Official Protocol Title:	A Phase III Study of Lenalidomide and Low-Dose Dexamethasone With or Without Pembrolizumab (MK3475) in Newly Diagnosed and Treatment Naïve Multiple Myeloma (KEYNOTE 185)
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TITLE:

A Phase III Study of Lenalidomide and Low-Dose Dexamethasone With or Without Pembrolizumab (MK3475) in Newly Diagnosed and Treatment Naïve Multiple Myeloma (KEYNOTE 185).

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-3475-185-08	04-JUN-2020	To discontinue data collection following the database lock for the final analysis, as all participants remaining on study are in survival follow-up.
MK-3475-185-07	12-APR-2018	Clarified that pharmacokinetic/anti-drug antibody samples were the only samples available from the treatment phase suitable for additional safety analysis and may provide information regarding increased risk and/or imbalance of deaths for pembrolizumab plus lenalidomide in subjects with multiple myeloma.
MK-3475-185-06	06-OCT-2017	Added treatment discontinuation statement to reflect the US FDA clinical hold based on safety data.
MK-3475-185-05	07-DEC-2016	Updated pneumonitis as a reason for permanent discontinuation of treatment for consistency across the pembrolizumab program. Added collection of additional information regarding allogeneic stem cell transplants and complications following treatment with pembrolizumab.
MK-3475-185-04	12-JUL-2016	Clarified the exclusion criteria to ensure that patients who may have a history of pneumonitis are excluded from the study (when applicable).

Document	Date of Issue	Overall Rationale
MK-3475-185-03 (Amendment not implemented)	20-MAY-2016	N/A (Amendment was not distributed to the study sites)
MK-3475-185-02 (Amendment specific to the UK)	20-JAN-2016	Updated contraception language in accordance with the Lenalidomide global pregnancy prevention plan to comply with agency request.
MK-3475-185-01	18-APR-2016	Added the Lenalidomide Adult Pregnancy Risk Minimization Plan for Clinical Trials and included supplementation information in appendices to reinforce and adhere to the pregnancy prevention plan and risk mitigation program established for the use of lenalidomide.
MK-3475-185-00	28-JUL-2015	Original protocol

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0	Trial Summary	Updated duration of survival follow-up to 12 months following discontinuation visit.	To allow for closure of the study.
2.1	Trial Design	Updated follow-up after stem cell transplant (SCT) to provide for completion of follow-up at the end of the trial.	Survival follow-up will continue for at least 12 months following the last discontinuation visit. Follow-up post allogeneic-SCT will end when the trial closes.
5.10	Beginning and End of the Trial	Updated criteria for end of the trial to include Sponsor decision to close.	To broaden the criteria for ending the trial.
7.1.5.4.1 7.1.5.5.2 7.2.3.2.1	Safety Follow-up Visit Follow-up Post-Allogeneic Stem Cell Transplantation Adverse Events Follow-up Post-Allogeneic Stem Cell Transplantation	Updated criteria for completion of safety follow-up after discontinuation and after SCT to include end of trial.	To broaden the criteria for ending safety follow-up.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.1.5.5.1	Survival Follow-up	Updated criteria for completion of safety follow-up after discontinuation	Survival follow-up will continue for at least 12 months following the last discontinuation visit.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.2.3.6 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 reference to Future Biomedical Research "sub-trial".	Template Update.
7.1.5.5	Efficacy Follow-up Visits	Updated the heading name.	Template update for clarification.

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	A phase III study of Lenalidomide and low-dose Dexamethasone with or without Pembrolizumab (MK-3475) in Newly Diagnosed and Treatment-Naïve Multiple Myeloma (KEYNOTE 185).
Trial Phase	Phase III
Clinical Indication	Treatment of subjects with newly diagnosed and treatment-naïve Multiple Myeloma, ineligible for auto-SCT.
Trial Type	Interventional
Type of control	Active control without placebo
Route of administration	Intravenous (IV), Oral (PO)
Trial Blinding	Unblinded Open-label
Treatment Groups	(1) Investigational arm (Arm A): Pembrolizumab (MK-3475) 200 mg every 3 weeks (Q3W) + Lenalidomide 25 mg daily on days 1-21 and low-dose Dexamethasone 40 mg. daily on days 1, 8, 15, and 22 of repeated 28-day cycles OR (2) Control arm (Arm B): Lenalidomide 25 mg daily on days 1-21 and low-dose Dexamethasone 40 mg daily on days 1, 8, 15, and 22 of repeated 28-day cycles.
Number of trial subjects	Approximately 640 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 41 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, each subject will receive treatment based on the arm to which they have been randomized. In both arms, treatment on trial will continue until documented confirmed disease progression, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements or administrative reasons. After the end of treatment, each subject will be followed for 30 days for AE monitoring (serious adverse events (SAEs) and events of clinical interest will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed for at least 12 months after their discontinuation visit for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first. On 03-JUL-2017, the US FDA placed KN183 (pembrolizumab/pomalidomide/dexamethasone for Refractory or Relapsed and Refractory Multiple Myeloma [rrMM]), KN185, and cohort 1 of KN023 (pembrolizumab/lenalidomide/dexamethasone for rrMM) on clinical hold based on safety data from KN183 and KN185 presented to the DMC. The FDA determined that the risks of pembrolizumab plus pomalidomide or lenalidomide outweighed any

	potential benefit for patients with multiple myeloma. Based on this decision, the treatment phase of KN183 and KN185 is closed effective immediately. All subjects must stop study treatment, complete the Discontinuation Visit and move into the long-term safety and survival follow-up per protocol.

Randomization Ratio	1:1

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, active-controlled, multicenter, open-label trial of lenalidomide (Len) and low-dose dexamethasone (Dex) with or without pembrolizumab (MK-3475) in subjects with newly diagnosed, treatment-naïve multiple myeloma (MM) who are ineligible for autologous stem cell transplant (auto-SCT). Subjects will be stratified based on age (<75 vs. ≥75 years old) and International Staging System stage (ISS I or II vs. ISS III).

Approximately 640 subjects will be enrolled in this trial to examine the safety and efficacy of pembrolizumab 200 mg fixed dose administered every 3 weeks (Q3W) in combination with lenalidomide 25 mg daily on days 1 to 21 and low-dose dexamethasone 40 mg on days 1, 8, 15, and 22 of repeated 28-day cycles compared to lenalidomide 25 mg daily on days 1 to 21 and low-dose dexamethasone 40 mg on days 1, 8, 15, and 22 of repeated 28-day cycles. Adverse events (AEs) will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In both arms, treatment on trial will continue until documented confirmed disease progression, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements or administrative reasons.

After the end of treatment, each subject will be followed for 30 days for AE monitoring (serious adverse events [SAEs] and events of clinical interest [ECIs] will be collected for 90 days after the end of treatment). Subjects who undergo allogeneic stem-cell transplant (allo-SCT) within 24 months after their last dose of pembrolizumab will be followed for ECI for up to 18 months post-transplant or until the end of the trial. Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed for at least 12 months after their discontinuation visit for overall survival until death, withdrawal of consent, or the end of the study, whichever comes first.

The primary objective of the trial is to compare the Progression Free Survival (PFS) according to the International Myeloma Working Group response criteria (IMWG criteria

[1]) of pembrolizumab in combination with lenalidomide and low-dose dexamethasone compared to treatment with lenalidomide and low-dose dexamethasone (standard of care [SOC]) alone in subjects newly diagnosed with treatment-naïve multiple myeloma (MM) who are ineligible for auto-SCT. Secondary objectives include safety and tolerability, other efficacy parameters such as overall survival (OS), second Progression Free Survival (PFS2), overall response rate (ORR), disease control rate (DCR), and duration of response (DOR). Changes in health-related quality-of-life assessments, percentage of subjects who achieve negative minimal residual disease (MRD), analysis of programmed cell death-ligand 1 receptor (PD-L1) expression and corresponding efficacy, along with the relationship of candidate efficacy/resistance biomarkers and antitumor activity of pembrolizumab will be investigated as exploratory objectives.

A group-sequential design based on pre-specified criteria using an independent, external Data Monitoring Committee (DMC) to monitor safety and efficacy will be used in this trial. Additionally, a separate Clinical Adjudication Committee (CAC, Section 7.3.3) will evaluate efficacy endpoints (e.g., PFS, ORR) for the purpose of confirming each efficacy event according to the pre-defined IMWG 2011 criteria, functioning as independent central reviewers, blinded to study treatment. One efficacy interim PFS analysis will be conducted when approximately 50% of the expected PFS events (i.e., ~ 115) have occurred. A final analysis for OS will be conducted after approximately 195 deaths have occurred. Additional details are in Section 8.7.

Enrollment will not be paused during the planned interim analyses.

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

On 03-JUL-2017, the US FDA placed KN183, KN185 and cohort 1 of KN023 on clinical hold based on safety data from KN183 and KN185 presented to the DMC. The FDA determined that the risks of pembrolizumab plus pomalidomide or lenalidomide outweighed any potential benefit for patients with multiple myeloma. Based on this decision, the treatment phase of KN183 and KN185 is closed effective immediately. All subjects must stop study treatment, complete the Discontinuation Visit and move into the long-term safety and survival follow-up per protocol.

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

2.2 Trial Diagram

The trial design is depicted in Figure 1.

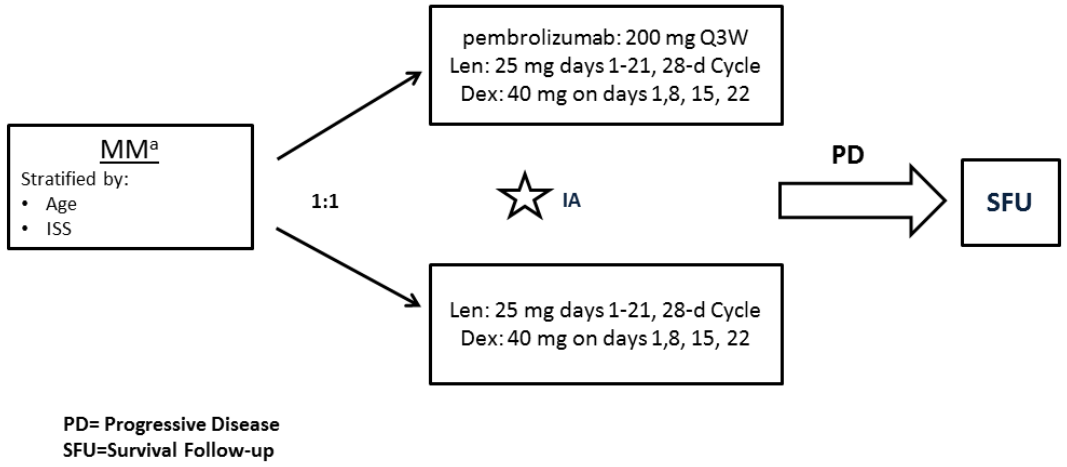

Figure 1 Trial Diagram

Abbreviations not defined above: mg – milligram(s), Q3W – every three weeks, MM[a] – newly diagnosed, treatment-naïve multiple myeloma (ineligible for auto-SCT), IA – interim analysis, ISS – international staging system, Len – lenalidomide, Dex – dexamethasone.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In subjects with newly diagnosed, treatment naïve multiple myeloma (MM) who are ineligible for auto-SCT:

(1) **Objective:** To compare the Progression Free Survival (PFS) as assessed by CAC blinded central review according to the International Myeloma Working Group response criteria (IMWG criteria [1]) between treatment arms.

Hypothesis: Pembrolizumab in combination with lenalidomide and low-dose dexamethasone prolongs PFS as assessed by CAC blinded central review using IMWG criteria [1] compared to treatment with lenalidomide and low-dose dexamethasone (SOC) alone.

3.2 Secondary Objective(s) & Hypothesis(es)

In subjects with newly diagnosed, treatment naïve multiple myeloma (MM) who are ineligible for auto-SCT:

(1) **Objective**: To compare the Overall Survival (OS) between treatment arms.

Hypothesis: Pembrolizumab in combination with lenalidomide and low-dose dexamethasone prolongs OS compared to treatment with lenalidomide and low-dose dexamethasone (SOC) alone.

(2) **Objective:** To evaluate Overall Response Rate (ORR), DCR, Duration of Response (DOR), as assessed by CAC blinded central review using IMWG criteria [1], and second Progression Free Survival (PFS2) by investigator assessment, between treatment arms.

(3) **Objective**: To evaluate the safety and tolerability in both treatment arms.

3.3 Exploratory Objectives

In subjects with newly diagnosed, treatment naïve multiple myeloma (MM) who are ineligible for auto-SCT:

(1) **Objective:** To evaluate changes in health-related quality-of-life assessments from baseline using the EORTC QLQ-C30 and QLQ-MY20.

(2) **Objective:** To characterize patient utilities using EuroQol EQ-5D.

(3) **Objective:** To evaluate pharmacokinetic (PK) parameters and the presence of anti-drug antibodies (ADA) following intravenous (IV) administration of 200 mg pembrolizumab Q3W in combination with lenalidomide and low-dose dexamethasone (Section 4.2.3.3).

(4) **Objective:** To identify molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to pembrolizumab and other treatments in this study, so as to define novel predictive and pharmacodynamic biomarkers and understand the mechanism of action of pembrolizumab (See Section 4.2.3.5).

(5) **Objective:** To evaluate the percentage of subjects with complete response/stringent complete response (CR/sCR) who achieve negative minimal residual disease (MRD).

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

Pembrolizumab (previously known as MK-3475 and SCH 9000475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between the programmed cell death-1 receptor (PD-1) and its ligands, PD-L1 and PD-L2, without antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity. Pembrolizumab is approved in the US for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [3]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [4, 5, 6, 7, 8]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [9, 10]. The structure of murine PD-1 has been resolved [11]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM), and an immunoreceptor tyrosine based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70 which are involved in the CD3 T-cell signaling cascade [9, 12, 13, 14]. 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 [15, 16]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [17, 18]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [19]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [15, 20, 21, 22]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation

in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [15]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [23]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

4.1.2 Preclinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma (MEL), and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN- γ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [24, 25, 26, 27, 28, 29]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (refer to the IB).

In a Phase 1/2 study of 135 subjects with advanced melanoma, treatment with pembrolizumab produced an ORR of 38% (95% CI, 25% to 44%). Many of the responses were durable, with a median duration that had not been reached after a median follow-up time of 11 months [30].

4.1.3 Ongoing Clinical Trials

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

4.2.1.1 Multiple Myeloma

Multiple myeloma (MM) is a malignant monoclonal plasma cell disorder characterized by end-organ damage, usually referred to as myeloma CRAB (calcium [elevated], renal failure, anemia, bone lesions) features. Multiple myeloma is considered the second most common hematological malignancy accounting for 10% of all diagnoses, with an estimate of 26,850 new cases and 11,240 deaths in the United States in 2014 [31]. This malignant neoplasm primarily affects elderly individuals with a median age at the time of diagnosis of around 70 years [32].

The diagnosis of MM is based on the presence of ≥10% monoclonal plasma cells in the bone marrow or biopsy-proven bony or extramedullary plasmacytoma, presence of monoclonal protein (m-protein) in serum and/or urine and evidence of any CRAB feature that can be attributed to the underlying plasma cell proliferative disorder, specifically [33]:

- Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >177 μmol/L (>2 mg/dL)
- Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
- Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography (PET)-CT

Alternatively, in the absence of CRAB features, patients with any of the following biomarkers of malignancy: clonal bone marrow plasma cell percentage ≥60%, involved/uninvolved serum free light chain (FLC) ratio ≥ 100 or more than one focal bone lesion in magnetic resonance imaging (MRI), are also considered to have active MM according to the new IMWG criteria [1] for the diagnosis of MM [33].

Treatment should be initiated in all patients considered to have active MM and the selected approach usually depends on patient performance status, comorbidities, and chronological age, defining up front if a patient is a candidate for standard auto-SCT [34, 35]. As patients between the ages of 65 and 75 are generally considered ineligible for auto-SCT, almost 70% of all MM patients are treated with therapeutic strategies that incorporate the use of proteasome inhibitors or immunomodulatory imide drugs (IMiDs) instead of auto-SCT [34, 36].

For newly diagnosed MM patients who are not candidates for auto-SCT, there are 3 worldwide recommended first-line regimens: the combination of melphalan, prednisone and thalidomide (MPT), the combination of bortezomib, melphalan and prednisone (VMP), and the combination of lenalidomide with low-dose dexamethasone (Rd) [34, 35].

A meta-analysis of published data from 6 randomized trials confirmed an improvement in PFS and OS with MPT compared with MP [37]. The reported median PFS and OS with MPT were 20.3 and 39.3 months, respectively. Bortezomib, melphalan, and prednisone is another well-established SOC regimen. The final analysis of the Phase III VISTA trial after a median follow-up of 60 months confirmed the superiority of VMP to MP in terms of median time to second-line antimyeloma therapy (31 months vs 20.5 months) and median OS (56 months vs 43 months) [38].

Lenalidomide in combination with low-dose dexamethasone (Rd) has recently been approved for first-line treatment of MM patients who are not candidates for auto-SCT based on the results of the Phase 3 FIRST trial [39]. In the FIRST trial, 1623 transplant-ineligible patients received either continuous Rd administered until disease progression or intolerance or for a

fixed duration of 18 cycles (Rd 18; 72 weeks). Lenalidomide in combination with low-dose dexamethasone (Rd) was compared with MPT administered for 12 cycles. With a median follow-up of 37 months, continuous Rd significantly extended PFS and OS compared with MPT. The median PFS was 25.5 months for Rd, compared with 20.7 months for Rd18 and 21.2 months for MPT. The 4-year estimated OS was 59% for Rd, 56% for Rd18, and 51% for MPT. In addition, Rd was superior to MPT across all other efficacy end points, including time to disease progression (TTP), time to treatment failure (TTF), time to second-line anti-myeloma therapy, and duration of response. Additionally, Rd was also generally better tolerated than MPT.

Despite all advances in front-line treatment, nearly all MM patients relapse, as illustrated by the lack of a plateau in the survival curves from clinical trials that evaluate currently available treatment options [40]. Although retreatment with previously used drugs or the use of a different class of first-generation drugs can be a sensible strategy [41], patients who become refractory to both proteasome inhibitors and IMiDs have limited salvage therapeutic options and a very poor outcome.

4.2.1.2 Rationale for Evaluating anti-PD-1 Therapy in Multiple Myeloma

Hematologic malignancies are known to be responsive to a variety of immunotherapies. While data are currently limited, there is some indication that PD-L1/PD-1 biology may be an important mechanism of tumor immune escape in these diseases.

Several studies in hematologic malignancies have shown increased expression of PD-L1 in B-cell lymphomas, chronic lymphocytic leukemia, acute myeloid leukemia, and MM [42, 43]. PD-L1 is expressed on most MM plasma cells but not in normal plasma cells [44], and PD-L1 overexpression enhanced MM invasiveness and rendered tumor cells less susceptible to cytotoxic T lymphocytes (CTLs). This effect can be alleviated by anti–PD-L1 blockage, demonstrating the importance of the PD-1/PD-L1 pathway in this process [45, 46]. In addition, a recent report demonstrated increased levels of PD-L1 on MM cells together with enhanced PD-1 expression on T cells with an “exhausted” phenotype. The immunosuppressive effects of myeloma can be overcome by PD-L1 blockade [47].

