

<b>Official Protocol Title:</b>	A Phase I Multi-Cohort Trial of Pembrolizumab (MK-3475) in Combination with Backbone Treatments for Subjects with Multiple Myeloma
<b>NCT number:</b>	NCT02036502
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**TITLE:**

A Phase I Multi-Cohort Trial of Pembrolizumab (MK-3475) in Combination with Backbone Treatments for Subjects with Multiple Myeloma

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## TABLE OF CONTENTS

<b>DOCUMENT HISTORY .....</b>	<b>12</b>
<b>SUMMARY OF CHANGES.....</b>	<b>15</b>
<b>1.0 TRIAL SUMMARY.....</b>	<b>17</b>
<b>2.0 TRIAL DESIGN.....</b>	<b>18</b>
<b>2.1 Trial Design .....</b>	<b>18</b>
<b>2.2 Trial Diagram.....</b>	<b>21</b>
<b>3.0 OBJECTIVE(S) &amp; HYPOTHESIS(ES).....</b>	<b>22</b>
<b>3.1 Primary Objective(s) &amp; Hypothesis(es) .....</b>	<b>22</b>
<b>3.2 Secondary Objective(s) &amp; Hypothesis(es).....</b>	<b>22</b>
<b>3.3 Exploratory Objectives.....</b>	<b>22</b>
<b>4.0 BACKGROUND &amp; RATIONALE.....</b>	<b>23</b>
<b>4.1 Background .....</b>	<b>23</b>
4.1.1 Pharmaceutical and Therapeutic Background .....	23
4.1.2 Pre-clinical and Clinical Trials .....	24
4.1.3 Ongoing Clinical Trials.....	24
4.1.4 Rationale for IMiDs as a Combination Agent: .....	29
4.1.5 Rationale for Lenalidomide and Low-dose Dexamethasone in Multiple Myeloma .....	29
4.1.6 Rationale for Proteasome Inhibitors as a Combination Agent.....	31
4.1.7 Rationale for Carfilzomib and Low-dose Dexamethasone in Multiple Myeloma .....	31
<b>4.2 Rationale.....</b>	<b>32</b>
4.2.1 Rationale for the Trial and Selected Subject Population .....	32
4.2.1.1 Rationale for Evaluating anti-PD-1 Therapy in Multiple Myeloma .....	32
4.2.2 Rationale for Dose Selection/Regimen.....	33
4.2.3 Rationale for Endpoints .....	34
4.2.3.1 Safety Endpoints .....	34
4.2.3.2 Efficacy Endpoints.....	34
4.2.3.3 Biomarker Research.....	35
4.2.3.4 Future Biomedical Research.....	36

<b>5.0</b>	<b>METHODOLOGY</b>	<b>37</b>
<b>5.1</b>	<b>Entry Criteria</b>	<b>37</b>
5.1.1	Diagnosis/Condition for Entry into the Trial	37
5.1.2	Subject Inclusion Criteria	37
5.1.3	Subject Exclusion Criteria	42
<b>5.2</b>	<b>Trial Treatment(s)</b>	<b>46</b>
5.2.1	Dose Selection/Modification	49
5.2.1.1	Dose Selection	49
5.2.1.2	Dose Modification (Escalation/Titration/Other)	49
5.2.1.2.1	Guidelines for Dose Modification	49
5.2.1.2.2	Dose Modification Guidelines for Pembrolizumab	50
5.2.1.2.3	Dose Modification Guidelines for Lenalidomide (after DLT Evaluation Period)	56
5.2.1.2.3.1	Lenalidomide Dose Adjustments for Hematologic Toxicities during Multiple Myeloma Treatment	56
5.2.1.2.3.2	Other Grade 3 and 4 Lenalidomide Toxicities in MM	57
5.2.1.2.3.3	Recommended Lenalidomide Dose Adjustments for Subjects with Impaired Renal Function	58
5.2.1.2.4	Dose Modification Guidelines for Dexamethasone	58
5.2.1.2.4.1	Dose Modification Guidelines for Dexamethasone for Elderly Subjects > 75 Years of Age	59
5.2.1.2.4.2	Supportive Care Guidelines Specific to Dexamethasone	60
5.2.1.2.5	Cohort 2: Dose Modification Guidelines for Carfilzomib	60
5.2.2	Timing of Dose Administration	62
5.2.3	Definition of Disease Progression	62
5.2.4	Guidelines for Study Drug Administration	62
5.2.5	Rules for Dose Determination and Confirmation	63
5.2.5.1	Dose Determination	63
5.2.5.2	Dose Confirmation	64
5.2.5.3	Expansion Cohort	66
5.2.6	Definition of Dose Limiting Toxicities	67
5.2.7	Replacement of Subjects in DLT Evaluation Period	68
5.2.8	Trial Blinding/Masking	69

