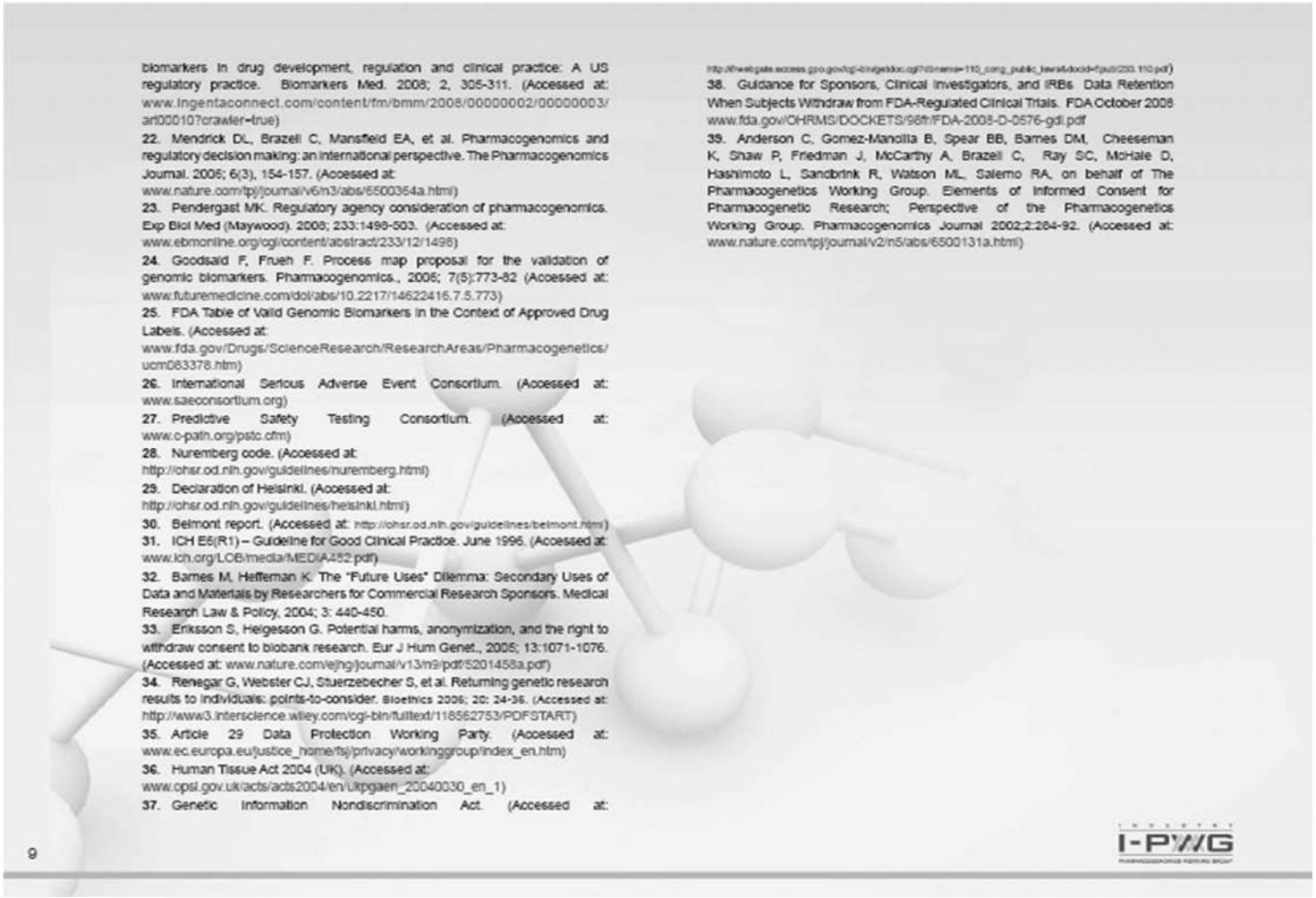

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12.4 ECOG Performance Status