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for Fixed Dose Pembrolizumab

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose recently approved in some countries for treatment of melanoma subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

An open-label Phase I trial (KEYNOTE-001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels: 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) and a dose expansion cohort evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated, and no dose limiting

toxicities were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No Maximum Tolerated Dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations (Cohorts B2 and D) of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg Q3W vs. 10 mg/kg Q3W have been completed and one randomized Cohort (Cohort B3) evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg Q3W versus 10 mg/kg Q3W. The ORR was 28% (22/79) in the 2 mg/kg Q3W group and 28% (21/76) in the 10 mg/kg Q3W group (per RECIST 1.1 by independent central review). The proportion of subjects with drug-related AEs, Grade 3-5 drug-related AEs, serious drug-related AEs, and death or discontinuation due to an AE was comparable between groups. Cohort D, which compared 2 mg/kg Q3W vs. 10 mg/kg Q3W in advanced melanoma subjects naïve to ipilimumab, also demonstrated overall similarity in efficacy and safety profiles between two doses. In Cohort B3, advanced melanoma subjects (irrespective of prior ipilimumab therapy) were randomized to receive pembrolizumab at 10 mg/kg Q2W versus 10 mg/kg Q3W. The ORR was 35.0% (41/117) in the 10 mg/kg Q2W group and 30.8% (33/107) in the 10 mg/kg Q3W group (per RECIST 1.1 by independent central review; cut-off date of 18-April-2014). The proportion of subjects with drug-related AEs, Grade 3-5 drug-related AEs, serious drug related AEs, and death or discontinuation due to an AE was comparable between groups.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide a response similar to that for 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety was found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose. A 2 mg/kg Q3W dose is approved for metastatic melanoma in the US.

A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 1139 subjects from Keynote-001 (cut-off date of 18-April-2014) and KEYNOTE-002 (cut-off date of 12-May-2014), of which the majority (94.6%, N=1077) were patients with advanced melanoma. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. Additionally, this comparison also demonstrates that the 200 mg Q3W regimen provides no substantive differences in PK variability (range of the distribution of individual exposures) as seen with weight-based dosing.

In translating to other solid tumor indications, similarly flat exposure-response relationships for efficacy and safety in subjects with melanoma can be expected, as the antitumor effect of

pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, non-small cell lung cancer, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types. Preliminary serum concentration data are available from subjects with hematologic malignancies which include Hodgkin's lymphoma (HL), myelodysplastic syndrome (MDS), relapsed/refractory mediastinal large B cell lymphoma (MLBCL), MM, and PD-L1 positive non-Hodgkin's lymphoma (NHL) cancers who received 10 mg/kg Q2W in KEYNOTE-013.

The observed data were compared to simulated PK profiles at a dose of 10 mg/kg Q2W from the population PK models in which the majority of the analysis population was subjects with melanoma. The distribution of concentration-time profiles in subjects with hematologic malignancies is contained within the distribution for subjects with melanoma, indicating the consistency of the PK profile across both populations (Figure 2). Thus, the 200 mg Q3W fixed dose regimen is considered an appropriate fixed dose for other solid tumor indications as well.

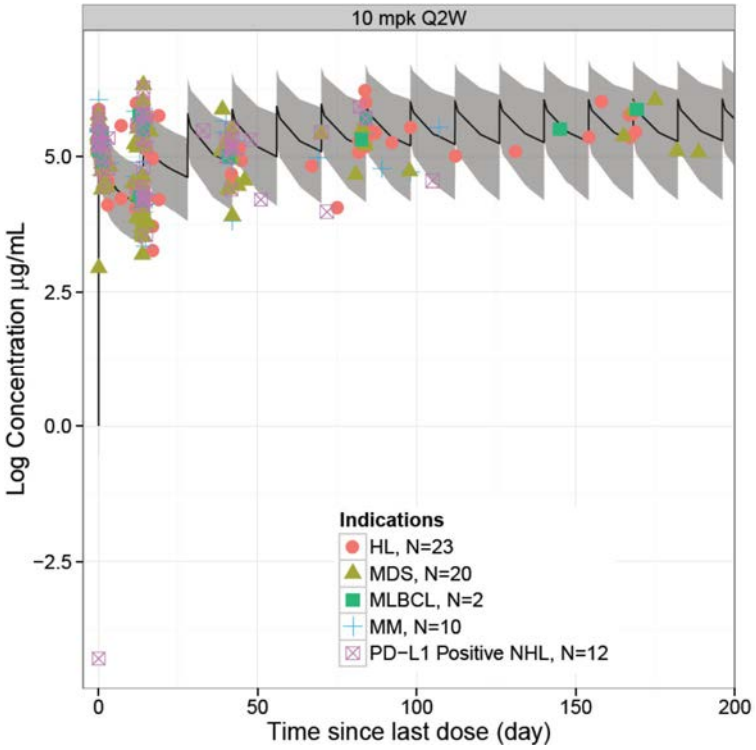

Figure 2 Consistency of Observed Concentration Data in KEYNOTE-013 Subjects with Hematologic Malignancies Receiving 10 mg/kg Q2W Pembrolizumab with Predicted Pharmacokinetic Profile for this Dose Regimen (Preliminary Results)

Solid markers represent observed pembrolizumab serum concentrations in subjects with Hodgkin lymphoma (HL), Myelodysplastic syndrome (MDS), relapsed/refractory mediastinal large B cell lymphoma (MLBCL), Multiple Myeloma (MM), and PD-L1 positive

non-Hodgkin lymphoma (NHL) Cancers (KEYNOTE-013). Solid line represents median predicted concentration-time profile, based on population PK model for subjects with Melanoma. Shaded areas represent 90% prediction interval for the prediction.

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

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the optimal dose for pembrolizumab.

4.2.2.2 Rationale for the Use of Lenalidomide in Combination with Low-Dose Dexamethasone in Combination with Pembrolizumab

Immunomodulatory imide drugs (Thalidomide, Lenalidomide, and Pomalidomide) are a class of immunomodulatory agents, which are a mainstay in myeloma therapy and could be rationally combined with anti-PD-1 therapy. IMiDs derive their designation as "immunomodulators" designed as therapeutic immune stimulators derived from the parent compound thalidomide. Lenalidomide, and now pomalidomide, are approved therapies for MM. The immunostimulatory properties of IMiDs, in contrast to other active myeloma classes such as proteasome inhibitors, could synergize with anti-PD-1 therapies. Published literature suggests that IMiDs have T-cell co-stimulatory and positive effects on antigen presenting cells (APCs). T-cell co-stimulation has been demonstrated by increased IFN-g and IL-2 production, which results in clonal T-cell expansion and increased natural killer (NK) cell activity [48]. There is also evidence of increased IL-12 production in the setting of T-cell costimulation, which activates APCs [49].

KEYNOTE-023 (NCT02036502) is an ongoing multicenter, phase 1 dose-escalation study designed to evaluate the safety and efficacy of pembrolizumab in combination with lenalidomide and low-dose dexamethasone in subjects with relapsed/refractory multiple myeloma (rrMM). This study evaluated the safety and efficacy of pembrolizumab in combination with lenalidomide and low-dose dexamethasone. Key eligibility criteria included measurable disease, failure of ≥2 prior therapies including a proteasome inhibitor and an IMiD, and Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1. A modified 3 + 3 design was used for dose determination, with cohorts of 3-6 subjects treated with pembrolizumab 2 mg/kg Q2W + lenalidomide 10 mg or 25 mg on days 1-21 and dexamethasone 40 mg weekly, repeated every 28 days. After preliminary MTD/minimally acceptable dose (MAD) identification, additional subjects received pembrolizumab 200 mg Q2W + lenalidomide and dexamethasone for dose confirmation. Upon determination of the final MTD/MAD, subjects enrolled in the dose expansion cohort. Treatment continued for

24 months or until confirmed disease progression or unacceptable toxicity. Response was evaluated monthly using IMWG 2006 criteria.

In the study interim analysis, of the 17 subjects enrolled in the dose determination and confirmation stages, 3 subjects experienced DLTs in the pembrolizumab 2 mg/kg, 25-mg lenalidomide cohort: grade 3 neutropenia and grade 3 pneumonia in 1 subject each; and grade 4 neutropenia, grade 3 tumor lysis syndrome, and grade 4 hyperuricemia in the same subject. Based on the dose confirmation stage, pembrolizumab 200 mg + lenalidomide 25 mg and dexamethasone 40 mg was determined as the MTD/MAD.

Thirty-three additional subjects were enrolled in the expansion cohort. Median age for the total population was 62 years old, 72% had ≥3 prior therapies, 86% had prior auto-SCT, and 64% were refractory to bortezomib, Also, 76% (38/50) were refractory to lenalidomide, with 50% of subjects double, triple, or quadruple refractory. Thirty-six subjects (72%) experienced treatment-related AEs, most commonly thrombocytopenia (28%), neutropenia (24%), diarrhea (16%), and fatigue (14%). A total of twenty-three subjects experienced grade 3-4 treatment-related AEs, most commonly neutropenia (23%) and thrombocytopenia (8%).

With a median follow-up of 9.7 months, the overall response rate was 76% for the subjects evaluated for efficacy in dose determination/confirmation stages, including 4 VGPRs and 9 PRs. Sixteen out of the 17 subjects (94%) had a reduction in M protein or free light chains. In lenalidomide refractory subjects (n = 9), the overall response rate was 56%, with 2 VGPRs and 3 PRs. The DCR was 88% for the total population and 78% in lenalidomide refractory subjects. The median duration of response was 9.7 months and median time to response was 1.2 months. Overall, pembrolizumab in combination with lenalidomide and dexamethasone was associated with a tolerable safety profile and promising antimyeloma activity in heavily pretreated subjects with rrMM. Adverse events were consistent with the individual safety profiles of pembrolizumab, lenalidomide, and dexamethasone.

4.2.2.3 Rationale for the Use of Lenalidomide in Combination with Low-Dose Dexamethasone as the Comparator

Lenalidomide in combination with low-dose dexamethasone is the standard of care for patients with newly diagnosed, treatment-naïve MM who are ineligible for auto-SCT. Lenalidomide in combination with low-dose dexamethasone (Rd) was recently approved for first-line treatment of MM patients not eligible for auto-SCT based on the results of the Phase 3 FIRST trial (39). In the FIRST trial, 1623 transplant-ineligible patients received either continuous Rd administered until disease progression or intolerance or for a fixed duration of 18 cycles (Rd 18; 72 weeks). Continuous Rd was compared with MPT administered for 12 cycles. With a median follow-up of 37 months, continuous Rd significantly extended PFS and OS compared with MPT. The median PFS was 25.5 months for Rd, compared with 20.7 months for Rd18 and 21.2 months for MPT. The 4-year estimated OS was 59% for Rd, 56% for Rd18, and 51% for MPT. In addition, Rd was superior to MPT across all other efficacy end points, including response rate TTP, TTF, time to second-line anti-myeloma therapy, and duration of response. Additionally, Rd was also generally better tolerated than MPT.

This Phase III trial will establish the efficacy of pembrolizumab in combination with lenalidomide and low-dose dexamethasone in subjects with newly diagnosed, treatment-naïve MM who are ineligible for auto-SCT.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy objective of this study is to compare the Progression Free Survival (PFS) as assessed by CAC blinded central review according to the IMWG criteria [1] between treatment arms.

The secondary efficacy endpoints will include OS, PFS2, ORR, DCR, and DOR.

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard response assessment criteria may not provide a comprehensive response assessment of immunotherapeutic agents such as pembrolizumab. Therefore in the setting where a subject in the investigational arm, receiving pembrolizumab in combination with lenalidomide and low dose dexamethasone, is assessed by the investigator as confirmed PD according to IMWG criteria [1], based on the development of new bone lesions or soft tissue plasmacytomas or on a definite increase in the size of existing bone lesions or soft tissue plasmacytomas, study treatment may be continued upon Sponsor consultation if the investigator considers the subject is deriving clinical benefit and providing subsequent radiographic imaging and laboratory testing shows evidence of reduction in tumor burden from the prior time point where initial PD was observed. If repeat imaging and laboratory testing shows a reduction in the tumor burden compared to the initial result demonstrating PD, treatment may be continued or resumed. If repeat imaging and laboratory testing confirms progressive disease, subjects will be discontinued from study therapy. However, laboratory and/or imaging testing should occur at any time where there is clinical suspicion of progression.

4.2.3.2 Patient Reported Outcomes

EORTC QLQ-C30, EORTC QLQ-MY20, and EQ-5D are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

EORTC QLQ-C30

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

instrument also contains 2 global scales that use 7-point scale scoring with anchors (1=very poor and 7=excellent).

EuroQoL-5D

The EuroQol-5D (EQ-5D) is a standardized instrument for use as a measure of health outcome. The EQ-5D will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life years. The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [37]. Each dimension is rated on a three-point scale from 1 (extreme problem) to 3 (no problem). The EQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the assessment. The EQ-5D will always be completed by subjects first before completing the EORTC QLQ-C30.

EORTC QLQ-MY20

EORTC QLQ-MY20 is a quality of life questionnaire developed to assess the extent of symptoms or problems in subjects receiving treatment for multiple myeloma. The tool is used in conjunction with the EORTC QLQ-C30 and follows the same 4-point scale described above. It contains 2 functioning scales (future perspective, body image) and 2 symptom scales (disease symptoms, side effects of treatment).

4.2.3.3 Safety Endpoints

The safety and tolerability of pembrolizumab in combination with lenalidomide and low-dose dexamethasone or lenalidomide and low-dose dexamethasone alone in subjects with newly diagnosed, treatment-naïve MM who are ineligible for auto-SCT will be characterized in this study. The safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, lenalidomide or low-dose dexamethasone including SAEs and ECIs.

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

4.2.3.4 Pharmacokinetic Endpoints

Blood samples will be obtained to measure the pharmacokinetics of serum pembrolizumab in combination with lenalidomide and low-dose dexamethasone. The pembrolizumab in combination with lenalidomide and low-dose dexamethasone serum maximum concentration (C_{max}) and minimum concentration (C_{trough}) at planned visits and times will be summarized.

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

4.2.3.5 Planned Exploratory Biomarker Research

Introduction: Cancer immunotherapies are an important novel class of antitumor agents. However, much remains to be learned about how cancer immunotherapies work and how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy as well as determinants of adverse events in the course of our clinical trials. To that end we seek to define novel predictive/pharmacodynamic biomarkers and the best strategies of combination therapy with immuno-oncology drugs. To fully leverage the clinical data collected in this trial, biospecimens (blood components, tumor material, etc.) will be collected to support biomarker analyses of cellular components (e.g., protein, DNA, RNA, metabolites) and other blood soluble molecules. Investigations may include but are not limited to:

Germline (blood) for Genetic Analyses (e.g., SNP analyses, whole exome sequencing, whole genome sequencing):

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

Genetic (DNA) analyses from tumor:

The application of new technologies, such as next-generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (i.e., mutations, methylation status, microsatellite instability, etc.). Key molecular changes of interest to immune-oncology drug development are the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) is one of the major mechanisms of neo-antigen presentation in the context of a tumor. There is a potential that in the hyper-mutated state, the presence of neo-

antigen mutational patterns and the detection of increased T-cell clonality, both of which can be determined by use of next-generation sequencing methods, may correlate with response to pembrolizumab therapy and/or that the converse, the 'hypomutated' state (the absence of neo-antigens) may correlate with non-response. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations it is necessary to compare the tumor genome with the germline genome. Microsatellite instability (MSI) may also be evaluated as this is an important biomarker for some cancers (i.e., colorectal cancer).

Tumor and blood RNA analyses:

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

Proteomic Analyses using Blood or Tumor:

Tumor and blood samples from this study may undergo proteomic analyses (e.g., PD-L1 IHC). PD-L1 protein level, as assessed by IHC in tumor sections, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and a PD-L1 IHC diagnostic is marketed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (i.e., TNBC, H&N and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic profiling using a variety of platforms that could include but are not limited to cytometry, immunohistochemistry, immunoassay, liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

Other blood-derived Biomarkers:

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

Planned Genetic Analysis

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

4.2.3.6 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 review committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

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

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in Section 4.2.2.2, the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with newly diagnosed, treatment-naïve multiple myeloma (MM) who are ineligible for auto-SCT and are at least 18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

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

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

3. Have a confirmed diagnosis of active multiple myeloma and measurable disease defined as:

    a. ≥10% bone marrow plasma cell percentage or biopsy proven bony or extramedullary plasmacytoma and

    b. Serum monoclonal protein (M-protein) levels ≥ 0.5 g/dL or

    c. Urine monoclonal protein (M-protein) levels ≥200 mg/24-hours or

    d. For subjects without measurable serum and urine M-protein levels, an abnormal serum free light chain ratio (FLC κ/λ) with involved FLC level ≥100 mg/L. (Normal serum FLC κ/λ value: 0.26 - 1.65).

    e. Presence of CRAB features (hypercalcemia and/or renal impairment and/or anemia and/or bone disease; see Section 4.2.1.1 for the definition of CRAB features.

        - in the absence of CRAB features, subjects with any of the following biomarkers of malignancy: clonal bone morrow plasma cell percentage ≥60%, involved/uninvolved serum free light chain (FLC) ratio ≥ 100 or more than one focal bone lesion in MRI would also be eligible.

4. Must be ineligible to receive treatment with auto-SCT due to age (≥65 years old) or any significant coexisting medical condition (cardiac, renal, pulmonary or hepatic dysfunction), likely to have a negative impact on tolerability of auto-SCT. Subjects < 65 years old who refuse auto-SCT are not eligible for this study. Note: Sponsor review and approval of participants <65 years old is required before randomization.

5. Be able to provide at screening, archival (≤60 days prior to screening date) or newly obtained bone marrow biopsy or aspirate material for disease assessment at the local institutions and MRD characterization for central analysis. Subjects that have agreed to participate in the bone marrow aspirate exploratory sub-study (selected US sites ONLY) should be able to provide a newly obtained bone marrow aspirate for central analysis.

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

7. Must demonstrate adequate organ function as defined in Table 1; all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	>1,000.0/mcL
Platelets[a]	≥75,000.0/mcL
Hemoglobin[a]	≥7.5g/dL
Renal	
Creatinine **OR** Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or creatinine clearance)	≤1.5 X upper limit of normal (ULN) **OR** ≥30.0 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 (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

a. Hemoglobin and platelet requirements cannot be met by use of recent transfusion or growth factor support (Granulocyte colony stimulating factor - GCSF or erythropoietin) within **2** weeks prior to treatment initiation.
b. Creatinine clearance should be calculated per central standard.

8. Female subjects of childbearing potential should have two negative urine pregnancy tests (with a sensitivity of at least 25mIU/ml) prior to the first dose of study medication. The pregnancy tests must be obtained within 10-14 days AND within 24 hours prior to receiving the first dose of study medication as per lenalidomide pregnancy prevention plan. The study doctor must verify that the results of these tests are negative. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

9. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for 28 days prior to starting lenalidomide, during the course of the study, during any dose interruptions, and through 28 days after the last dose of lenalidomide (or 120 days after the last dose

of pembrolizumab (Section 5.7.5). Female subjects of child-bearing potential are those who. 1) have achieved menarche at some point, 2) have not undergone a hysterectomy or bilateral oophorectomy or 3) have not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

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

10. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 28 days after the last dose of lenalidomide (or 120 days after the last dose of -pembrolizumab).

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

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

12. Subject is able to swallow capsules and is able to take and tolerate oral medications on a continuous basis.

5.1.3 Subject Exclusion Criteria

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

1. Has oligo-secretory myeloma, smoldering MM, monoclonal gammopathy of undetermined significance, Waldenström's macroglobulinemia, or any history of plasma cell leukemia.

2. History of repeated infections, primary amyloidosis, hyperviscosity or POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).
3. 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.

    Note: A short course of 40 mg of dexamethasone (≤4 days) or equivalent for emergency use is allowed after consultation with the Sponsor. In such cases, baseline m-protein values from serum and urine should be obtained before the short steroid course and be repeated prior to study drug administration on Cycle 1 Day 1.

4. Has had prior anti-myeloma therapy including but not limited to low-dose dexamethasone, IMiDs, proteasome inhibitors, chemotherapy, monoclonal antibody, auto-SCT or radiation therapy prior to entry in the study.