<b>5.3</b>	<b>Randomization or Treatment Allocation.....</b>	<b>69</b>
<b>5.4</b>	<b>Stratification.....</b>	<b>69</b>
<b>5.5</b>	<b>Concomitant Medications/Vaccinations (Allowed &amp; Prohibited).....</b>	<b>69</b>
5.5.1	Acceptable Concomitant Medications .....	69
5.5.1.1	Concomitant Medications for Cohort 2 Carfilzomib.....	70
5.5.2	Prohibited Concomitant Medications.....	70
<b>5.6</b>	<b>Rescue Medications &amp; Supportive Care.....</b>	<b>71</b>
5.6.1	Supportive Care Guidelines .....	71
5.6.2	Supportive Care Guidelines Specific to Lenalidomide.....	72
5.6.2.1	Hematologic Toxicity .....	72
5.6.2.2	Venous Thromboembolism.....	72
5.6.2.3	Lactose Intolerance .....	73
5.6.2.4	Allergic Reactions.....	73
5.6.2.5	Tumor Lysis Syndrome.....	73
5.6.2.6	Hepatotoxicity.....	73
5.6.2.7	Second Primary Malignancies .....	74
5.6.3	Supportive Care Guidelines Specific for Carfilzomib [Cohort 2] .....	74
5.6.3.1	“First-Dose-Like Effect” .....	74
5.6.3.2	Tumor Lysis Syndrome.....	74
5.6.3.3	Renal Function.....	75
5.6.3.4	Hydration .....	75
5.6.4	Other Adverse Events on Combination Therapy .....	75
<b>5.7</b>	<b>Diet/Activity/Other Considerations.....</b>	<b>76</b>
5.7.1	Diet.....	76
5.7.2	Blood Donation.....	76
5.7.3	Contraception.....	76
5.7.3.1	Dose Determination, Dose Confirmation, and Expansion Cohort 1.....	76
5.7.3.2	Expansion Cohort 2.....	78
5.7.4	Use in Pregnancy .....	81
5.7.5	Use in Nursing Women.....	81
<b>5.8</b>	<b>Subject Withdrawal/Discontinuation Criteria.....</b>	<b>81</b>
<b>5.9</b>	<b>Subject Replacement Strategy.....</b>	<b>82</b>