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

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

12.5 Recommended Supportive Care Guidelines for Tumor Lysis Syndrome Prevention and Treatment in Subjects with CLL and DLBCL

1. Subjects with CLL and DLBCL will be admitted to the inpatient service the day prior to dinaciclib treatment for a minimum of the first treatment (C1D1 dose).
2. Premedication and IV hydration for dinaciclib for CLL and DLBCL are described in Section 5.2.1.3.1 (Table 6).
3. Using the Cairo-Bishop definition of laboratory TLS, K, calcium, potassium, and uric acid will be evaluated at 3 and 5 hours after the start of the first dinaciclib infusion (C1D1) as part of a TLS work- up (Section 5.2.1.3.3). Subjects with a positive TLS work-up should remain in the hospital and follow-up should be initiated. If necessary, subjects must be admitted overnight for observation.
    - If serum potassium > 4.5 mmol/L, then the subject should receive a 30 g dose of Kayexalate (or equivalent).
    - If serum potassium > 5.0 mmol/L, then the subject should receive 10 units of IV regular insulin and one ampule of D50 IV. During this time period, trial treatment administration should be discontinued.
    - If serum potassium > 5.5 mmol/L, then the subject should be considered for emergent intermittent or continuous hemodialysis.

During this time period, trial treatment administration should be discontinued.

Subjects who do not have laboratory TLS may receive Dose 2 (Day 8) of Cycle 1, as well as all subsequent therapies, as an outpatient.

This will allow inpatient monitoring of subjects during the most critical window of vulnerability to tumor lysis, yet allow subjects who tolerate dinaciclib to eventually be treated in the outpatient setting.

4. Subjects who develop clinical evidence of CRS or who have hyperkalemia requiring dialysis will receive immediate steroid therapy with 20 mg of IV dexamethasone (or equivalent). CRS is described in the NCI CTCAE current version. It occurs during or shortly after drug infusion and generally resolves within 24 hours of completing the infusion. Generally, the first manifestation of this syndrome is tachycardia followed by a constellation of symptoms. Subjects starting therapy with a normal pulse whose rate increases to >100 beats per minute post-therapy should be administered therapy for CRS. The signs and symptoms of CRS may include allergic reaction (including drug fever), arthralgia, bronchospasm, cough, dizziness, dyspnea, fatigue, headache, hypertension or hypotension, myalgia, nausea, pruritus, rash, rigors, chills, sweating, tachycardia, tumor pain, urticaria, and vomiting.
5. Subjects who require dialysis for hyperkalemia and/or other symptoms of TLS will be administered prophylactic antibiotics for gram-negative organisms (Zosyn 4.5 g IV every 8 hours or equivalent) and gram-positive organisms (vancomycin 1 g IV every 12 hours or equivalent) until dialysis is discontinued.

6. Subjects requiring intervention for TLS or demonstrating CRS symptoms should have their serum electrolytes, phosphate, calcium and magnesium checked every 8 to 12 hours post-therapy. If treatment is required, Amphojel or equivalent phosphate-binding agents are recommended. In this setting, calcium supplementation should only be given for symptomatic hypocalcemia to avoid renal precipitation of calcium phosphate crystals.
7. Subject may be discharged home the morning following the first dinaciclib infusion once their chemistry laboratory results have been reviewed by the treating physician.
8. It is recommended to inform the local renal consultant service of inpatient admissions for the first dinaciclib treatment for each subject. Administration of the first dinaciclib dose should occur at the beginning of the day.

12.6 Drugs that Interact with CYP3A4

Information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

12.7 Revised iwCLL Response Guidelines

CLL response assessment is based on the 2008 International Workshop (iwCLL) guidelines (Blood 2008;111:5446-5456) with the following clarifications/revisions.