   Note: Major surgery is permitted, as long as the subject has recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

5. Is currently participating and receiving anti-myeloma study therapy or has participated in an anti-myeloma study of an investigational agent and received anti-myeloma study therapy or used an investigation device prior to entry in the study.

6. Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. (Subjects who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of Graft versus Host Disease (GVHD) and it was not performed as treatment for multiple myeloma).

7. Has known hypersensitivity to dexamethasone, lenalidomide, or pembrolizumab.

8. Has peripheral neuropathy ≥ Grade 2.

9. Has a known additional malignancy that is progressing or requires active treatment within the last 5 years. 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 the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

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 compliance 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-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

16. Has a known Human Immunodeficiency Virus (HIV), or a known, active Hepatitis B (HBV), or a known, active Hepatitis C (HCV) infection.

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

18. Is unable or unwilling to undergo thromboembolic prophylaxis including, as clinically indicated, aspirin, Coumadin (warfarin) or low-molecular weight heparin.

19. Has lactose intolerance.

20. Has an invasive fungal infection.

21. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or Sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

5.2 Trial Treatment(s)

The treatment(s) to be used in this trial are outlined below in Table 2.

Table 2 Trial Treatment

Study Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
pembrolizumab	200 mg	Q3W	IV infusion	every 21 days	Experimental
lenalidomide	25 mg	Days 1 to 21	oral	28-day cycle	Standard of care
dexamethasone	40 mg[a]	Days 1, 8, 15, 22	oral	28-day cycle	Standard of care

[a] A low-dose dexamethasone dose of 20 mg on Days 1, 8, 15, and 22 in subjects aged **> 75 years** is recommended [39].

After ensuring subjects meet disease related inclusion/exclusion criteria through previous consultation with the Sponsor, study personnel will access Integrated Voice Response System (IVRS)/Integrated Web Response System (IWRS) to obtain randomization number and study drug assignment. Cycle 1 treatment must be given within 3 calendar days of randomization number assignment in IVRS/IWRS.

All supplies indicated in Table 2 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number.

The trial site is responsible to record the lot number, manufacturer and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

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.

Subjects in the investigational arm (Arm A) should start treatment with all 3 drugs (pembrolizumab, lenalidomide and low-dose dexamethasone) on cycle 1 day 1 (C1D1). Subjects will receive 200 mg pembrolizumab by IV infusion within a 30-minute period along with lenalidomide PO 25 mg and low-dose dexamethasone PO 40 mg. After C1D1, pembrolizumab infusions will continue every 21 days (Q3W). Lenalidomide PO 25 mg will be given daily, on days 1-21 and low-dose dexamethasone PO 40 mg will be given daily, on days 1, 8, 15, and 22 of repeated 28-day cycles.

In the control arm (Arm B), subjects should start treatment on cycle 1 day 1 (C1D1) with both drugs, lenalidomide PO 25 mg and low-dose dexamethasone PO 40 mg. Lenalidomide PO 25 mg will be given daily on days 1-21 and low-dose dexamethasone PO 40 mg will be given daily on days 1, 8, 15, and 22 of repeated 28-day cycles.

NOTE: For subjects aged > 75 years, a daily low-dose dexamethasone dose of 20 mg on days 1, 8, 15, and 22 of repeated 28-day cycles is recommended when combined with pembrolizumab and lenalidomide or with lenalidomide alone [39].

All subjects under treatment with lenalidomide must receive appropriate anti-coagulation prophylaxis therapy after an initial assessment of each subject's underlying risk factors. The appropriate anti-coagulation prophylaxis treatment should be selected according to institutional practice. Examples of commonly used thrombo-embolic prophylaxis medications include aspirin, low molecular weight heparin, and vitamin K antagonists.

For both groups, if the dose of one drug in the regimen (i.e., pembrolizumab, lenalidomide, or low-dose dexamethasone) is delayed the treatment with the other drugs may continue as scheduled. Missed doses should be skipped, not delayed, if not given within the allowed window (+/- 3 days). If either pembrolizumab, lenalidomide, or low-dose dexamethasone is discontinued due to unacceptable toxicity, subjects can continue to receive study treatment with the remaining study drugs without discontinuing from study. Cross-over between the arms is not permitted in the study.

Details on the preparation and administration of pembrolizumab are provided in the Pharmacy Manual. For additional information regarding lenalidomide or dexamethasone, please refer to local prescribing information.

5.2.1.2 Dose Modification

5.2.1.2.1 Dose Modification Guidelines for Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 and Table 4. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 3 Dose Modification Guidelines for Hematological Drug-Related Adverse Events

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

Table 4 Dose Modification Guidelines for Non-Hematological Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/ Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Type 1 diabetes mellitus (if new onset) or Hyper-glycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyper-thyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypo-thyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication.
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4 or recurrent 2	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 (recurrent Grade 2 for pneumonitis) drug-related AE that recurs, or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Refer to Table 8 – Infusion Reaction Treatment Guidelines for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AEs may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

5.2.1.2.2 Dose Modification Guidelines for Lenalidomide

Lenalidomide should be taken orally at about the same time each day, either with or without food. Lenalidomide capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed.

The criteria presented in this section for dose modification are meant as general guidelines, and they are based on current US standards of clinical practice. Local standards and prescribing information may differ and should be followed. Lenalidomide dose modifications for toxicity must be performed as clinically indicated at the discretion of the investigator. For additional information please refer to lenalidomide local prescribing information.

Dose modification guidelines, as summarized in Table 5 below, are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicity judged to be related to lenalidomide.

Table 5 Dose Adjustments for Hematologic Toxicities for Lenalidomide

Platelet counts	
Thrombocytopenia	
When Platelets	**Recommended Course**
Fall to <30,000/mcL	Interrupt lenalidomide treatment, follow CBC weekly
Return to ≥30,000/mcL	Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop <30,000/mcL	Interrupt lenalidomide treatment
Return to ≥30,000/mcL	Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily
Absolute Neutrophil counts (ANC)	
Neutropenia	
When Neutrophils	**Recommended Course**
Fall to <1000/mcL	Interrupt lenalidomide treatment, follow CBC weekly
Return to ≥1,000/mcL and neutropenia is the only toxicity	Resume lenalidomide at 25 mg daily or initial starting dose
Return to ≥1,000/mcL and if other toxicity	Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily
For each subsequent drop <1,000/mcL	Interrupt lenalidomide treatment
Return to ≥1,000/mcL	Resume lenalidomide at next lower dose. Do not dose below 2.5 mg daily

For other Grade 3/4 toxicities judged to be related to lenalidomide, hold treatment and restart at the physician's discretion at the next lower dose level when toxicity has resolved to ≤ Grade 2.

Since lenalidomide is primarily excreted unchanged by the kidney, adjustments to the dose of lenalidomide are recommended while on the study to provide appropriate drug exposure in subjects with moderate or severe renal impairment and in subjects on dialysis. Based on a PK study in subjects with renal impairment due to non-malignant conditions, lenalidomide

dose adjustment is recommended for subjects with CLcr ≤50 mL/min. The recommendations for dose adjustments are as follows (Table 6):

Table 6 Lenalidomide Dose Adjustments for Subjects with Renal Impairment

Category	Renal Function (Cockcroft-Gault)	Dose in MM
Moderate Renal Impairment	CLcr 30-50 mL/min	10 mg Every 24 hours
Severe Renal Impairment	CLcr < 30 mL/min (not requiring dialysis)	15 mg Every 48 hours
End Stage Renal Disease	CLcr < 30 mL/min (requiring dialysis)	5 mg Once daily. On dialysis days, administer the dose following dialysis.

After initiation of lenalidomide therapy, subsequent lenalidomide dose increase or decrease is based on individual subject treatment tolerance, as described in the lenalidomide prescribing information.

Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal. Subjects with a prior history of Grade 4 rash associated with thalidomide treatment should not receive lenalidomide. Lenalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Lenalidomide must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected and should not be resumed following discontinuation for these reactions.

Lenalidomide capsules contain lactose. Risk-benefit of lenalidomide treatment should be evaluated in subjects with lactose intolerance.

Hepatic failure, including fatal cases, has occurred in subjects treated with lenalidomide in combination with dexamethasone. In clinical trials, 15% of subjects experienced hepatotoxicity (with hepatocellular, cholestatic and mixed characteristics); 2% of subjects with multiple myeloma and 1% of subjects with myelodysplasia had serious hepatotoxicity events. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop lenalidomide in the event of elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

5.2.1.2.3 Dose Modification Guidelines for Dexamethasone

Low-dose dexamethasone will be given at 40 mg once orally on Days 1, 8, 15, and 22 (i.e., once weekly) of repeated 28-day cycles every 28 days. For subjects aged > 75 years in both arms, a daily dexamethasone dose of 20 mg on days 1, 8, 15, and 22 every 28 days is recommended [39].

The criteria presented in this section for dose modification are meant as general guidelines, and they are based on current US standards of clinical practice. Local standards and

prescribing information may differ and should be followed. Dexamethasone dose modifications for toxicity must be performed as clinically indicated at the discretion of the investigator. Refer to the dexamethasone local prescribing information, Table 7, and Table 8 for dose modification guidelines.

Table 7 Supportive Care Guidelines Specific to Dexamethasone

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1–2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by one dose level.
Gastrointestinal	> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	Edema >Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by one dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration > Grade 2 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone do not resume.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone dose by one dose level. If weakness persists despite above measures, decrease dose by one dose level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia > Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.

Table 8 Recommended Dose reduction levels for Dexamethasone

Dose Level	Dexamethasone dose (PO)
0	40 mg
-1	20 mg
-2	12 mg
-3	0 mg

5.2.2 Timing of Dose Administration

Subjects in the **investigational arm** (Arm A) should start treatment with all 3 drugs (pembrolizumab, lenalidomide and low-dose dexamethasone) on cycle 1 day 1 (C1D1). After C1D1, pembrolizumab infusions will continue every 21 days (Q3W). Lenalidomide administrations will continue daily, on days 1-21 and low-dose dexamethasone administrations will continue daily, on days 1, 8, 15, and 22 of repeated 28-day cycles.

In the **control arm (Arm B)**, subjects should start treatment on cycle 1 day 1 (C1D1) with both lenalidomide and low-dose dexamethasone. Lenalidomide administrations will continue daily, on days 1-21 and low-dose dexamethasone administrations will continue daily, on days 1, 8, 15, and 22 of repeated 28-day cycles.

NOTE: For subjects aged > 75 years in both arms, a daily low-dose dexamethasone dose of 20 mg on days 1, 8, 15, and 22 of repeated 28-day cycles is recommended when combined with pembrolizumab and lenalidomide or with lenalidomide alone [39].

All subjects under treatment with lenalidomide must receive appropriate anti-coagulation prophylaxis therapy. The appropriate anti-coagulation prophylaxis treatment should be selected according to institutional practice. Examples of commonly used thrombo-embolic prophylaxis medications include aspirin, low molecular weight heparin, and vitamin K antagonists.

Trial treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Trial treatment of lenalidomide and low-dose dexamethasone may be administered up to 3 days before or after the scheduled dosing date for administrative reasons per the investigator's judgment. Missed doses 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 (e.g., elective surgery, unrelated medical events, radiotherapy, patient vacation, and holidays) not related to study therapy. Subjects should be placed back on study therapy within 28 days of the scheduled interruption. The reason for interruption should be documented in the subject's study record. Dosing interruptions should be discussed with the Sponsor.

Delays for 12 weeks between pembrolizumab doses due to toxicity or delays for 28 days between lenalidomide or low-dose dexamethasone doses due to toxicity are also permitted. However, disease response assessments should continue to be performed according to schedule as detailed on the Trial Flow Chart (Section 6.0), independently of doses delays for both treatment groups. Dose delays should be discussed with the Sponsor.

For both groups, if the dose of one drug in the regimen (i.e., pembrolizumab, lenalidomide, or low dose dexamethasone) is delayed or interrupted the treatment with the other drugs may continue as scheduled. Missed doses should be skipped, not delayed, if not given within the allowed window (+/- 3 days). If either pembrolizumab, lenalidomide or low-dose

dexamethasone is discontinued due to unacceptable toxicity, subjects can continue to receive study treatment with the remaining study drugs without discontinuing from study.

Details on the preparation and administration of pembrolizumab are provided in the Pharmacy Manual. For details on the administration of lenalidomide or low-dose dexamethasone, please refer to the local prescribing information.

5.2.2.1 Pembrolizumab

Trial treatment of pembrolizumab should start on cycle 1 day 1 (C1D1) and continue every 21 days (Q3W) after all procedures/assessments have been completed as detailed in the Trial Flow Chart (Section 6.0).

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 21 days (Q3W). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

5.2.2.2 Lenalidomide

Trial treatment of lenalidomide should start on cycle 1 day 1 (C1D1). Lenalidomide PO 25 mg will be given daily on days 1-21 of repeated 28-day cycles. Subjects should be instructed that if a dose of lenalidomide has been missed and it has been less than 12 hours since the subject's regular dosing time, the subject should take lenalidomide as soon as the subject remembers. If it has been more than 12 hours, the dose must be skipped. Subjects should not take 2 doses at the same time. All subjects under treatment with lenalidomide must receive appropriate anti-coagulation prophylaxis therapy which should be selected according to institutional practice. Examples of commonly used thrombo-embolic prophylaxis medications include aspirin, low molecular weight heparin, and vitamin K antagonists. For details on the administration of lenalidomide, please refer to the local prescribing information.

5.2.2.3 Dexamethasone

Trial treatment of low-dose dexamethasone should start on cycle 1 day 1 (C1D1). Low-dose dexamethasone PO 40 mg will be given daily, on days 1, 8, 15, and 22 of repeated 28-day cycles. Missed doses should be skipped, not delayed, if not given within the allowed window (+/- 3 days). For details on the administration of low-dose dexamethasone, please refer to the local prescribing information.

NOTE: For subjects aged > 75 years in both arms, a daily low-dose dexamethasone dose of 20 mg on days 1, 8, 15, and 22 of repeated 28-day cycles is recommended when combined with pembrolizumab and lenalidomide or with lenalidomide alone [39].

5.2.3 Extent of Trial Treatment

All subjects who experience a complete response, very good partial response, a partial response, minor response or have stable disease may remain on treatment until documented confirmed disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements or administrative reasons.

On 03-JUL-2017, the US FDA placed KN183, KN185 and cohort 1 of KN023 on clinical hold based on safety data from KN183 and KN185 presented to the DMC. The FDA determined that the risks of pembrolizumab plus pomalidomide or lenalidomide outweighed any potential benefit for patients with multiple myeloma. Based on this decision, the treatment phase of KN183 and KN185 is closed effective immediately. All subjects must stop study treatment, complete the Discontinuation Visit and move into the long-term safety and survival follow-up per protocol.

5.2.4 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to treatment with pembrolizumab in combination with lenalidomide and low-dose dexamethasone (investigational arm, Arm A) or lenalidomide and low-dose dexamethasone (control arm, Arm B), respectively.

5.4 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

1. Age (<75 vs. ≥75 years old)

2. International Staging System stage (ISS I or II vs. ISS III)

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. Subject may remain on anti-coagulation therapy as long as the PT or PTT is within therapeutic range of the intended use of anticoagulants

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

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

  Note: Palliative localized radiation therapy to a site of pre-existing disease is permitted while on study.

  Note: For subjects in the investigational arm (Arm A) concomitant radiation may be permitted after consultation with the Sponsor for subjects with confirmed disease progression based on the development of new bone lesions or soft tissue plasmacytomas or a definite increase in the size of existing bone lesions or soft tissue plasmacytomas who in the opinion of the investigator may have a tumor flare reaction but otherwise is deriving clinical benefit from study treatment.
- Oral contraceptive
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, Bacillus Calmette-Guerin (BCG), and oral typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an adverse event, serious adverse event, or for use as a pre-medication when required.

Replacement doses of steroids (for example, prednisone 5-7.5 mg daily) are permitted while on study.

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

- **Pneumonitis**:
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:

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

  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider gastrointestinal (GI) consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis** that persists > 3 days, administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:

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

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g., propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

Table 9 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 9 Infusion Reaction Treatment Guidelines

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

Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

5.6.2 Prophylaxis or Anti-Thrombotic Supportive Treatment

Venous thromboembolic events (deep venous thrombosis [DVT] and pulmonary embolism [PE]) and arterial thromboses are increased in subjects treated with lenalidomide. A significantly increased risk of DVT (7.4%) and of PE (3.7%) occurred in subjects with multiple myeloma after at least one prior therapy who were treated with lenalidomide and dexamethasone therapy compared to subjects treated in the placebo and dexamethasone group (3.1% and 0.9%) in clinical trials with varying use of anticoagulant therapies. In the newly diagnosed multiple myeloma (NDMM) study in which nearly all subjects received antithrombotic prophylaxis, DVT was reported as a serious adverse reaction (3.6%, 2.0%, and 1.7%) in the Rd Continuous, Rd18, and MPT arms, respectively. The frequency of serious adverse reactions of PE was similar between the Rd Continuous, Rd18, and MPT arms (3.8%, 2.8%, and 3.7%, respectively).

Myocardial infarction (1.7%) and stroke (cerebrovascular accident [CVA]) (2.3%) are increased in subjects with multiple myeloma after at least one prior therapy who were treated with lenalidomide and dexamethasone therapy compared to subjects treated with placebo and dexamethasone (0.6% and 0.9%) in clinical trials. In the NDMM study, myocardial infarction (including acute) was reported as a serious adverse reaction (2.3%, 0.6%, and 1.1%) in the Rd Continuous, Rd18, and MPT arms, respectively. The frequency of serious adverse reactions of CVA was similar between the Rd Continuous, Rd18, and MPT arms (0.8%, 0.6 %, and 0.6%, respectively). Subjects with known risk factors, including prior thrombosis, may be at greater risk and actions should be taken to try to minimize all modifiable factors (e.g., hyperlipidemia, hypertension, smoking).

In controlled clinical trials that did not use concomitant thromboprophylaxis, 21.5% overall thrombotic events (Standardized MedDRA Query Embolic and Thrombotic events) occurred in subjects with refractory and relapsed MM who were treated with lenalidomide and dexamethasone compared to 8.3% thrombotic events in subjects treated with placebo and dexamethasone. The median time to first thrombotic event was 2.8 months. In the NDMM study in which nearly all subjects received antithrombotic prophylaxis, the overall frequency of thrombotic events was 17.4% of subjects in the combined Rd Continuous and Rd18 arms and 11.6% in the MPT arm. The median time to first thrombotic event was 4.37 months in the combined Rd Continuous and Rd18 arms. Thromboprophylaxis is recommended. The regimen of thromboprophylaxis should be based on an assessment of the subject's underlying risks. Instruct subjects to report immediately any signs and symptoms suggestive of thrombotic events. ESAs and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision in subjects receiving lenalidomide.

Investigator should select, according to institutional practice, the appropriate anti-coagulation prophylaxis treatment after an assessment of each subject's underlying risk factors. Examples of commonly used thrombo-embolic prophylaxis medications include aspirin, low molecular weight heparin, and vitamin K antagonists.

5.6.3 Tumor Lysis Syndrome

Fatal instances of tumor lysis syndrome have been reported during treatment with lenalidomide. The subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These subjects should be monitored closely, and appropriate precautions taken.