<b>5.10</b>	<b>Beginning and End of the Trial .....</b>	<b>83</b>
<b>5.11</b>	<b>Clinical Criteria for Early Trial Termination .....</b>	<b>83</b>
<b>6.0</b>	<b>TRIAL FLOW CHART .....</b>	<b>84</b>
<b>6.1</b>	<b>Trial Flow Chart Dose Determination, Dose Confirmation, and Cohort 1 (rrMM Subjects Allocated to Pembrolizumab Q2W, Lenalidomide and Low-dose Dexamethasone).....</b>	<b>84</b>
6.1.1	Trial Treatment Administration Schedule Dose Determination, Dose Confirmation, and Cohort 1 .....	87
6.1.2	Pembrolizumab PK and Anti-pembrolizumab Antibodies Procedures during Dose Determination, Dose Confirmation and Cohort 1.....	88
<b>6.2</b>	<b>Trial Flow Chart Cohort 2 – (2L rMM Subjects Allocated to Triplet with Pembrolizumab Q3W, Carfilzomib and Low-dose Dexamethasone) .....</b>	<b>90</b>
6.2.1	Trial Treatment Administration Schedule Cohort 2 .....	93
6.2.2	Pembrolizumab PK and Anti-pembrolizumab Antibodies Procedures during Cohort 2 .....	94
<b>7.0</b>	<b>TRIAL PROCEDURES .....</b>	<b>95</b>
<b>7.1</b>	<b>Trial Procedures .....</b>	<b>95</b>
7.1.1	Administrative Procedures.....	95
7.1.1.1	Informed Consent.....	95
7.1.1.1.1	General Informed Consent.....	95
7.1.1.1.2	Consent and Collection of Specimens for Future Biomedical Research.....	96
7.1.1.2	Inclusion/Exclusion Criteria .....	96
7.1.1.3	Subject Identification Card .....	96
7.1.1.4	Medical History .....	96
7.1.1.5	Prior and Concomitant Medications Review .....	96
7.1.1.5.1	Prior Medications.....	96
7.1.1.5.2	Concomitant Medications .....	96
7.1.1.6	Disease Details and Treatments.....	97
7.1.1.6.1	Disease Details.....	97
7.1.1.6.2	Prior Treatment Details.....	97
7.1.1.6.3	Subsequent Antineoplastic Therapy Status.....	97
7.1.1.7	Assignment of Screening Number .....	97

7.1.1.8	Assignment of Randomization Number.....	97
7.1.1.9	Trial Compliance (Medication/Diet/Activity/Other) .....	97
7.1.2	Clinical Procedures/Assessments.....	98
7.1.2.1	Adverse Event (AE) Monitoring.....	98
7.1.2.2	Physical Exam.....	99
7.1.2.2.1	Full Physical Exam .....	99
7.1.2.2.2	Directed Physical Exam.....	99
7.1.2.3	Vital Signs.....	99
7.1.2.4	Electrocardiogram (ECG) .....	99
7.1.2.5	Assessment of LVEF using ECHO.....	99
7.1.2.6	Eastern Cooperative Oncology Group (ECOG) Performance Scale .....	100
7.1.2.7	Assessment of Disease and Tumor Imaging.....	100
7.1.2.7.1	Criteria for Assessment of Disease .....	100
7.1.2.7.1.1	Myeloma Disease Measurements.....	100
7.1.2.7.2	Imaging for Subjects with Myeloma Bone Disease.....	100
7.1.2.7.3	Disease Assessment of Immunotherapeutic Agents .....	101
7.1.2.7.4	Timing of Disease Assessments .....	101
7.1.2.7.5	Initial Disease Assessment.....	101
7.1.2.7.6	Disease Assessment During Trial.....	102
7.1.2.7.7	Confirmation Assessments .....	102
7.1.2.7.8	Biopsy Collection and Correlative Studies Blood Collection .....	103
7.1.3	Laboratory Procedures/Assessments .....	105
7.1.3.1	Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis) .....	105
7.1.3.2	Pharmacokinetic/Pharmacodynamic Evaluations .....	107
7.1.3.2.1	Blood Collection for Pembrolizumab .....	107
7.1.3.2.2	Blood Collection for Anti-Pembrolizumab Antibodies .....	107
7.1.3.3	Future Biomedical Research.....	107
7.1.4	Other Procedures.....	108
7.1.4.1	Withdrawal/Discontinuation.....	108
7.1.4.1.1	Withdrawal From Future Biomedical Research .....	108
7.1.4.2	Blinding/Unblinding .....	108
7.1.4.3	Calibration of Equipment.....	108