NCI-WG CLL Response Criteria[A]	
Complete Remission (CR) Requires ALL of the following criteria as assessed at least 2 months after completion of therapy:	
Peripheral blood lymphocytes ($x10^9$/L)	<4
Lymphadenopathy	None by physical exam and CT scan
Hepatomegaly or splenomegaly	None by physical exam and CT scan
Symptoms	None
Blood counts:	
Neutrophils ($x10^9$/L), and	>1.5 without need for exogenous growth factors
Platelets ($x10^9$/L), and	>100 without need for exogenous growth factors
Hemoglobin (g/dL)	>11 without red blood cell transfusion or need for exogenous erythropoietin
Bone marrow	For subjects in clinical trials, at least 2 months after the last treatment and if clinical and laboratory criteria for CR has been achieved: normal cellularity for age; <30% of nucleated cells are lymphocytes; no lymphoid nodules. If hypocellular, repeat bone marrow biopsy at 4 weeks, or until peripheral blood counts have recovered (time interval should not exceed 6 months after last treatment).
CR with Incomplete Marrow Recovery (CRi) Meets all criteria for CR but have persistent anemia or thrombocytopenia or neutropenia related to drug toxicity	
Nodular Partial Remission Meets all criteria for CR but lymphoid nodules are present in the bone marrow sample obtained at least 2 months after last treatment.	
Partial Remission (PR) The following criteria must be documented for a minimum of 2 months:	

Blood lymphocytes, and	≥50% decrease from baseline
Lymphadenopathy, and	≥50% decrease in the sum products of up to 6 lymph nodes or in the largest diameter of the enlarged lymph node(s) from baseline. and No increase in any lymph node, an no new enlarged lymph node (in lymph nodes <2 cm, an increase of < 25% is not considered significant)
Liver or spleen (if abnormal before therapy) Plus, one or more of the following:	≥50% decrease from baseline (CT scan [clinical trials] or palpitation [general practice])
Neutrophils	>1.5 x10^9/L (1500/µL) without need for exogenous growth factors
Platelets	>100 x10^9/L (100,000/µL), or 50% improvement over baseline, without need for exogenous growth factors
Hemoglobin	>11 g/dL (110 g/L), or 50% improvement over baseline, without red blood cell transfusion or need for exogenous erythropoietin
Progressive Disease (PD) Characterized by at least one of the following during or after therapy:	

Lymphadenopathy	New lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates or ≥50% increase in greatest determined diameter of any previous site
Liver or spleen	≥50% increase from previous noted enlargement or the de novo appearance of hepatomegaly or splenomegaly
Blood lymphocytes	≥50% increase with ≥5000 B lymphocytes per microliter
Cytopenia	Progression of cytopenia attributable to CLL which occurs at least 3 months <u>after</u> treatment as documented by: - decrease of Hb levels by >20 g/L or to >100 g/L - decrease of platelets by >50% or to $<100x10^9$/L if the marrow biopsy demonstrates an infiltrate of clonal CLL cells
Other	Transformation to a more aggressive histology (e.g., Richter syndrome)
Stable disease (SD) <u>Subjects who have not achieved a CR or a PR, and who have not exhibited PD</u>	
A Blood. 2008;111:5446-5456.	

12.8 International Myeloma Working Group criteria for response assessment in multiple myeloma (IMWG criteria)

Durie et al. International uniform response criteria for multiple myeloma. Leukemia. 2006; 20:1467-1473.

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	Laboratory or Biochemical Relapse or Progressive Disease: requires any one or more of the following:
progression-free survival end points for all patients	Increase of ≥25% from baseline in
including those in CR (includes primary progressive	Serum M-component and/or (the absolute increase must be ≥0.5 g/dl)[b]
disease and disease progression on or off therapy)	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 (i.e., progressive disease requiring	Clinical relapse or progressive disease requires one or more of:
re-treatment or alternate treatment)[a]	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	Any one or more of the following:
studied is DFS)[d]	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.

12.9 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.