5.6.4 Second Primary Malignancies

In clinical trials in subjects with multiple myeloma receiving lenalidomide, an increase of invasive second primary malignancies, notably acute myeloid leukemia (AML) and MDS, have been observed. The increase of cases of AML and MDS occurred predominantly in NDMM subjects receiving lenalidomide in combination with oral melphalan (frequency of 5.3%) or immediately following high-dose intravenous melphalan and ASCT (frequency of up to 5.2%). The frequency of AML and MDS cases in the lenalidomide plus dexamethasone arms was observed to be 0.4%. Cases of B-cell malignancies (including Hodgkin's Lymphomas) were observed in clinical trials where subjects received lenalidomide in the post-ASCT setting. Subjects who received lenalidomide-containing therapy until disease progression did not show a higher incidence of invasive SPM than subjects treated in the fixed duration lenalidomide-containing arms. Monitor subjects for the development of second primary malignancies. Take into account both the potential benefit of lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide.

5.6.5 Radiotherapy

The use of radiotherapy while on study must be recorded in the trial database.

Localized palliative radiation therapy to a site of pre-existing disease may be permitted while on study for subjects in both treatment arms.

For subjects in the investigational arm (Arm A), definitive radiation may be permitted after consultation with the Sponsor, if disease progression is confirmed based on the development of new bone lesions or soft tissue plasmacytomas or a definite increase in the size of existing bone lesions or soft tissue plasmacytomas when in the opinion of the investigator the subject may have a tumor flare reaction but otherwise is deriving clinical benefit from study treatment and meet the additional criteria for treatment post progression defined on Section 7.1.2.8.6.

Following approval by the Sponsor, the subject may reinitiate or continue on treatment with lenalidomide and low-dose dexamethasone without interruption during the course of radiation therapy if the investigator believes that the risk of excessive bone marrow suppression or other toxicity is acceptable, and it is in the best interest of the subject to do so. For subjects in the investigational arm (Arm A), treatment with pembrolizumab must be withheld while receiving radiation therapy and may be restarted only after its completion.

However, subjects in the control arm (Arm B) who develop a new lesion or a definite increase in the size of existing bone lesions or soft tissue plasmacytomas that meets the criteria for confirmed disease progression according to IMWG, treatment must be discontinued for progressive disease regardless of whether radiation therapy is initiated.

However, subjects in the control arm (Arm B) who develop a new lesion or a definite increase in the size of existing bone lesions or soft tissue plasmacytomas that meets the criteria for disease progression according to IMWG, treatment must be discontinued for progressive disease regardless of whether radiation therapy is initiated.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 REVLIMID Risk Minimization (REMS™) Program

Because of the embryo-fetal risk, lenalidomide is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the **REVLIMID REMS™** program **(formerly known as the "RevAssist®" program)** in the United States and for study sites outside of the United States through country specific risk minimization programs**.**

Required components of the **REVLIMID REMS™** program include the following:

- Prescribers must be certified with the **REVLIMID REMS™** program by enrolling and complying with the REMS requirements.
- Subjects must sign a Patient-Physician agreement form and comply with the REMS requirements. In particular, female subjects of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements.
- Pharmacies must be certified with the **REVLIMID REMS™** program, must only dispense to subjects who are authorized to receive lenalidomide and comply with REMS requirements.

Further information about the **REVLIMID REMS™** program is available at PPD or by telephone at PPD

5.7.3 Lenalidomide Pregnancy Prevention Plan

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving lenalidomide within a clinical trial. The following PPP documents are included:

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 5.7.4) provides the following information:

- Potential risks to the fetus associated with lenalidomide exposure
- Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
- Requirements for counseling of all subjects receiving lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
- Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving lenalidomide in the study
- Pregnancy testing requirements for subjects receiving lenalidomide who are FCBP

2. The Lenalidomide Education and Counseling Guidance Document for each gender (female and male; Section 12.9.2 and Section 12.10 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of lenalidomide. A copy of this document must be maintained in the subject's records for each dispense.

3. The Lenalidomide Information Sheet (Section 12.10) will be given to each subject receiving lenalidomide. The subject must read this document prior to starting lenalidomide and each time the subject receives a new supply of lenalidomide.

5.7.4 Lenalidomide Risks of Fetal Exposure and Acceptable Birth Control Methods

5.7.4.1 Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. A teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

5.7.4.1.1 Definition of Females of Childbearing Potential

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal

(amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

5.7.4.1.2 Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

5.7.4.2 Counseling

5.7.4.2.1 Females of Childbearing Potential

For a FCBP, lenalidomide is contraindicated unless all of the following are met (i.e., all FCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She understands the potential teratogenic risk to the unborn child.
- She understands the need for effective contraception, without interruption, 28 days before starting lenalidomide, throughout the entire duration of lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- She understands and agrees to inform the investigator if a change or stop of method of contraception is needed.
- She must be capable of complying with effective contraceptive measures.
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy.
- She understands the need to commence lenalidomide as soon as it is dispensed following a negative pregnancy test.
- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 5.7.4) and in the Informed Consent.
- She acknowledges that she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

The investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding.
- Acknowledges the aforementioned requirements.

5.7.4.2.2 Females of Not Childbearing Potential

For a FNCBP, lenalidomide is contraindicated unless all of the following are met (i.e., all FNCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

5.7.4.2.3 Males

Traces of lenalidomide have been found in semen. Male subjects taking lenalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.

5.7.4.3 Contraception

5.7.4.3.1 Females of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while taking lenalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of lenalidomide (or 120 days for subjects enrolled in the experimental treatment arm; receiving pembrolizumab).

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to

determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g., desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in subjects with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a subject is currently using combined oral contraception the subject should switch to another one of the highly effective methods listed above. The risk of venous thromboembolism continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

5.7.4.3.2 Males

Male subjects must practice complete abstinence (NOTE: True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

5.7.4.4 Pregnancy Precautions for Lenalidomide Use

5.7.4.4.1 Before Starting Lenalidomide

5.7.4.4.1.1 Females of Childbearing Potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting lenalidomide.

5.7.4.4.1.2 Males

Male subjects must practice complete abstinence (NOTE: True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy

5.7.4.4.2 During and After Study Participation

5.7.4.4.2.1 Female Subjects

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

- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide (or 120 days post discontinuation of pembrolizumab (Arm A).

- At each visit, the investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.

- If a FCBP considers the need to change or to stop a method of contraception, the investigator must be notified immediately.

- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.

- If pregnancy or a positive pregnancy test does occur in a subject, lenalidomide must be immediately discontinued.

- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide must be discontinued during this evaluation.

- Females must agree to abstain from breastfeeding while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

5.7.4.4.2.2 Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide (or 120 post discontinuation of pembrolizumab (Arm A), even if he has undergone a successful vasectomy.

- Must not donate semen or sperm while receiving lenalidomide, during dose interruptions or for at least 28 days after the last dose of lenalidomide.

- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.

- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking lenalidomide, the investigator must be notified immediately.

5.7.4.4.2.3 Additional Precautions

- Subjects should be instructed to never give lenalidomide to another person.

- Subjects should be instructed to return any unused capsules to the study doctor.

- Subjects should not donate blood while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

- No more than a 28-day lenalidomide supply may be dispensed with each cycle of lenalidomide.

- If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, lenalidomide and low dose dexamethasone, the subject will immediately be removed from the study and the Sponsor should be notified by the site without delay within 24 hours.

- Study investigators from United States sites should report any suspected fetal exposure to lenalidomide to Celgene Corporation (at PPD) and to FDA via the MedWatch Program (at PPD).

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment but agrees to continue to participate in the regularly scheduled study activities.

- Documented disease progression as assessed by the investigator. (i.e., 2 consecutive assessments are needed for disease progression. Clinical deterioration will not be considered progression). Note: Subjects with documented disease progression may continue to receive trial treatment, at the discretion of the study investigator prior consultation with the Sponsor, if they meet the criteria outlined in Section 7.1.2.8.6.

- Unacceptable adverse experiences as described in Sections 5.2.1.2 and 5.6.1.

- Intercurrent illness that prevents further administration of treatment.

- The subject has a confirmed positive serum pregnancy test.

- Subjects who receive any non-protocol specified anti-myeloma therapy prior to documented progression will be discontinued from all study treatment (including lenalidomide and low dose dexamethasone); however, tumor assessments must continue at 4 week intervals until documented progression.

- Noncompliance with trial treatment or procedure requirements.

  - Subjects experiencing a > 12 weeks delay between pembrolizumab doses in the investigational arm (Arm A) or > 28 day delay for both lenalidomide and low dose dexamethasone in the control arm (Arm B) due to an adverse event(s) related to study treatment must be discontinued from treatment.

  - Subjects experiencing >28 days delays in all study drugs due medical/surgical events or logistical reasons unrelated to study therapy must be discontinued from treatment.

  NOTE: For both groups, if either pembrolizumab, lenalidomide or low-dose dexamethasone is discontinued due to unacceptable toxicity, subjects can continue to receive study treatment with the remaining study drugs without discontinuing from study.

- The subject is lost to follow-up.

- Administrative reasons.

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

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit,

discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator), or the Sponsor ends the trial, whichever occurs first.

5.11 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete,
2. Poor adherence to protocol and regulatory requirements,
3. Plans to modify or discontinue the development of the study drug pembrolizumab.
4. A request made by the U.S. Food and Drug Administration or other similar Health Authority due to safety concerns.

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

6.0 TRIAL FLOW CHART

6.1 Trial Flow Chart

Trial Period:	**Screening Phase**	**Treatment Cycles**						**End of Treatment**		**Post-treatment**	
		Cycles 1-3 to be repeated beyond 3 cycles									
Treatment Cycle/Title: (28 days cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon[o]	Post-Treatment Safety Follow-up	Efficacy Follow-up Visits	Survival Follow-up
Cycle Day (visit day) (± 3 days after C1D1 unless otherwise specified)	(-28 to -1 days)	**1** (+ 3 days)	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon	Every 4 weeks post Discon (± 7 days)	Every 12 weeks (± 7 days) or as directed by the Sponsor
Administrative Procedures											
Informed Consent	X										
Informed Consent for Future Biomedical Research	X										
Inclusion/Exclusion Criteria	X										
Subject Identification Card	X										
Demographics and Medical History	X										
International Staging System (ISS)	X										
Prior and Concomitant Medication Review[d]	X	X	X	X	X	X	X	X	X		
Register REVLIMID REMS™ program (US ONLY) or country specific risk mitigation program	X										
Pregnancy Prevention Counseling[l]	X	X		X		X					
Obtain randomization number and study drug assignment using IVRS/IWRS	X										
Pembrolizumab Administration		**See Section 6.1.1**									
Lenalidomide Administration											
Dexamethasone Administration											
Post-study anticancer therapy status									X	X	X
Survival Status[p]		⟷							⟷		X
Clinical Procedures/Assessments											
Review Adverse Events[d]	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X	X		X		X		X			
Directed Physical Examination (Arm A only)			X		X		X				
Vital Signs and Weight [a,d]	X	X	X	X	X	X	X	X			

Trial Period:	**Screening Phase**	**Treatment Cycles**						**End of Treatment**		**Post-treatment**	
		Cycles 1-3 to be repeated beyond 3 cycles									
Treatment Cycle/Title: (28 days cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon[o]	Post-Treatment Safety Follow-up	Efficacy Follow-up Visits	Survival Follow-up
Cycle Day (visit day) (± 3 days after C1D1 unless otherwise specified)	(-28 to -1 days)	**1** (+ 3 days)	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon	Every 4 weeks post Discon (± 7 days)	Every 12 weeks (± 7 days) or as directed by the Sponsor
12-Lead Electrocardiogram	X										
ECOG Performance Status	X	X		X		X		X			
Skeletal survey	X										
MRI or CT or PET/CT for extramedullary soft tissue plasmacytoma	X										
Disease Response Assessment by IMWG 2011 criteria [1][n]		X[n]		X		X		X	X	X	
Laboratory Procedures/Assessments: analysis performed by local laboratory											
Pregnancy Test – Urine or Serum β-HCG [b]	X	X[b]		X		X		X	X		
Archival or new Bone Marrow Biopsy or Aspirate for disease characterization[c]	X										
Laboratory Procedures/Assessments: analysis performed by central laboratory											
PT/INR and aPTT	X[e]										
CBC with Differential[d,n]	X[e]	X[n]	X	X	X	X	X	X	X		
Comprehensive blood Chemistry Panel[d,n]	X[e]	X[n]	X	X	X	X	X	X	X		
LDH	X[e]					X		X	X		
Urinalysis	X[e]					X			X		
T3, (or FT3 per local standard), FT4 and TSH	X[e]					X			X		
Serum protein electrophoresis with M-protein quantitation	X	X		X		X		X	X	X[f]	
Quantitative Serum Immunoglobulin	X	X		X		X		X	X	X[f]	
Serum immunofixation	X	X		X		X		X	X	X[f]	
Serum free light chain assay	X	X		X		X		X	X	X[f]	
24 hr urine protein electrophoresis with M-protein quantitation	X	X		X		X		X	X	X[f]	
24 hr urine immunofixation	X	X		X		X		X	X	X[f]	
β2 microglobulin	X										
Archival or new Bone Marrow Biopsy or Aspirate	X										

Trial Period:	**Screening Phase**	**Treatment Cycles**						**End of Treatment**		**Post-treatment**	
		Cycles 1-3 to be repeated beyond 3 cycles									
Treatment Cycle/Title: (28 days cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon[o]	Post-Treatment Safety Follow-up	Efficacy Follow-up Visits	Survival Follow-up
Cycle Day (visit day) (± 3 days after C1D1 unless otherwise specified)	(-28 to -1 days)	**1** (+ 3 days)	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon	Every 4 weeks post Discon (± 7 days)	Every 12 weeks (± 7 days) or as directed by the Sponsor
for Minimal Residual Disease Characterization[m]											
Bone Marrow Aspirate for Bone Marrow Exploratory Sub-Study[c]	X			X				X			
Whole Blood for Correlative Studies (RNA/DNA)[j]		X		X				X			
Blood for biomarker studies (Plasma and serum)	X										
Anti-pembrolizumab Antibodies for the investigational arm (Arm A) only [g]		X	X		X				X		
Pharmacokinetics for the investigational arm (Arm A) only [g]		X	X		X				X		
Blood for Genetic analysis [h]		X									
Patient Reported Outcomes											
EuroQol EQ-5D[i]		X		X		X		X	X		
EORTC QLQ-C30 [i]		X		X		X		X	X		
EORTC QLQ-MY20[i]		X		X		X		X	X		

a. Investigational arm (Arm A) should have vital signs measurements on Day 1 of each cycle and on the day of pembrolizumab infusion before and immediately after each administration of the study drug. Weight measurement not required post infusion.

b. For females of child bearing potential two negative pregnancy tests (sensitivity of at least 25mIU/ml) must be obtained within 10-14 days AND within 24 hours prior to C1D1 weekly during Cycle 1and then monthly in women with regular menstrual cycles, or every 2 weeks in women with irregular menstrual cycles Refer to Section 7.1.5.2 Pregnancy Testing for additional details .

c. Bone marrow analysis for all subjects at baseline will include bone marrow morphology, IHC and cytogenetics by standard FISH panel for disease status assessment at local institution. If FISH is not available, then do standard karyotyping. An archival or newly obtained sample may be used at Screening. For subjects who agree to participate in the optional biomarker sub-study, freshly obtained bone marrow aspirate sample may be collected at C1D1, C2D1 and at time of discontinuation.
Note: If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissues that would ordinarily be discarded at the end of the trial will be retained for FBR. A copy of the local pathology report, with subject information removed, should also be sent to the lab to accompany the biopsy specimen.

d. Control arm (Arm B) only, measure CBC with differential, comprehensive blood chemistry panel, vital signs, review AEs, prior and concomitant medications, and perform a physical examination on Day 1 of each cycle. Subjects in Arm B only need 1 visit per month on Day 1 of each cycle. For subjects who discontinue pembrolizumab in Arm A, but continue on the study, subsequent visits are also only needed once per month.

e. Laboratory safety tests for Screening are to be performed within 10 days prior to the first dose of trial treatment. Laboratory safety tests are not required to be repeated on Cycle 1

Trial Period:	Screening Phase	Treatment Cycles						End of Treatment		Post-treatment	
		Cycles 1-3 to be repeated beyond 3 cycles									
Treatment Cycle/Title: (28 days cycles)	Screening (Visit 1)	Cycle 1		Cycle 2		Cycle 3		Discon[o]	Post-Treatment Safety Follow-up	Efficacy Follow-up Visits	Survival Follow-up
Cycle Day (visit day) (± 3 days after C1D1 unless otherwise specified)	(-28 to -1 days)	**1** (+ 3 days)	**22**	**1**	**15**	**1**	**8**	At time of Discon	30 days post Discon	Every 4 weeks post Discon (± 7 days)	Every 12 weeks (± 7 days) or as directed by the Sponsor

Day 1. See Section 7.1.3.1 for additional details regarding laboratory safety tests.

f. Myeloma laboratory testing should be performed in the follow-up period for all subjects who discontinue study treatment for reasons other than disease progression.

g. Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at C1D1, C1D22, C2D15, C5D15 and every 4 pembrolizumab infusions thereafter, and 30 days after discontinuation of study drug (or until the subject starts new anti-cancer therapy). Pharmacokinetic/anti-drug antibody (PK/ADA) samples may be used to conduct additional safety analysis, if needed.

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

i. Patient reported outcomes (PROs) are assessed on day 1 of Cycle 1 (every 28-day cycle) through Cycle 4 and then every 3 cycles (i.e., Cycle 7, 10, 13, etc.) while the subject is receiving study treatment, at treatment discontinuation, and at 30 days post treatment discontinuation (post-treatment safety follow-up).

j. Whole blood for correlative studies (RNA/DNA) should only be collected at C1D1, C2D1 and at discontinuation.

k. Cycle 1 treatment must be administered within 3 calendar days of randomization number assignment in IVRS/IWRS, after ensuring subjects meet disease criteria through previous consultation with the Sponsor.

l. The Lenalidomide Education and Counseling Guidance Document must be completed for all subjects and signed by a trained counselor prior to each dispensing of lenalidomide in accordance with the REVLIMID REMS™/country-specific risk mitigation program. A copy of this document must be maintained in the subject's records for each dispense for all countries/sites where lenalidomide is provided centrally by the Sponsor.

m. All subjects in this study need to provide an archival or new bone marrow biopsy or fresh aspirate for minimal residual disease (MRD) characterization for central analysis at Screening, and fresh bone marrow biopsy or aspirate material at the time of achieving a Complete Response (CR), and at 6 months and 1 year after achieving a CR.

n. Disease Response Assessment by IMWG 2011 criteria, CBC with Differential, and Comprehensive blood Chemistry Panel do not need to be performed on Cycle 1 Day 1.

o. On 03-JUL-2017, the US FDA placed KN183, KN185 and cohort 1 of KN023 on clinical hold based on safety data from KN183 and KN185 presented to the DMC. The FDA determined that the risks of pembrolizumab plus pomalidomide or lenalidomide outweighed any potential benefit for patients with multiple myeloma. Based on this decision, the treatment phase of KN183 and KN185 is closed effective immediately. All subjects must stop study treatment, complete the Discontinuation Visit and move into the long-term safety and survival follow-up per protocol.