7.1.5	Visit Requirements.....	109
7.1.5.1	Screening Period .....	109
7.1.5.2	Treatment Period.....	109
7.1.5.3	Post-Treatment Visits.....	110
7.1.5.3.1	Safety Follow-Up Visit.....	110
7.1.5.4	Efficacy Follow-Up Visits.....	110
7.1.5.4.1	Survival Follow-Up .....	111
7.1.5.4.2	Follow-up After Allogeneic Stem Cell Transplantation.....	111
7.1.5.5	Survival Status .....	111
<b>7.2</b>	<b>Assessing and Recording Adverse Events .....</b>	<b>112</b>
7.2.1	Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor.....	113
7.2.2	Reporting of Pregnancy and Lactation to the Sponsor .....	113
7.2.3	Immediate Reporting of Adverse Events to the Sponsor.....	114
7.2.3.1	Serious Adverse Events .....	114
7.2.3.2	Events of Clinical Interest.....	115
7.2.3.2.1	Adverse Events Follow-up post-Allogeneic Stem Cell Transplantation .....	116
7.2.3.3	Protocol-Specific Exceptions to Serious Adverse Event Reporting.....	116
7.2.4	Evaluating Adverse Events .....	117
7.2.5	Sponsor Responsibility for Reporting Adverse Events .....	120
<b>8.0</b>	<b>STATISTICAL ANALYSIS PLAN .....</b>	<b>120</b>
<b>8.1</b>	<b>Statistical Analysis Plan Summary .....</b>	<b>120</b>
8.1.1	Efficacy Analyses .....	121
8.1.2	Safety Analyses.....	121
8.1.3	Power and Sample Size.....	121
<b>8.2</b>	<b>Statistical Analysis Plan .....</b>	<b>122</b>
8.2.1	Responsibility for Analyses .....	122
8.2.2	Hypotheses/Estimation .....	122
8.2.3	Analysis Endpoints .....	122
8.2.3.1	Efficacy Endpoints.....	122
8.2.3.2	Safety Endpoints .....	123



8.2.4	Analysis Populations.....	123
8.2.4.1	Efficacy Analysis Populations .....	123
8.2.4.2	Safety Analysis Populations .....	123
8.2.5	Statistical Methods.....	124
8.2.5.1	Statistical Methods for Efficacy Analyses .....	124
8.2.5.2	Statistical Methods for Safety Analyses .....	125
8.2.5.3	Summaries of Baseline Characteristics, Demographics, and Other Analyses.....	126
8.2.6	Multiplicity .....	126
8.2.7	Sample Size and Power Calculations.....	126
8.2.8	Subgroup Analyses and Effect of Baseline Factors .....	127
8.2.9	Interim Analysis.....	127
8.2.10	Compliance (Medication Adherence).....	127
8.2.11	Extent of Exposure.....	128
<b>9.0</b>	<b>LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES .....</b>	<b>128</b>
<b>9.1</b>	<b>Investigational Product .....</b>	<b>128</b>
<b>9.2</b>	<b>Packaging and Labeling Information .....</b>	<b>129</b>
<b>9.3</b>	<b>Clinical Supplies Disclosure.....</b>	<b>129</b>
<b>9.4</b>	<b>Storage and Handling Requirements.....</b>	<b>129</b>
<b>9.5</b>	<b>Returns and Reconciliation.....</b>	<b>129</b>
<b>10.0</b>	<b>ADMINISTRATIVE AND REGULATORY DETAILS.....</b>	<b>129</b>
<b>10.1</b>	<b>Confidentiality.....</b>	<b>129</b>
10.1.1	Confidentiality of Data .....	129
10.1.2	Confidentiality of Subject Records .....	130
10.1.3	Confidentiality of Investigator Information.....	130
10.1.4	Confidentiality of IRB/IEC Information.....	130
<b>10.2</b>	<b>Compliance with Financial Disclosure Requirements.....</b>	<b>131</b>
<b>10.3</b>	<b>Compliance with Law, Audit and Debarment .....</b>	<b>131</b>
<b>10.4</b>	<b>Compliance with Trial Registration and Results Posting Requirements .....</b>	<b>133</b>
<b>10.5</b>	<b>Quality Management System.....</b>	<b>133</b>
<b>10.6</b>	<b>Data Management.....</b>	<b>134</b>