12.10 Lymphoma B Symptoms and Constitutional Symptoms

Lymphoma B Symptoms:

Lymphoma B symptoms are a set of clinical criteria used in the initial diagnosis and treatment of Hodgkin Lymphoma. These criteria are used in this trial as part of the initial assessment of Lymphoma disease staging and as a measure of the response to trial treatment.

The criteria are as follows:

- 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.

Source: Lister TA, Crowther D, Sutcliffe, SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7:1630-1636.

Constitutional Symptoms:

For all subjects with CLL, constitutional symptoms should be assessed at the time points described in Section 6.0 and Section 7.1.3.3.

Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:

- Unintentional weight loss of 10% or more within the previous 6 months;
- Significant fatigue (ie, ECOG PS 2 or worse; inability to work or perform usual activities);
- Fevers higher than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection; or
- Night sweats for more than 1 month without evidence of infection.

Source: Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood. 2008 Jun 15; 111(12): 5446–5456.

12.11 Common Terminology Criteria for Adverse Events V4.0

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

12.12 Abbreviations

Abbreviation/Term	Definition
ABC	activated B-cell–like
ADA(s)	antidrug antibody(ies)
AE(s)	adverse event(s)
ALT	alanine transaminase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASaT	all subjects as treated
AST	aspartate aminotransaminase
β–hCG	beta-human chorionic gonadotropin
BID	twice daily
BCL2	B-cell lymphoma 2
Ca	calcium
CBC	complete blood count
CD	cluster of differentiation
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulations
CI	principal coordinator
CLL	chronic lymphocytic leukemia
CR	complete remission
CRS	cytokine release syndrome
CSR	clinical trial report
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
CYP3A4	cytochrome P450 3A4
DLBCL	diffuse large B ell lymphona
DLT	dose-limiting toxicities
DNA	deoxyribonucleic acid
DOR	duration of response

Abbreviation/Term	Definition
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EMEA	European Medicines Evaluation Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FDG	fluorodeoxyglucose
FIH	first in human
FISH	flourescence in situ hybridization
FLC	free light chain
G6PD	glucose-6-phosphate dehydrogenase deficiency
GCB	germinal center B-cell–like
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GFR	glomerular filtration rate
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council on Harmonization
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgVH	immunoglobulin heavy chain
IMiD	pomalidomide, lenalidomide, or thalidomide
IMWG	International Myeloma Working Group criteria for response assessment in multiple myeloma
INR	International normalized ratio
irAE	immune-related adverse events
IRBs/ERCs	institutional review boards/ethics committees

Abbreviation/Term	Definition
ITSM	immunoreceptor tyrosine-based switch motif
IUD	intrauterine device
IV	intravenous
IVRS/IWRS	interactive voice response system/ integrated web response system
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
K	potassium
mAb	monoclonal antibody
MM	multiple myeloma
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
NHL	non-Hodgkin lymphoma
NSAID(s)	non-steroidal anti-inflammatory drugs
ORR	objective response rate
OS	overall survival
P	phosphorus
PBPK	physiologically based pharmacokinetic
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO, po	orally
POEMS syndrome	plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
PR	partial remission
PT	prothrombin time
PTT	partial thromboplastin time

Abbreviation/Term	Definition
Q2W	every 2 weeks
Q3W	every 3 weeks
RNA	ribonucleic acid
RPTD	recommended Phase 2 dose
rrCLL	relapsed or refractory chronic lymphocytic leukemia
rrDLBCL	relapsed or refractory diffuse large B-cell lymphoma
rrMM	relapsed or refractory multiple myeloma
SAE(s)	serious adverse event(s)
sCR	stringent complete remission
SCT	stem cell transplant
SPEP	serum M protein by electrophoresis
T1DM	type 1 diabetes mellitus
T3	triothyronine
Tregs	regulatory T cells
TLS	tumor lysis syndrome
ULN	upper limit of normal
UPEP	urine M protein by electrophoresis

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	