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

6.1.1 Trial Treatment Administration Schedule

	Each Cycle = 28 Days (Cycles 1-3 to be repeated beyond 3 cycles)											
	Cycle 1				Cycle 2				Cycle 3			
Group A Investigational Arm[e]												
Trial Treatment/ Cycle Day (± 3 days)	Days 1-7 (wk 1)	Days 8-14 (wk 2)	Days 15-21 (wk 3)	Days 22-28 (wk 4)	Days 1-7 (wk 1)	Days 8-14 (wk 2)	Days 15-21 (wk 3)	Days 22-28 (wk 4)	Days 1-7 (wk 1)	Days 8-14 (wk 2)	Days 15-21 (wk 3)	Days 22-28 (wk 4)
Pembrolizumab (Q3W)[a]	1			22			15			8		
Lenalidomide[b]	1 to 21				1 to 21				1 to 21			
Dexamethasone[c]	1	8	15	22	1	8	15	22	1	8	15	22
Pill count for Lenalidomide and Dexamethasone (Both groups) [d]	1				1				1			
Group B Control Arm[e]												
Lenalidomide[b]	1 to 21				1 to 21				1 to 21			
Dexamethasone[c]	1	8	15	22	1	8	15	22	1	8	15	22

a. Pembrolizumab will be administered as 200 mg every 21 days (3 weeks) as an IV infusion over 30 minutes.
b. Lenalidomide will be administered as 25 mg PO, once daily on Days 1 to 21 of repeated 28-day cycles. Lenalidomide must be prescribed through and in compliance with the REVLIMID REMS™ program. Refer to local prescribing information.
c. Low-dose dexamethasone will be administered as 40 mg PO, once daily on Days 1, 8, 15 and 22 of repeated 28-day cycles. A dexamethasone dose of 20 mg on Days 1, 8, 15 and 22 in subjects aged > 75 years is recommended. Refer to local prescribing information.
d. Site should document drug accountability as per their institutional guidelines for both groups.
e. On 03-JUL-2017, the US FDA placed KN183, KN185 and cohort 1 of KN023 on clinical hold based on safety data from KN183 and KN185 presented to the DMC. The FDA determined that the risks of pembrolizumab plus pomalidomide or lenalidomide outweighed any potential benefit for patients with multiple myeloma. Based on this decision, the treatment phase of KN183 and KN185 is closed effective immediately. All subjects must stop study treatment, complete the Discontinuation Visit and move into the long-term safety and survival follow-up per protocol.

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 subject's cancer will be recorded separately and not listed as medical history.

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before the first dose of study medication.

7.1.1.5.2 REVLIMID REMS™ program

Because of the embryo-fetal risk, lenalidomide is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the **REVLIMID REMS™** program **(formerly known as the "RevAssist®" program**) in the United States and for

study sites outside of the United States through country specific risk minimization programs. Please refer to Section 5.7.2.2 for further details.

7.1.1.5.3 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 as defined in Section 7.2.

7.1.1.5.4 Subsequent Anti-myeloma Therapy Status

The investigator or qualified designee will review all new anti-myeloma therapy initiated after the last dose of trial treatment, as well as any SCT details, including the conditioning regimen, date, and type of transplant. If a subject initiates a new anti-myeloma therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up Visit must occur before the first dose of the new therapy. Once new anti-myeloma 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 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

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

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

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

Interruptions from the protocol specified treatment are permitted in cases of medical/ surgical events or logistical reasons (e.g., elective surgery, unrelated medical events, radiotherapy, patient vacation, and holidays) not related to study therapy. Patients should be placed back

on study therapy within 28 days of the scheduled interruption. Delays for 12 weeks between pembrolizumab doses due to toxicity or delays for 28 days between lenalidomide or low-dose dexamethasone doses due to toxicity are also permitted previous consultation with the Sponsor. For both groups, if the dose of one drug in the regimen (i.e., pembrolizumab, lenalidomide, or low dose dexamethasone) is delayed the treatment with the other drugs may continue as scheduled. Missed doses should be skipped, not delayed, if not given within the allowed window (+/- 3 days). For both groups, if either pembrolizumab, lenalidomide or low-dose dexamethasone is discontinued due to unacceptable toxicity, subjects can continue to receive study treatment with the remaining study drugs without discontinuing from study. Study treatment interruptions require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

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

For those medications taken at home (lenalidomide and low dose dexamethasone), subjects will be provided with a medication diary in which to record study drug doses and will be instructed to bring this diary and study drug containers (lenalidomide and dexamethasone) to clinic visits

The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual. For instructions about administration of lenalidomide or dexamethasone please refer to the local prescribing information.

Prior to discontinuing patients from therapy, consult with Sponsor and submit the Treatment Termination & Disease Assessment Termination Form.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Oncologic Disease Details

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

7.1.2.2 International Staging System (ISS)

Use the International Staging System (ISS) at Screening for subject classification [50] (Refer to Section 12.8).

7.1.2.3 Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (Section 12.6). Toxicities will

be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

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

7.1.2.4 Electrocardiogram

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

7.1.2.5 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening (height need be taken at screening only) and repeated as per the frequency defined in the Study Flow Chart. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs. Full physical exams should be performed in accordance with local requirements.

7.1.2.5.1 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration. Subjects should have a full physical exam on Day 1 of each cycle after cycle 1. New clinically significant abnormal findings should be recorded as AEs. Directed physical exams should be performed in accordance with local requirements.

7.1.2.6 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). Subjects in the control arm (Arm B) should have vital signs measurements only on Day 1 of each cycle; subjects in the investigational arm (Arm A) should have vital signs measurements on Day 1 of each cycle and on the day of pembrolizumab infusion before and immediately after each administration of the study drug. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only. Weight measurement is not required post infusion.

7.1.2.7 Eastern Cooperative Oncology Group (ECOG) Performance Status

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

7.1.2.8 Assessment of Disease and Tumor Response

7.1.2.8.1 Criteria for Assessment of Measurable Disease for Subject's Eligibility

Investigators will use central myeloma laboratory results to determine subject eligibility. Subjects will be considered to have measurable disease if:

- Serum monoclonal protein (M-protein) levels ≥ 0.5 g/dL OR
- Urine monoclonal protein (M-protein) levels ≥200 mg/24-hours OR
- for subjects without measurable serum and urine M-protein levels, an abnormal serum free light chain ratio (FLC κ/λ) with involved FLC level ≥100 mg/L. (Normal serum FLC κ/λ value: 0.26 - 1.65).

AND

- Presence of CRAB features (hypercalcemia and/or renal impairment and/or anemia and/or bone disease)
  - in the absence of CRAB features, subjects with any of the following biomarkers of malignancy: clonal bone morrow plasma cell percentage ≥60%, involved/uninvolved serum free light chain (FLC) ratio ≥ 100 mg/L or more than one focal bone lesion in MRI would also be eligible.

7.1.2.8.2 Criteria for Assessment of Disease Response

Clinical Adjudication Committee (CAC) and investigator assessment of antitumor activity for both treatment arms will be based on the International Myeloma Working Group response criteria (IMWG criteria [1]; see Appendix 12.7). The IMWG criteria will be applied by the site as the primary measure for assessment of disease response and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of trial treatment). The IMWG criteria will be applied by the CAC as the primary measure for assessment of tumor response and date of disease progression.

A subject will be assessed on disease progression according to IMWG criteria if any of the following occurs:

- Increase of ≥ 25% from lowest response value (nadir) in any of the following:
  - Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL). Increases of ≥ 1 g/dL as sufficient to define disease progression if starting m-component is ≥ 5 g/dL.

- 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
- Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels; bone marrow plasma cell percentage; the absolute percentage must be ≥ 10%

- 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) that can be attributed solely to the plasma cell proliferative disorder.

All categories above require two consecutive assessments made at any time before classification as disease progression and/or the institution of any new anti-myeloma therapy. Bone marrow assessments need not to be confirmed.

The central laboratory vendor will receive serum and urine samples from the sites, including baseline, for myeloma laboratory testing on day 1 every 28 days cycle. For urine myeloma laboratory testing, 24-hour urine collection is mandatory for all subjects enrolled in the study in order to assess response based on IMWG criteria. **Disease response assessment should be performed every 4 weeks regardless of study treatment delays.**

For assessment of disease response, both the investigator and the CAC will analyze results from a full myeloma laboratory panel (serum and urine electrophoresis, serum and urine immunofixation, immunoglobulin quantification, and free light change assay) along with calcium, creatinine, and hemoglobin laboratory results, radiographic imaging (x-ray survey or MRI/CT/PET as clinically indicated) for subjects with bone disease and a bone marrow biopsy or aspirate (for confirmation of complete response or disease progression via increase in plasma cell percentage).

7.1.2.8.2.1 Myeloma Laboratory Testing Disease Measurements

Myeloma Laboratory Panel

For all subjects, the central laboratory vendor will receive serum and urine samples from the sites, including baseline, for myeloma laboratory testing on day 1 of every 28 days cycle regardless of study treatment delays. For urine myeloma laboratory testing 24-hour urine collection is mandatory for all subjects enrolled in the study in order to assess response based on IMWG criteria. A full myeloma laboratory panel will be performed consisting of serum and urine electrophoresis, serum and urine immunofixation, immunoglobulin quantification, and free light change assay. Results will be communicated in an expedited manner to the sites.

Note: If a short course of 40 mg dexamethasone (≤4 days) or equivalent for emergency use is used after previous consultation with the Sponsor baseline m-protein values from serum and urine should be obtained before the short steroid course and be repeated prior to study drugs administration on Cycle1 Day 1.

More information can be found in the Laboratory Manual.

7.1.2.8.2.2 Imaging for Subjects with Myeloma Bone Disease

Skeletal survey by conventional radiography must be performed at baseline (within 28 days of C1D1) to determine the extent of the subject's myeloma bone disease. The use of conventional or low dose CT scan or 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 C1D1.

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 PET/CT should be performed at baseline within 28 days of C1D1. 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 C1D1. During the course of the study 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 complete remission (CR) or stringent complete remission (sCR) assessment. The same modality of imaging used at screening should be performed for subsequent assessments.

Copies of all imaging studies used for tumor response assessment, including baseline, should be available for review by the Sponsor.

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 Timing of Disease Assessments

Antitumor activity for both treatment arms will be based on the International Myeloma Working Group response criteria (IMWG criteria [1] and will be performed every 28-day treatment cycle (Table 10).

Table 10 Disease Response Assessments

Indication	Assessment Frequency
Newly diagnosed, treatment naïve **MM**, ineligible for auto-SCT	Every 28 days (4 weeks) following first assessment.

7.1.2.8.4 Initial Disease Assessment

Initial disease assessments must be performed within 28 days prior to the first dose of trial treatment (See 6.0 – Trial Flow Charts).

Bone marrow aspirates/biopsies performed as part of standard of care prior to signing informed consent may be used for screening if performed within 60 days of Day 1. Refer to the Procedures Manual for additional details.

Myeloma laboratory testing for baseline disease assessment should be performed within 28 days prior to administration of the first dose of study drug. Sites should prioritize sending serum and urine samples to the central laboratory vendor from subjects in screening. The central laboratory vendor will communicate results to the site in a prompt manner.

NOTE: If a short course of 40 mg dexamethasone (≤4 days) or equivalent for emergency use is used after previous consultation with the Sponsor baseline m-protein values from serum and urine should be obtained before the short steroid course and be repeated prior to study drugs administration on Cycle1 Day 1.

NOTE: For urine myeloma laboratory testing, a 24-hour urine collection is mandatory for all patients enrolled in the study in order to assess response based on IMWG criteria.

7.1.2.8.5 Disease Assessment During Trial

For all patients, the central laboratory vendor will receive serum and urine samples from the sites on day 1 of every 28-day cycle for myeloma laboratory central testing during the trial. For urine myeloma laboratory testing, 24-hour urine collection is mandatory for all patients enrolled in the study.

Myeloma disease assessments should be performed by the investigator every 28 days and will be based on the IMWG criteria. There is a ±3 day window for assessments performed after Day 1. Disease assessments should not be delayed because of delays in the start of treatment cycles.

Disease assessments should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Two consecutive results from myeloma laboratory tests are needed to confirm biochemical-based disease progression. Subjects who have disease progression may continue on treatment if they meet the criteria for treatment beyond disease progression defined in Section 7.1.2.8.6.

Prior to discontinuing patients from therapy, consult with Sponsor and submit the Treatment Termination & Disease Assessment Termination Form.

7.1.2.8.6 Treatment Beyond Disease Progression

In the setting where a subject in the investigational arm (Arm A) receiving pembrolizumab in combination with lenalidomide and low dose dexamethasone is assessed by the investigator as confirmed PD according to IMWG criteria [1] based on:

- the development of new bone lesions or soft tissue plasmacytomas OR
- a definite increase in the size of existing bone lesions or soft tissue plasmacytomas

Study treatment consisting on pembrolizumab, lenalidomide and low dose dexamethasone may be continued upon Sponsor consultation if the investigator considers the subject is deriving clinical benefit and providing subsequent radiographic imaging and laboratory testing shows evidence of reduction in tumor burden from the prior time point where initial PD was observed. If repeat imaging and laboratory testing shows a reduction in the tumor burden compared to the initial result demonstrating PD, treatment may be continued/resumed. If repeat imaging and laboratory testing confirms progressive disease, subjects will be discontinued from study therapy. However, laboratory and/or imaging testing should occur at any time where there is clinical suspicion of progression.

Subjects may continue to receive study treatment after an initial PD assessment if the following criteria are met:

- Absence of signs and symptoms (including worsening of laboratory values other than myeloma laboratory results) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive disease at a critical anatomical site.

7.1.2.8.7 Biopsy Collection and Correlative Studies Blood Collection

All subjects enrolled into this study must be able to provide an archived or newly obtained bone marrow biopsy or aspirate sample for disease characterization by the local laboratory at Screening. Bone marrow analysis will include bone marrow morphology, IHC, Cytogenetics by standard FISH panel. If FISH is not available, then do standard karyotyping.

Additionally, all subjects enrolled into this study must be able to provide an archived or newly obtained bone marrow biopsy or aspirate sample for MRD characterization by central analysis at baseline, at the time of achieving a CR and at 6 months and 1 year after achieving a CR.

Additionally, a subset of subjects (up to 50 subjects per arm from selected sites only) could choose to participate in a Bone marrow sub-study and may choose to provide a newly

obtained bone marrow aspirate sample at baseline (screening or C1D1), C2D1 and at the time of discontinuation to undergo testing for the purposes of biomarker characterization. Refer to Procedures Manual for additional details.

Note: *For the bone marrow aspirate exploratory sub-study, only one sample is required for baseline. If an archival sample was used for disease characterization at Screening, a newly obtained sample will be collected on C1D1 for baseline.

Bone marrow biopsies OR aspirates will be collected as per Table 11 below:

Table 11 Bone Marrow Biopsy or Aspirate Assessments

Indication	Timing of Biopsy or Aspirate
Bone marrow biopsy OR aspirates (All subjects)	Screening, confirmation of CR, 6 months and 1 year after achieving a CR; or as clinically indicated.
Bone marrow aspirates for Bone Marrow Aspirate Exploratory Sub-Study (selected sites only, central laboratory)	Newly obtained aspirate at baseline (Screening or C1D1), C2D1, and at the time of discontinuation

Whole blood for correlative biomarker studies should be collected as shown in Table 12:

Table 12 Blood Collection for Correlative Biomarker Studies

Indication	Timing of Correlative Blood Collection
Whole blood (RNA/DNA)	Cycle 1 Day 1, Cycle 2 Day 1 and at time of discontinuation. (See Section 6.0 for Trial Flow Chart and Procedures Manual for further details).

7.1.2.9 Patient Reported Outcomes (PROs)

Patient reported outcomes (PROs) are assessed on day 1 of Cycle 1 (every 28-day cycle) through Cycle 4 and then every 3 cycles (i.e., Cycle 7, 10, 13, etc.) while the subject is receiving study treatment, at treatment discontinuation, and at 30 days post treatment discontinuation (post-treatment safety follow-up). Patient reported outcomes are to be administered by trained site personnel and completed electronically by subjects themselves. It is strongly recommended that all electronic PROs (ePROs) be administered prior to drug administration, adverse event evaluation, and disease status notification; an exception to this recommendation may occur at the treatment discontinuation visit. The PROs should be administered in the following order: EuroQol EQ-5D first, EORTC QLQ-C30, and EORTC MY20 at the time points specified in the Trial Flow Charts.

7.1.3 Laboratory Procedures/Assessments

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

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

Table 13 Laboratory Tests

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

a. Absolute values or percentage per central laboratory.
b. Perform on females of childbearing potential only. Urine pregnancy test (Sensitivity of 25mIU/ml) is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
c. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial
d. Total T3 is preferred, if not available free T3 may be tested.
e. Test only if part of Standard of Care locally.
f. Blood Urea Nitrogen is preferred; if not available, urea may be tested.

Laboratory safety tests for Screening should be performed within 10 days prior to the first dose of trial treatment. **Laboratory safety tests do not need to be repeated on Cycle 1 Day 1**. After Cycle 1, all laboratory tests will be performed by a central laboratory on Day 1 of each cycle and prior to pembrolizumab infusions for the investigational arm (Arm A). Specific laboratory tests may be performed locally, in parallel to central laboratory tests, at the discretion of the investigator, to ensure subject's safety prior to treatment. After Screening, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

Both PK and anti-pembrolizumab antibody samples for subjects who receive pembrolizumab in the investigational arm (Arm A):

Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at C1D1, C1D22, C2D15, C5D15 and every 4 pembrolizumab infusions thereafter, and 30 days after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab.

7.1.3.2.1 Pharmacokinetic Evaluations

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

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

Blood Collection for Serum MK-3475 sample collection, storage and shipment instructions for serum samples will be provided in the procedure manual. Pharmacokinetic samples should be drawn according to the PK collection schedule for subjects who receive

pembrolizumab (MK-3475). Every effort should be taken to collect samples at 30 days (±3 days) after end of pembrolizumab treatment**.**

7.1.3.2.2 Blood Collection for Serum MK-3475

Sample collection, storage and shipment instructions for serum samples will be provided in the procedure manual. PK samples should be drawn according to the PK collection schedule for subjects who receive pembrolizumab. Every effort should be taken to collect samples at 30 days after the end of pembrolizumab treatment.

NOTE: If ongoing ADA and PK results continue to be consistent with existing ADA and PK data from other pembrolizumab clinical trials, it may be decided to discontinue further sample collection in this study.

7.1.3.2.3 Blood Collection for Anti-pembrolizumab (MK-3475) 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 ADA collection schedule for subjects who receive pembrolizumab (MK-3475). Every effort should be taken to collect samples at 30 days after end of pembrolizumab treatment for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis.

NOTE: If ongoing ADA and PK results continue to be consistent with existing ADA and PK data from other pembrolizumab clinical trials, it may be decided to discontinue further sample collection in this study.

7.1.3.3 Planned Genetic Analysis Sample Collection

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

7.1.3.4 Future Biomedical Research Sample Collection

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

- Leftover DNA for future use
- Leftover bone marrow aspirate samples

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

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

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.

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Equipment

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

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. Visit requirements are outlined in Section 6.0.

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

- Laboratory safety tests, as specified in Table 1, are to be performed within 10 days prior to the first dose of trial treatment. These tests are not required to be repeated on Cycle 1 Day 1.

- Archival (≤ 60 days prior to date of Screening) bone marrow biopsy or aspirate results previously done for disease assessment as part of routine clinical management will be acceptable for screening purposes.

- For females of child bearing potential, a urine pregnancy test (sensitivity of at least 25 mIU/ml) will be performed within 10-14 days and within 24 hours prior to the first dose of trial treatment. The study doctor must confirm the results of these tests as negative. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

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

7.1.5.2 Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of child bearing potential as defined in the lenalidomide pregnancy prevention plan.

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days

while taking lenalidomide, at study discontinuation, and 28 days following the last dose of lenalidomide.

7.1.5.3 Treatment Period

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

On 03-JUL-2017, the US FDA placed KN183, KN185 and cohort 1 of KN023 on clinical hold based on safety data from KN183 and KN185 presented to the DMC. The FDA determined that the risks of pembrolizumab plus pomalidomide or lenalidomide outweighed any potential benefit for patients with multiple myeloma. Based on this decision, the treatment phase of KN183 and KN185 is closed effective immediately. All subjects must stop study treatment, complete the Discontinuation Visit and move into the long-term safety and survival follow-up per protocol.

7.1.5.4 Post-Treatment Visits

7.1.5.4.1 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 and ECIs that occur within 90 days of the end of treatment or before initiation of a new antineoplastic treatment should also be followed and recorded.

In the event a subject receives an allo-SCT within 24 months of the last dose of pembrolizumab or before the trial ends, the following events will be collected as ECIs (see Section 7.2.3.2) through 18 months from the date of allo-SCT: GVHD, febrile syndrome treated with steroids, pulmonary complications, hepatic veno-occlusive disease and/or sinusoidal syndrome, immune-mediated AEs, critical illness, and transplant-related mortality. If available and relevant to an event post allo-SCT, concomitant medications and/or laboratory results may be reported. Additional medically important AEs may be submitted at the investigator's discretion.

7.1.5.5 Efficacy Follow-up Visits

Subjects who discontinue trial treatment for a reason other than confirmed disease progression will move into the Follow-Up Phase to monitor disease status and should be assessed every 4 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, (4) withdraw of consent or (5) the end of the trial, whichever occurs first. The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks). Every effort should be made to collect information regarding disease response assessment in the follow-up period. Prior to discontinuing patients from therapy, consult with Sponsor and

submit the Treatment Termination & Disease Assessment Termination Form. NOTE: For both groups, if either pembrolizumab, lenalidomide, or low dose dexamethasone is discontinued due to unacceptable toxicity, subjects can continue to receive study treatment with the remaining study drugs without discontinuing from study.

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

7.1.5.5.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-myeloma therapy, the subject moves into the survival follow-up phase and should be contacted approximately every 12 weeks for at least 12 months following their discontinuation visit for assessment of survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

Survival status data may be requested more frequently than every 12 weeks. The Sponsor may request these additional data at time points such as prior to data cleaning, an external Data Monitoring Committee (eDMC) safety review, and/or efficacy interim analyses. All subjects who are in the Survival Follow-Up Phase and not known to have died prior to the request for these additional survival data will be contacted at that time.

7.1.5.5.2 Follow-up Post-Allogeneic Stem Cell Transplantation

In the event a subject receives an allo-SCT within 24 months of the last dose of pembrolizumab or before the end of the study, the following events will be collected as ECIs (see Section 7.2.3.2) through 18 months from the date of allo-SCT: GVHD, febrile syndrome treated with steroids, pulmonary complications, hepatic veno-occlusive disease and/or sinusoidal syndrome, immune-mediated AEs, critical illness, and transplant-related mortality. If available and relevant to an event post allo-SCT, concomitant medications and/or laboratory results may be reported. Additional medically important AEs may be submitted at the investigator's discretion. Post-allogeneic SCT ECIs that occur after the normal safety follow-up period must be assessed for seriousness and causality and reported to the Sponsor as follows: within 24 hours if serious regardless of causality, or if non-serious and considered to be drug-related; and 5 calendar days if non-serious and not considered to be drug-related.

7.1.5.6 Survival Status

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

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

All adverse events that occur after the consent form is signed but before 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 greater than 1000 mg or greater. For lenalidomide or dexamethasone an overdose will be defined as any dose that is considered both excessive and medically important by local standards. No specific information is available on the treatment of overdose of pembrolizumab, lenalidomide or dexamethasone. In the event of overdose, pembrolizumab, lenalidomide or dexamethasone 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), including the pregnancy of a male subject's female partner that occurs during the trial.

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

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

Additionally, study investigators from United States sites should report any suspected fetal exposure to lenalidomide to Celgene Corporation (at PPD) and to FDA via the MedWatch Program (at PPD).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 14 for additional details regarding each of the above criteria.

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

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

3. Additional Adverse Events of Clinical Interest:

A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document." This document can be found in the administrative binder and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

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

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

7.2.3.2.1 Adverse Events Follow-up Post-Allogeneic Stem Cell Transplantation

In the event a subject receives an allo-SCT within 24 months of the last dose of pembrolizumab or before the trial ends, the following events will be collected as ECIs through 18 months from the date of allo-SCT: GVHD, febrile syndrome treated with steroids, pulmonary complications, hepatic veno-occlusive disease and/or sinusoidal syndrome, immune-mediated AEs, critical illness, and transplant-related mortality.

If available and relevant to an event post allo-SCT, concomitant medications and/or laboratory results may be reported. Additional medically important AEs may be submitted at the investigator's discretion. Post-allogeneic SCT ECIs that occur after the normal safety follow-up period must be assessed for seriousness and causality and reported to the Sponsor as follows: within 24 hours if serious regardless of causality, or if non-serious and considered to be drug-related; and 5 calendar days if non-serious and not considered to be drug-related.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

The Sponsor will monitor unblinded aggregated events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the

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

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

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 14 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Executive Oversight Committee

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

7.3.2 Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

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

A DMC recommendation will be communicated to the Sponsor as agreed to in the DMC Charter.

7.3.3 Clinical Adjudication Committee

A Clinical Adjudication Committee (CAC) will evaluate the following events for the purposes of confirming them according to the criteria in Section 8.0 – Statistical Analysis Plan, as well as evaluating the presence of confounding factors.

1) Antitumor response (e.g., PFS, ORR, DOR) assessment based on IMWG criteria [1] including confirmation of disease progression.

The following information will be submitted by the Sponsor to the CAC for their review:

- The subject's myeloma laboratory results.
- All imaging results
- Local pathology results including results of bone marrow samples for confirmation of CR or sCR.

The role of the CAC is to ensure that all treatment outcomes are judged uniformly, using standard criteria and processes. The CAC will be composed of 3 members who are qualified by training and experience to evaluate MM disease progression and response assessment according to IMWG criteria [1] using data provided by the Sponsor. The specific data provided, and the timing of the reviews, will be described in the Adjudication Charter.

All personnel involved in the adjudication process will remain blinded to treatment allocation throughout the trial. Specific details regarding endpoint definitions can be found in the Adjudication Charter.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. A separate PK analysis plan as well as biomarker analysis plan will be provided. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will also be included in the sSAP.

On 03-JUL-2017, the US FDA placed KN183, KN185 and cohort 1 of KN023 on clinical hold based on safety data from KN183 and KN185 presented to the DMC. The FDA determined that the risks of pembrolizumab plus pomalidomide or lenalidomide outweighed any potential benefit for patients with multiple myeloma. Based on this decision, the treatment phase of KN183 and KN185 is closed effective immediately. All subjects must stop study treatment, complete the Discontinuation Visit and move into the long-term safety and survival follow-up per protocol.

Due to the current status of the study the statistical analysis of this section may be modified and will be reported in the CSR.

8.1 Statistical Analysis Plan Summary

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

<table>
<tr><td>Study Design Overview</td><td>Phase III Study of Lenalidomide and Low-dose Dexamethasone with or without Pembrolizumab in Newly Diagnosed and Treatment-Naïve Multiple Myeloma.</td></tr>
<tr><td>Treatment Assignment</td><td>Approximately 640 subjects with treatment-naive multiple myeloma will be randomized in a 1:1 ratio between two treatment groups. The two treatment arms are as follows:
<table>
<tr><th>Treatment Arm</th><th>Treatment Dose and Schedule</th></tr>
<tr><td>Treatment Arm A*</td><td>Pembrolizumab 200 mg + lenalidomide + low-dose dexamethasone</td></tr>
<tr><td>Treatment Arm B*</td><td>Lenalidomide + low-dose dexamethasone</td></tr>
<tr><td colspan="2">*This is an open label study
Stratification factors are 1) age (<75 years vs ≥ 75 years) and 2) ISS stage (I or II vs. III).</td></tr>
</table></td></tr>
<tr><td>Analysis Populations</td><td>Efficacy: Intention-to-treat (ITT) population.
Safety: All Subjects as Treated (ASaT)</td></tr>
<tr><td>Primary Endpoint</td><td>1. Progression-free survival (PFS) – per IMWG 2011</td></tr>
<tr><td>Secondary Endpoint</td><td>2. Overall Survival (OS)</td></tr>
<tr><td>Statistical Methods for Key Efficacy Analyses</td><td>The primary hypothesis will be evaluated by comparing pembrolizumab in combination with SOC (lenalidomide +low-dose dexamethasone) versus SOC (lenalidomide + low-dose dexamethasone) on PFS using a stratified log-rank test. Estimation of the hazard ratio will be done using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.</td></tr>
<tr><td>Statistical Methods for Key Safety Analyses</td><td>The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. No Tier 1 events are defined for this study. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The between-treatment confidence intervals will be calculated using the Miettinen and Nurminen method. No formal treatment comparisons with p-values will be carried out.</td></tr>
<tr><td>Interim Analyses</td><td>One efficacy interim analysis for PFS will be performed in this trial. Results will be reviewed by a DMC for evaluation of superiority as well as a non-binding futility assessment. This interim analysis will be conducted after all subjects have been enrolled and approximately 115 PFS events have been observed; details are provided in Section 8.7.</td></tr>
</table>

Multiplicity	The family-wise type I error rate for this study is strongly controlled at 2.5% (one-sided). For the PFS efficacy hypothesis, a Hwang-Shih-DeCani alpha-spending function with the gamma parameter (-8) is constructed to implement group sequential boundaries that control the type I error rate. For the PFS futility hypothesis, a Hwang-Shih-DeCani beta-spending function with the gamma parameter (-4) is constructed to implement group sequential boundaries that control the type II error rate. Further details of the interim analysis strategy can be found in Section 8.72. For the OS hypothesis, there will be only one analysis when ~ 195 OS events are observed. The secondary OS hypothesis will be tested sequentially with one-sided alpha level of 2.5% if pembrolizumab (MK-3475) in combination with SOC is superior to the SOC in PFS and hence no multiplicity adjustment will be required.
Sample Size and Power	The planned sample size is approximately 640 subjects. The primary endpoint of the study is PFS. The expected median PFS time in the control group is 25.5 months. For PFS, based on 227 events, the study has 90% power to detect a hazard ratio of 0.65 (pembrolizumab in combination with SOC vs. SOC) at alpha = 2.5% (one-sided). For OS, based on 195 events, the study has ~ 70% power to detect a hazard ratio of 0.70 (pembrolizumab in combination with SOC vs. SOC) at alpha = 2.5% (one-sided).

8.2 Responsibility for Analyses/In-House Blinding

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

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IVRS.

Although the trial is open label, analyses or summaries generated by randomized treatment assignment, actual treatment received, and/or PD-L1 biomarker status will be limited and documented. Further documentation will be provided in the sSAP. In addition, the CAC central review will be performed without knowledge of treatment group assignment.

Treatment-level results at the interim PFS analysis will be provided by the external unblinded statistician to the DMC. Key enrollment metrics and study data will also be monitored by the external unblinded statistician to inform the timing of the interim PFS. Limited additional SPONSOR personnel may be unblinded to the treatment level and/or PD-L1 biomarker results of the first PFS analyses, if required, in order to act on the recommendations of the DMC or facilitate regulatory filing after the PFS analysis. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician.

The DMC will serve as the primary reviewer of the unblinded results of the PFS analyses and will make recommendations for discontinuation of the study or modification to an executive oversight committee of the SPONSOR. Depending on the recommendation of the DMC, the Sponsor may prepare a regulatory submission. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee

may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the DMC Charter.

8.3 Hypotheses/Estimation

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

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

Primary

Progression-free survival (PFS) – the International Myeloma Working Group response criteria (IMWG 2011) **by CAC blinded central review**

PFS is defined as the time from randomization to the first documented disease progression per IMWG 2011 based on CAC blinded central review or death due to any cause, whichever occurs first. See Section 8.6.1 for definition of censoring.

Secondary

Overall Survival (OS) OS is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up.

Overall Response Rate (ORR) – the International Myeloma Working Group response criteria (IMWG 2011 criteria) for partial, or better, responses **by CAC blinded central review.**

ORR is defined as the proportion of the subjects in the analysis population who achieved at least a partial response (CR+VGPR+PR) according to the IMWG 2011.

Duration of Response (DOR) – the International Myeloma Working Group response criteria (IMWG 2011) **by CAC blinded central review.**

For subjects who demonstrated at least a partial response, response duration is defined as the time from first documented evidence of at least a partial response until disease progression or death. Response duration for subjects who have not progressed or died at the time of analysis will be censored at the date of their last assessment.

Disease Control Rate (DCR) - the International Myeloma Working Group response criteria (IMWG 2011) for at least a partial response **by CAC blinded central review.**

Disease control rate is defined as the percentage of subjects who have achieved confirmed CR, VGPR, PR, or have demonstrated SD for at least 12 weeks prior to any evidence of progression.

Second Progression Free Survival (PFS2) - the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever occurs first, **by investigator assessment**.

8.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.3.3.

8.5 ANALYSIS POPULATIONS

8.5.1 Efficacy Analysis Populations

The Intention-to-Treat (ITT) population will serve as the population for primary efficacy analysis. All randomized subjects will be included in this population. Subjects will be included in the treatment group to which they are randomized. Details on the approach to handling missing data are provided in Section 8.6.1 Statistical Methods for Efficacy Analyses.

8.5.2 Safety Analysis Populations

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

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

Details on the approach to handling missing data for safety analyses are provided in Section 8.6.2 Statistical Methods for Safety Analysis.

8.6 STATISTICAL METHODS

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives and exploratory endpoints will be described in the supplemental statistical analysis plan (sSAP), this includes the ePRO data described in 7.1.2.9 and minimum residual disease (MRD). In addition, a separate SAP will describe the analysis of PK data described in Section 7.1.3.2

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.7 Interim Analysis and Section 8.8, Multiplicity. Nominal p-values will be provided for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity.

Progression-free Survival (PFS)

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

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per IMWG 2011, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event. Subjects without documented PD/death will be censored at the last disease assessment date.

In order to evaluate the robustness of the primary endpoint PFS per IMWG 2011 criteria by CAC blinded central review, we will perform two sensitivity analyses with a different set of censoring rules. The first sensitivity analysis is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of an anticancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 15 below. In case there are imbalances between treatment groups in disease assessment schedules or censoring patterns, additional PFS sensitivity analyses may be performed as supportive analyses, for

example: 1) A PFS analysis using time to scheduled disease assessment visit from randomization as opposed to actual disease assessment time; and, 2) Finkelstein's (1986) likelihood-based score test [51] for interval-censored data, which modifies the Cox proportional hazards model for interval censored data in which the interval will be constructed so that the left endpoint is the date of the last disease assessment without documented PD and the right endpoint is the date of documented PD or death, whichever occurs earlier.

Table 15 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥ 2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Progressed at date of documented PD or death

The proportional hazards assumption of the Cox model will be examined using both graphical and analytical methods for the primary PFS analysis. The log[-log] of the survival function vs. time for PFS will be plotted for each treatment arm. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with immunotherapies, for example, using Restricted Mean Survival Time (RMST) method [52], parametric method etc. Details will be described in supplemental SAP.

The common hazard ratio across strata assumption will be examined using the two-step approach of Mehrotra et al. [53]. In this method, the HR will first be estimated separately for each stratum using an unstratified Cox model and then the stratum specific estimates will be combined into an overall estimate using a weighted approach. Details will be described in the supplemental SAP.

Overall Survival (OS)

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. A stratified Cox proportional hazards model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and

its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. Age and ISS stage will be used as the stratification factors in both the stratified log-rank test and the stratified Cox model. The test of the OS hypothesis will be assessed by evaluation of the treatment difference in OS using the stratified log-rank test.

Exploratory analyses to adjust for the effect of subsequent lines of therapy on OS may be performed based on recognized methods (e.g., the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1989) [54], two-stage model, etc. The choice of the method will be based on an examination of the appropriateness of the data to the assumptions required by the method. Further details of sensitivity analyses will be described in supplemental SAP.

Overall Response Rate (ORR)

The stratified Miettinen and Nurminen's method based on sample size weighting will be used for comparison of the ORR between the treatment groups. A 95% confidence interval for the difference in response rates between the active arms and the standard therapy arm will be provided. Age and ISS stage will be used as the stratification factors in the analysis.

Duration of Response (DOR)

Response duration will be summarized descriptively using Kaplan-Meier medians and quartiles, results permitting. Only the subset of subjects who achieve at least a partial response will be included in this analysis.

Disease Control Rate (DCR)

The stratified Miettinen and Nurminen's method based on sample size weighting will be used for comparison of the DCR between the treatment groups. A 95% confidence interval for the difference in DC rates between the active arms and the standard therapy arm will be provided. Age and ISS stage will be used as the stratification factors in the analysis.

Second Progression-free Survival (PFS2)

The non-parametric Kaplan-Meier method will be used to estimate the PFS2 curves. The treatment difference in PFS2 will be assessed by the stratified log-rank test. A stratified Cox proportional hazards model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. Age and ISS stage will be used as the stratification factors in both the stratified log-rank test and the stratified Cox model.

Further details of PFS2 analyses will be described in supplemental SAP.

Table 16 summarizes the primary analysis approach for primary and secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint.

Table 16 Analysis Strategy for Primary and Secondary Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Endpoint			
PFS per IMWG 2011 by CAC blinded central review	Testing: Stratified Log-rank test. Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (details in Table 15)
Secondary endpoints			
OS	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last date known alive
ORR per IMWG 2011 by CAC blinded central review	Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered non-responders
DOR per IMWG 2011 by CAC blinded central review	Summary statistics using Kaplan-Meier method	All responders in ITT	Censored at last assessment date if responding at the time of analysis
DCR per IMWG 2011 by CAC blinded central review	Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered as disease not under control.
PFS per investigator assessment	Testing: Stratified Log-rank test. Estimation: Stratified Cox model with Efron's tie handling method	ITT	Details to be provided in sSAP
† Statistical models are described in further detail in the text. For stratified analyses, Age and ISS stage will be used as the stratification factors in the stratified log-rank test, stratified Cox model and stratified Miettinen and Nurminen test.			

8.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 17). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95%

confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. No formal treatment comparisons with p-values will be carried out.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital signs, and ECG parameters will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

For this protocol, there are no Tier 1 events. In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, any drug related AE, any serious AE, any Grade 3-5 AE, an AE which is both Grade 3-5 and drug-related, an AE which is both drug-related and serious, dose modification due to AE, and who discontinued due to an AE, and death will be considered Tier 2 endpoints. 95% confidence intervals (Tier 2) will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method (1985) [55], an unconditional, asymptotic method.

To properly account for the potential difference in follow-up time between the study arms, which is expected to be longer in the pembrolizumab containing arms, AE incidence density adjusted for treatment exposure analyses may be performed as appropriate. Based on emerging external data, the supportive analysis strategy for safety parameters may be modified to improve the integrity and efficiency of the design. Should this happen, the change will be documented in supplemental SAP, if not in a protocol amendment, at the earliest time before any unblinding of the data.

Table 17 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any Grade 3-5 AE	X	X
	Any Serious AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	Any Grade3-5 and Drug-Related AE	X	X
	Dose Modification due to AE	X	X
	Discontinuation due to AE	X	X
	Death	X	X
	Specific AEs, SOCs (including ≥4 subjects in one of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs (incidence <4 subjects in all of the treatment groups)		X
	Change from Baseline Results (Labs, ECGs, Vital Signs)		X

† Adverse Experience references refer to both Clinical and Laboratory AEs.
Note: SOC=System Organ Class; X = results will be provided.

Time to Grade 3-5 AE

In addition to tiered approach, exploratory analysis will be performed on time to first Grade 3-5 AE. Time to first Grade 3-5 AE is defined as the time from the first day of study drug to the first event of Grade 3-5 AE. The Kaplan-Meier method will be used to estimate the curve of time to first Grade 3-5 AE. The treatment difference in time to first Grade 3-5 AE will be assessed by the unstratified log-rank test. An unstratified Cox proportional hazards model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the unstratified Cox model with a single treatment covariate will be reported. More details will be described in supplemental SAP.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects randomized, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 INTERIM ANALYSES

8.7.1 Efficacy Interim Analyses

There is one efficacy interim analysis planned in this study. Results will be reviewed by a DMC.

This interim analysis will evaluate PFS for potential early detection of superiority of pembrolizumab in combination with SOC versus SOC as well as evaluate PFS for potential early detection of futility. In this study, the futility bounds are non-binding, which means the bounds are considered guidance rather than strict bounds. The interim analysis will take place when all subjects are enrolled and approximately 115 PFS events are observed in all subjects.

Table 18 summarizes the timing, number of events and decision guidance for the interim analysis and the final analysis. For the superiority hypothesis of PFS, a Hwang-Shih-DeCani alpha-spending function with gamma parameter (-8), is used to construct group sequential boundaries to control the type I error rate. For the futility hypothesis of PFS, a Hwang-Shih-DeCani beta-spending function with gamma parameter (-4), is used to construct group sequential boundaries to control the type II error rate. The Hwang-Shih-DeCani alpha-spending function is considered to be more conservative than the O'Brien-Fleming bound. The actual boundaries and the alpha level will be determined from the actual number of events observed at the time of the interim analysis using the corresponding alpha-spending function.

If superiority is declared for the PFS hypothesis at the interim analysis, the study will continue to follow subjects for OS. If superiority is not declared for the PFS hypothesis at the time of the interim analysis and if the study is not stopped for futility, then a final test of superiority for PFS will be conducted when approximately 227 PFS events have occurred. A final analysis for OS will be performed when approximately 195 OS events have occurred. If superiority for PFS is achieved at the interim analysis for PFS, an analysis of OS without formal statistical testing will be conducted to support the PFS regulatory filing. If this should occur, a nominal adjustment (alpha=0.00001) will be made for the final OS analysis. A supportive PFS analysis will be conducted at the time of the final OS analysis.

Table 18 Decision Guidance at Each Efficacy Analysis

Analysis	Criteria for Conduct of Analysis	Testing	Value	Efficacy	Non-binding Futility
Interim PFS Analysis	All subjects enrolled and ~ 115 PFS events are observed (~ 20 months after trial starts)	PFS: pembrolizumab in combination with SOC vs. SOC	HR at bound p value (1-sided)	~0.54 ≤ 0.0004	~0.99 ≥ 0.48
Final PFS Analysis:	PFS analysis and ~227 PFS events are observed (~30 months after trial starts)	PFS: pembrolizumab in combination with SOC vs. SOC	HR at bound p value (1-sided)	~0.77 ≤ 0.0249	Not applicable
OS analysis	OS Events: - Overall: 195 (~56 months after trial starts)	OS: pembrolizumab in combination with SOC vs. SOC	HR p value (1-sided)	~0.76 ≤ 0.025	Not applicable

8.8 Multiplicity

A step-down approach is used to control the type I error rate for the testing of endpoints. The primary endpoint PFS is tested first, if significant, then the secondary endpoint OS is tested.

8.9 Sample Size and Power Calculations

The study will randomize approximately 640 subjects in a 1:1 ratio among the two treatment arms: pembrolizumab in combination with SOC (combination therapy), and SOC (control).

The interim PFS analysis will be performed after approximately 115 PFS events accrue, this will occur ~20 months after the first subject is enrolled.

If the PFS null hypothesis is neither accepted nor rejected at the time of the interim analysis, then a final PFS analysis will be conducted after approximately 227 PFS events have been observed in the trial.

An OS analysis will be performed after approximately 195 deaths have occurred.

The primary endpoint of the study is PFS. The study has ~90% power to detect a hazard ratio of 0.65 (pembrolizumab in combination with SOC vs. SOC) at alpha = 2.5% (one-sided). The sample size calculation is based on the following assumptions: 1) progression-free survival follows an exponential distribution with a median of 25.5 months in the control arm, 2) an enrollment period of 18 months and at least 12 months follow-up, and 3) a cumulative dropout rate of 2% at the end of the first year and 5% at 4 years.

The secondary endpoint of the study is OS. Assuming that the PFS null hypothesis is rejected, the study has ~70% power to detect a hazard ratio of 0.70 (pembrolizumab in combination with SOC vs. SOC) at alpha = 2.5% (one-sided). These calculations are based on the following assumptions: 1) OS follows an exponential distribution with 70% overall survival at 36 months in the control arm (Arm B), 2) an enrollment period of 18 months and at least 38 months follow-up, and 3) the same dropout rate as above.

The assumed median PFS and OS in the control arm (Arm B) are observed from standard of care in patients with previously untreated multiple myeloma who are ineligible for SCT [39].

The sample size and power calculations were performed using EAST 6 software.

8.10 Subgroup Analyses and Effect of Baseline Factors

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

- Stratification factors
  - Age (<75 years vs. ≥ 75 years).
  - International Staging System disease stage (I or II vs. III)
- Sex (female vs. male)
- ECOG status (0 vs. 1)
- Geographic region
- Race (White vs. Non White)

8.11 COMPLIANCE (MEDICATION ADHERENCE)

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

8.12 EXTENT OF EXPOSURE

The extent of exposure will be summarized as duration of treatment in cycles.

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 19.

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 19 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
MK-3475 100 mg/4 mL	Solution for Injection	Provided centrally by the Sponsor.
Lenalidomide	Hard capsule	Provided centrally by the Sponsor except in specific countries where commercial product may be sourced locally.
Dexamethasone	Tablet	Provided centrally by the Sponsor except in specific countries where commercial product may be sourced locally.

All other supplies not indicated in Table 19 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

9.2 Packaging and Labeling Information

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

Subjects will receive open label vials as required to support treatment. No kitting is required.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

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

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

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

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

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

10.6 Data Management

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

his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided 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 7.1.3.3 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may

be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in Future Biomedical Research protocol and consent. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

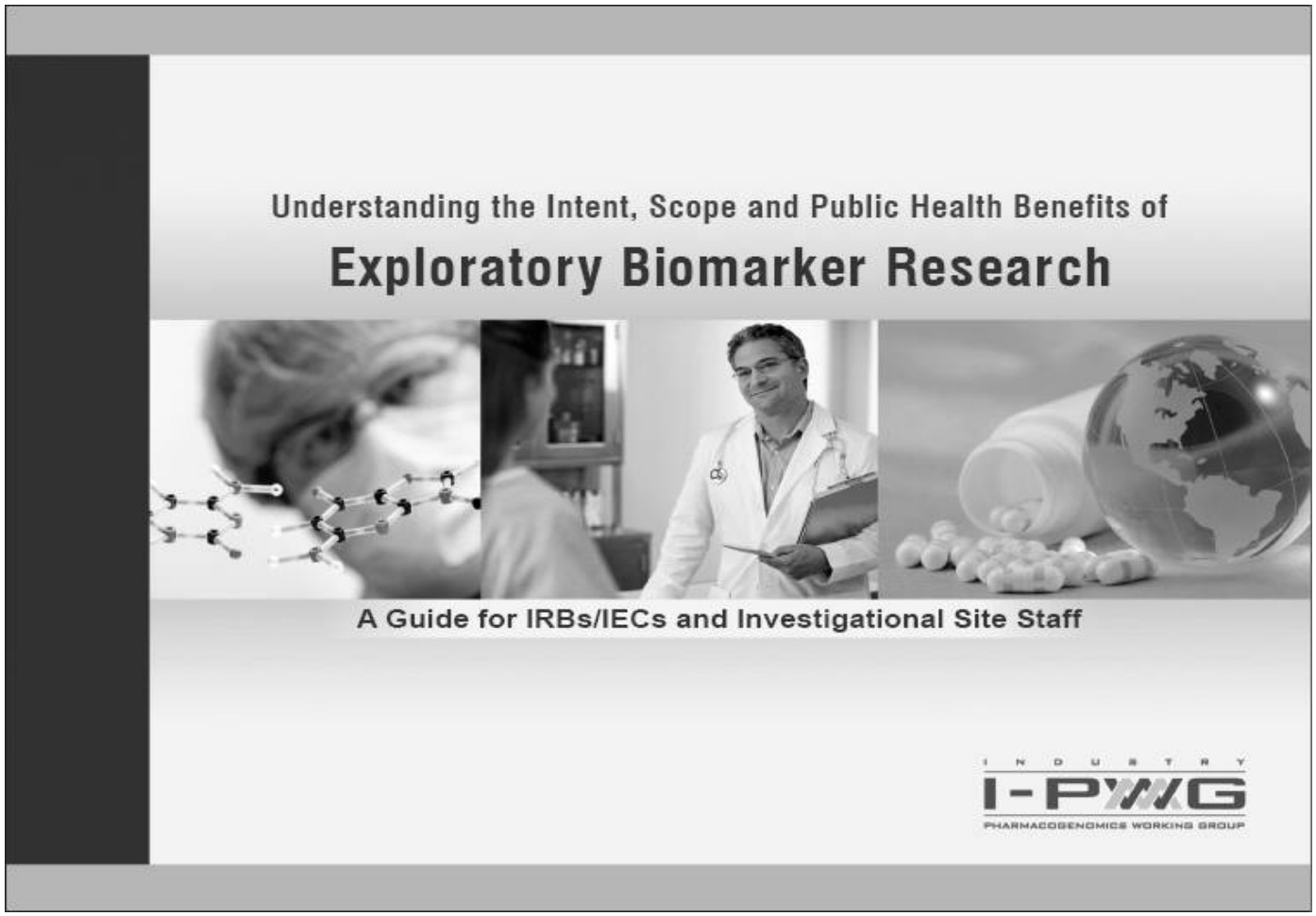
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

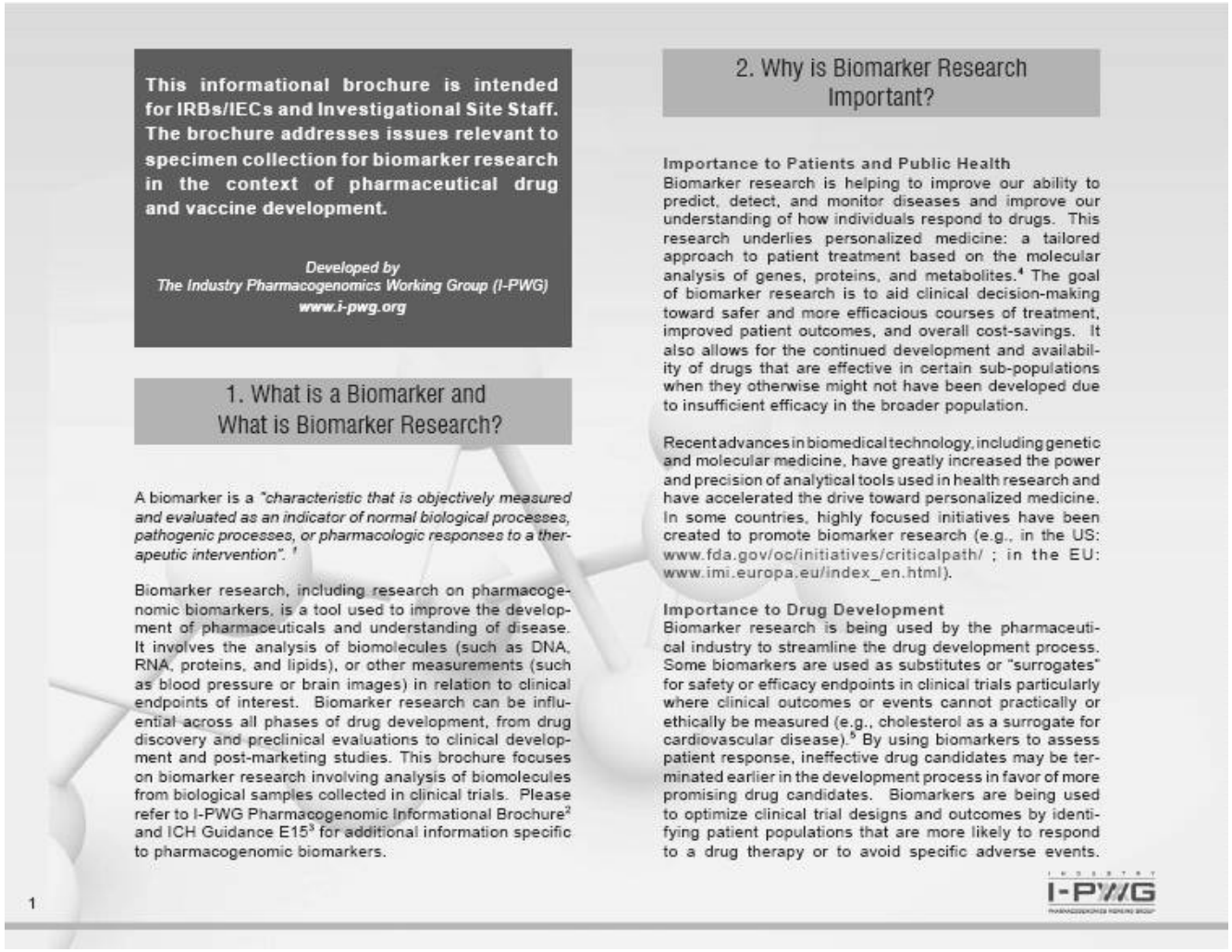
13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker

2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

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





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

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

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

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

Importance to Drug Development

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

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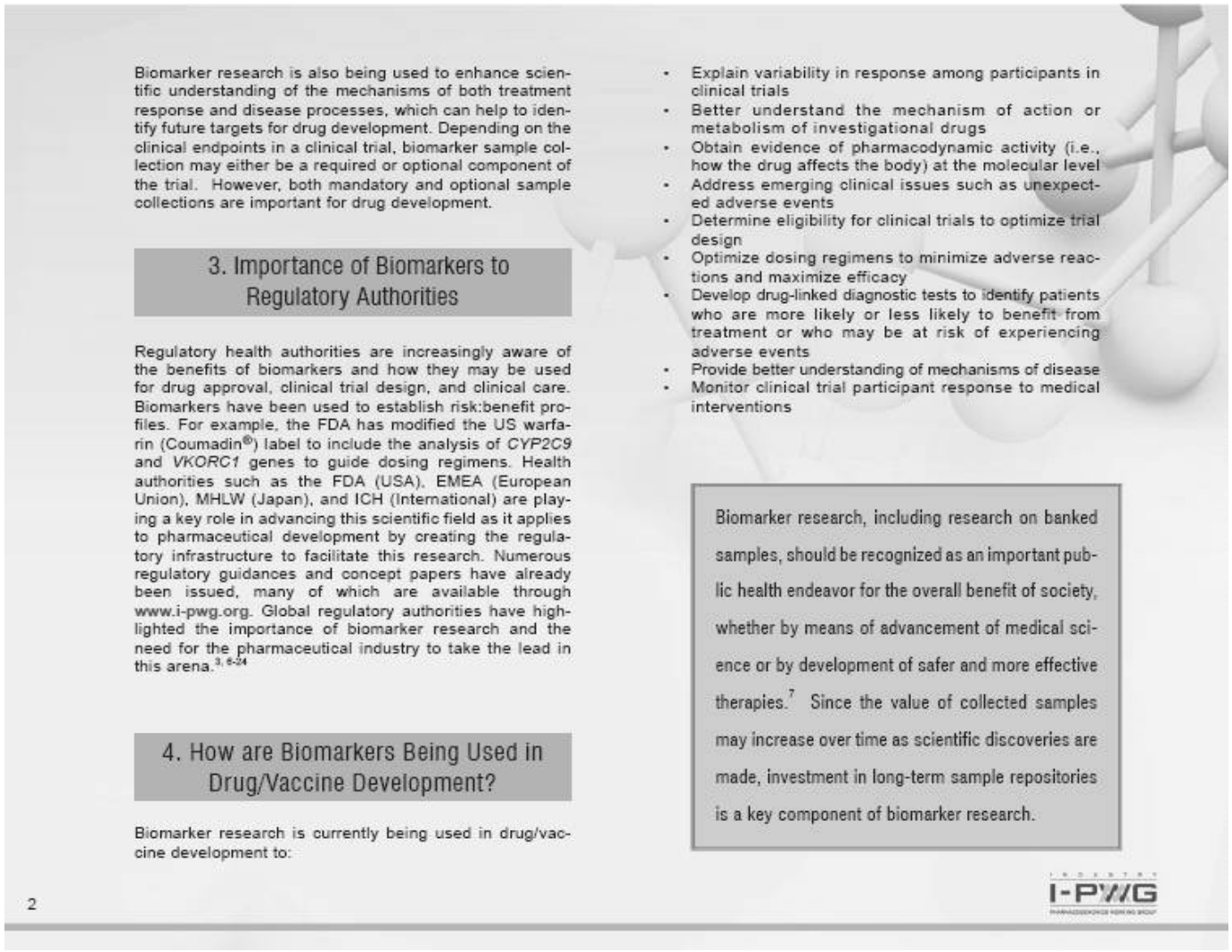
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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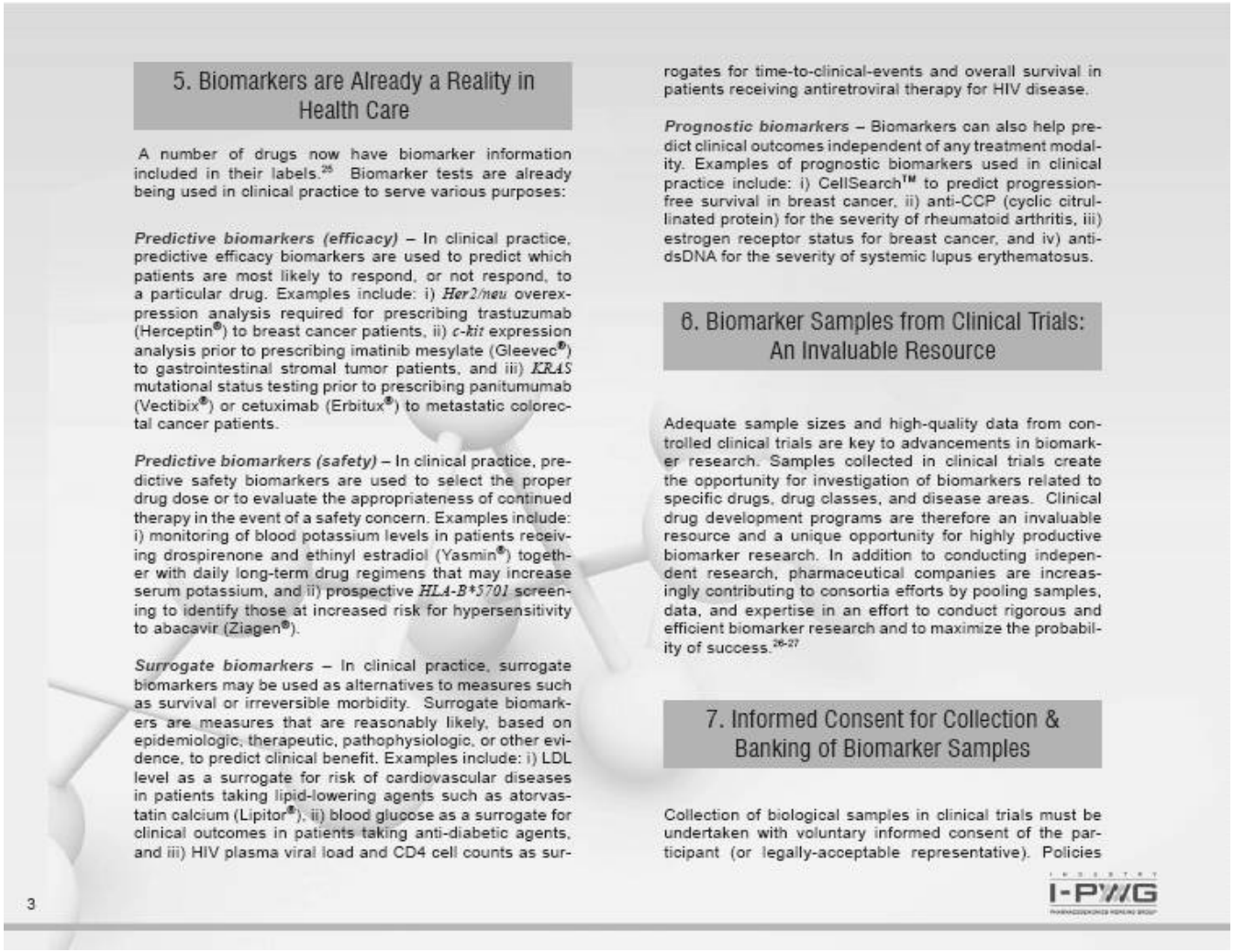

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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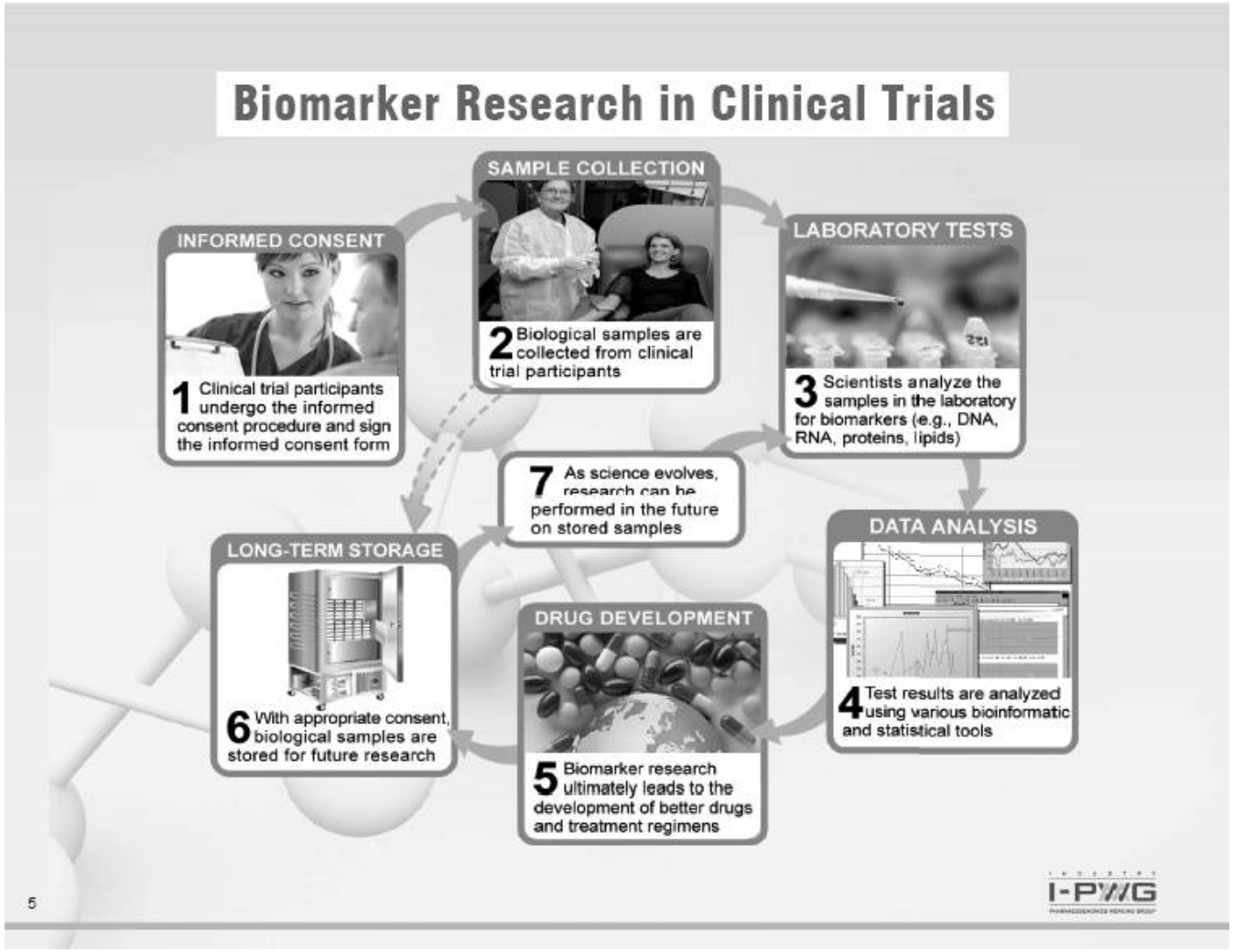
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the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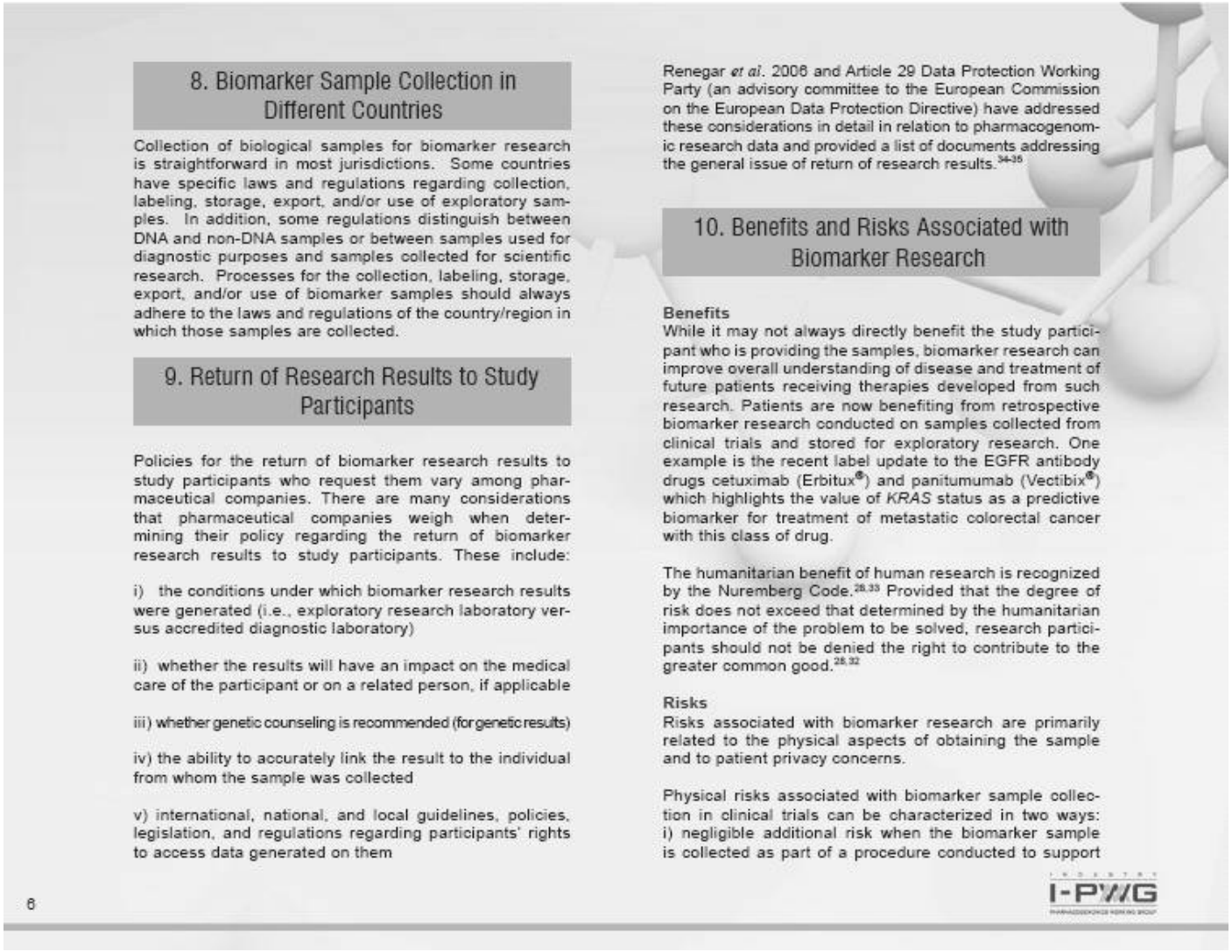

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[35-37]

12.Where to Get More Information?

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

13. What is I-PWG?

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

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

14. Contributing authors

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I-PWG


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12.4 List of Abbreviations

Abbreviation/Term	Definition
ADA	anti-drug antibodies
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	Absolute Neutrophil Count
APC	antigen presenting cells
aPTT	activated partial thromboplastin time
ASaT	All Subjects as Treated
AST	aspartate aminotransferase
auto-SCT	autologous-stem cell transplant
ß-HCG	Beta Human Chorionic Gonadotropin
BCG	Bacillus-Calmette Guerin (vaccine)
CIITA	Class II Transactivator
C1D1	Cycle 1 day 1
CAC	Clinical Adjudication Committee
CBC	complete blood count
CDC	complement dependent cytotoxicity
CFR	Code of Federal Regulations
CHL	classical Hodgkin's lymphoma
CI	confidence interval
CL	clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CML	chronic myeloid leukemia
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	Cytotoxic T-Lymphocyte
CTLA-4	cytotoxic t-lymphocyte-associated antigen-4
C_{trough}	minimum concentration
DCR	disease control rate
DKA	diabetic ketoacidosis
DNA	deoxyribonucleic acid
DOR	duration of response
DVT	deep vein thrombosis
EBMT	European Group for Blood and Marrow Transplantation
ECG	electrocardiogram
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act

Abbreviation/Term	Definition
FDAMA	Food and Drug Administration Modernization Act
FLC	free light chain
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCSF	granulocyte colony stimulating factor
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage - Colony Stimulating Factor
GVHD	Graft Versus Host Disease
HCB	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	human immunodeficiency virus
HL	Hodgkin's lymphoma
hr	hour
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
INR	international normalized ratio
ir	Immune-related
IRB	Institutional Review Board
ISS	International Staging System
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	immunoreceptor tyrosine-based switch motif
IV	Intravenous
IVRS	integrated voice response system
IWG	International Working Group
IWRS	integrated web response system
LDH	lactate dehydrogenase
mAb	Monoclonal antibody
MACOP-B	methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin
MAD	minimally acceptable dose
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Melanoma
MGUS	Monoclonal Gammopathy of Undetermined Significance
MLBCL	mediastinal large b-cell lymphoma
MM	multiple myeloma
m-protein	monoclonal protein
MPT	melphalan, prednisone, thalidomide
MRD	minimal residual disease
MRI	magnetic resonance imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MTD	maximum tolerated dose
N/A	not applicable
NCI	National Cancer Institute
NDMM	newly diagnosed multiple myeloma
NHL	non-hodgkin's lymphoma
NK	natural killer
NSAID	non-steroidal anti-inflammatory drug

Abbreviation/Term	Definition
ORR	overall response rate
OS	overall survival
OTC	over-the-counter
PD	Progressive Disease
PD-1	programmed cell death 1 receptor
PD-L1	programmed cell death-ligand 1 receptor
PD-L2	programmed cell death-ligand 2 receptor
PE	pulmonary embolism
PET	positron emission tomography
PFS	progression free survival
PFS2	second progression-free survival
PI	Principal Investigator
PIN	personal identification number
PK	pharmacokinetic
PO	oral administration
PPP	pregnancy prevention plan
PR	partial response
PRO	patient reported outcome
PT	prothrombin time
QLQ-C30	Quality Of Life Questionnaire-Core 30
QLQ-MY20	Quality Of Life Questionnaire-Multiple Myeloma
Rd	lenalidomide with low-dose dexamethasone
REMS	Risk Evaluation and Mitigation Strategy
RMST	Restricted Mean Survival Time
RNA	ribonucleic acid
Q2W	every 2 weeks
Q3W	every 3 weeks
SAE	serious adverse events
SAP	statistical analysis plan
sCR	stringent complete response
SCT	stem cell transplant
SD	Stable Disease
SFU	Survival Follow-Up
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SJS	Stevens-Johnson syndrome (TEN)
SMM	Smoldering multiple myeloma
SOC	standard of care
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
T3	total thyroidothyronine
T4	free tyroxine
TEN	toxic epidermal necrolysis
TIL	Tumor Infiltrating Lymphocytes
TLS	Tumor Lysis Syndrome
TSH	thyroid stimulating hormone
TTF	time-to-treatment failure
TTP	time-to-disease progression
ULN	upper limit of normal
US	United States
V	Volume

Abbreviation/Term	Definition
VGPR	very good partial response
VMP	bortezomib, melphalan, prednisone
VTE	Venous Thromboembolic Events
WBC	white blood cell
WES	Whole Exome Sequencing
Y/N	Yes/No

12.5 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 utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

12.6 International Myeloma Working Group Criteria for Response Assessment in Multiple Myeloma (IMWG Criteria). Rajkumar et al. Blood, 2011; 117(18).

Table 1. IMWG uniform response criteria by response subcategory for multiple myeloma[7]

CR*	Stringent complete response (sCR)†	VGPR*	PR	SD	PD†
Negative immunofixation of serum and urine, *and*	CR as defined, *plus*	Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or*	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours	Not meeting criteria for CR, VGPR, PR, or PD	Increase of 25% from lowest response value in any of the following:
Disappearance of any soft tissue plasmacytomas, *and*	Normal FLC ratio *and*	≥ 90% reduction in serum M-component plus urine M-component < 100 mg/24 h	If the serum and urine M-protein are not measurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria		Serum M-component (absolute increase must be ≥ 0.5 g/dL), *and/or*
< 5% PCs in bone marrow	Absence of clonal PCs by immunohistochemistry or 2- to 4-color flow cytometry		If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in bone marrow PCs is required in place of M-protein, provided baseline percentage was ≥ 30%		Urine M-component (absolute increase must be ≥ 200 mg/24 h), *and/or*
			In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required		Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL)
					Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥ 10%)
					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) that can be attributed solely to the PC proliferative disorder

Adapted from Durie et al[7] and Kyle et al[13] with permission. All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

PCs indicate plasma cells.

*Clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

†Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels; "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.

Table 2. Additional response criteria and updates

MR in patients with relapsed refractory myeloma adopted from the EBMT criteria[8]	Immunophenotypic CR	Molecular CR
≥ 25% but ≤ 49% reduction of serum M protein *and* reduction in 24-hour urine M-protein by 50%-89%	Stringent CR *plus*	CR plus negative ASO-PCR, sensitivity 10^{-5}
In addition to the above criteria, if present at baseline, 25%-49% reduction in the size of soft tissue plasmacytomas is also required	Absence of phenotypically aberrant PCs (clonal) in BM with a minimum of 1 million total BM cells analyzed by multiparametric flow cytometry (with > 4 colors)	
No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)		

EBMT indicates European Group for Blood and Marrow Transplantation; PCs, plasma cells; and ASO-PCR, allele-specific oligonucleotide polymerase chain reaction.

Table 6 International Myeloma Working Group uniform response criteria: disease progression and relapse

Relapse subcategory	*Relapse criteria*
Progressive disease[a] To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive Disease: requires any one or more of the following: Increase of ⩾25% from baseline in Serum M-component and/or (the absolute increase must be ⩾0.5 g/dl)[b] Urine M-component and/or (the absolute increase must be ⩾200 mg/24 h Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dl. Bone marrow plasma cell percentage: the absolute % must be ⩾10%[c] Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[b] It is not used in calculation of time to progression or progression-free survival but is listed here as as something that can be reported optionally or for use in clinical practice 1 Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.5 mg/dl) [2.65 mmol/l] 4. Decrease in hemoglobin of ⩾2 g/dl [1.25 mmol/l] (see Table 3 for further details) 5. Rise in serum creatinine by 2 mg/dl or more [177 μmol/l or more]
Relapse from CR[a](To be used only if the end point studied is DFS)[d]	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ⩾5% plasma cells in the bone marrow[c] Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see below)

Abbreviations: CR, complete response; DFS, disease-free survival.
[a]All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.
[b]For progressive disease, serum M-component increases of ⩾1 gm/dl are sufficient to define relapse if starting M-component is ⩾5 g/dl.
[c]Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.
[d]For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

12.7 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.

12.8 International Staging System (ISS)

Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, Boccadoro M, Child JA, Avet-Loiseau H, Kyle RA, Lahuerta JJ, Ludwig H, Morgan G, Powles R, Shimizu K, Shustik C, Sonneveld P, Tosi P, Turesson I, Westin J. International staging system for multiple myeloma . J Clin Oncol. 2005 May 20;23(15):3412-20.

International Staging System;

Stage	Criteria	Median Survival (months)
I	Serum β_2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL	62
II	Not stage I or III*	44
IMIII	Serum β_2-microglobulin ≥ 5.5 mg/L	29

* There are two categories for stage II: serum β_2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum β_2-microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level.

12.9 Lenalidomide Education and Counseling Guidance Document for Female Subjects

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months)
- ☐ NOT FCBP

12.9.1 Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. Females of childbearing potential must agree not to become pregnant while taking lenalidomide.
   - ☐ That the required pregnancy tests performed are negative.
   - ☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving lenalidomide, while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide).

     One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

     - Examples of highly effective methods:
       - Intrauterine device (IUD)

- Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g., desogestrel])
- Tubal ligation
- Partner's vasectomy

– Examples of additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of lenalidomide and at the last dose of lenalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

– Two pregnancy tests will be performed prior to receiving lenalidomide, one within 10 to 14 days, and a second within 24 hours of the start of lenalidomide.

– Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking lenalidomide if menstrual cycles are regular.

– Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking lenalidomide if menstrual cycles are irregular.

– If the subject missed a period or has unusual menstrual bleeding.

– When the subject is discontinued from the study and at Day 28 after the last dose of lenalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of lenalidomide.

☐ The subject confirmed that she will stop taking lenalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will never share lenalidomide with anyone else.

☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

- ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
- ☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

12.9.2 Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject has not and will never share lenalidomide with anyone else.
   - ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
   - ☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.
2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving lenalidomide, while receiving lenalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: ____/____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

Lenalidomide Education and Counseling Guidance Document for Male Subjects

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

3. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [e.g., calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject confirmed that he has not impregnated his female partner while in the study.
   - ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking lenalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The subject has not and will never share lenalidomide with anyone else.
   - ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking lenalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
   - ☐ The subject confirmed that he will return unused lenalidomide capsules to the study doctor.
4. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: ____/____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

12.10 Lenalidomide Information Sheet

For subjects enrolled in clinical research studies

Please read this Lenalidomide Information Sheet before you start taking lenalidomide and each time you get a new supply. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

1. **Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects.

   If you are a female who is able to become pregnant:

   - **Do not take lenalidomide if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting lenalidomide
     - while taking lenalidomide
     - during breaks (dose interruptions) of lenalidomide
     - for at least 28 days after the last dose of lenalidomide
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days prior to the first dose of lenalidomide
     - 24 hours prior to the first dose of lenalidomide
     - weekly for the first 28 days
     - if you have regular menstrual periods: every 28 days after the first month
     - if you have irregular menstrual periods: every 14 days after the first month
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking lenalidomide if you become pregnant while taking lenalidomide**
     - If you suspect you are pregnant at any time during the study, you must stop lenalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation.

- **Do not breastfeed while taking lenalidomide and for at least 28 days after the last dose of lenalidomide**
- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not able to become pregnant:

In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

A small amount of lenalidomide is found in human semen. The risk to an unborn baby in females whose male partner is receiving lenalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking lenalidomide
  - During breaks (dose interruptions) of lenalidomide
  - For at least 28 days after the last dose of lenalidomide
- **Male subjects should not donate sperm or semen** while taking lenalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of lenalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

2. **All subjects:**

- **Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
- **Do not donate blood** while you take lenalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of lenalidomide.
- **Do not break, chew, or open lenalidomide capsules at any point.**
- You will get no more than a 28-day supply of lenalidomide at one time.
- Return unused lenalidomide capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

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	