<b>10.7</b>	<b>Publications .....</b>	<b>134</b>
<b>11.0</b>	<b>LIST OF REFERENCES.....</b>	<b>136</b>
<b>12.0</b>	<b>APPENDICES.....</b>	<b>143</b>
<b>12.1</b>	<b>Merck Code of Conduct for Clinical Trials.....</b>	<b>143</b>
<b>12.2</b>	<b>Collection and Management of Specimens for Future Biomedical Research.....</b>	<b>145</b>
<b>12.3</b>	<b>Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff .....</b>	<b>151</b>
<b>12.4</b>	<b>Multiple Myeloma Diagnostic Criteria .....</b>	<b>162</b>
<b>12.5</b>	<b>ECOG Performance Status.....</b>	<b>163</b>
<b>12.6</b>	<b>Common Terminology Criteria for Adverse Events V4.0 (CTCAE).....</b>	<b>164</b>
<b>12.7</b>	<b>MM Disease Response Criteria .....</b>	<b>165</b>
<b>12.8</b>	<b>List of Abbreviations .....</b>	<b>167</b>
<b>13.0</b>	<b>SIGNATURES.....</b>	<b>170</b>
<b>13.1</b>	<b>Sponsor's Representative .....</b>	<b>170</b>
<b>13.2</b>	<b>Investigator.....</b>	<b>170</b>

## LIST OF TABLES

Table 1	Adequate Organ Function Laboratory Values.....	39
Table 2	Adequate Organ Function Laboratory Values.....	41
Table 3	Combination Trial Dosing Cohorts.....	47
Table 4	Dose Modification Guidelines for Hematological Drug-Related Adverse Events.....	50
Table 5	Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab.....	52
Table 6	Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines.....	55
Table 7	Platelet Counts: Thrombocytopenia in MM.....	57
Table 8	Absolute Neutrophil Counts (ANC): Neutropenia in MM.....	57
Table 9	Lenalidomide Dose Reductions for Subjects with Other Grade 3 and 4 Toxicities.....	58
Table 10	Dexamethasone Dose Reductions for Subjects with Grade 3 and 4 Toxicities.....	59
Table 11	Dexamethasone Dose Reductions for Elderly Subjects > 75 Years of Age with Grade 3 and 4 Toxicities.....	59
Table 12	Supportive Care Guidelines Specific to Dexamethasone.....	60
Table 13	Dose Modifications for Toxicity during Carfilzomib Treatment.....	61
Table 14	Dose Level Reductions for Carfilzomib.....	61
Table 15	Dose Confirmation Rules.....	65
Table 16	Operating Characteristics of Design Based on the Toxicity Probability Interval (TPI) Approach.....	66
Table 17	Recommendations for the Management of Cytopenias.....	72
Table 18	Recommendations for the Management of Venous Thromboembolism.....	73
Table 19	Bone Marrow and Whole Blood Sample Collection (Dose Determination, Dose Confirmation, Cohort 1).....	103
Table 20	Bone Marrow and Whole Blood Sample Collection (Cohort 2).....	104
Table 21	Laboratory Tests.....	106
Table 22	Evaluating Adverse Events.....	118
Table 23	Summary of Analysis Strategy for Key Efficacy Endpoints.....	121
Table 24	Censoring Rules for the Analysis of DOR.....	124
Table 25	Analysis Strategy for Efficacy Variables.....	125
Table 26	Two-sided 95% Confidence Intervals of ORR with 30 Subjects.....	127
Table 27	Product Descriptions.....	128

**LIST OF FIGURES**

Figure 1 Trial Design..... 21  
Figure 2 Kaplan-Meier Graph of Overall Survival (ITT Population) ..... 25  
Figure 3 Kaplan-Meier Graph of Time to Progression Per IMWG 2011 Based  
on Confirmed Investigator Review (Primary Censoring Rule) (ITT  
Population) ..... 26  
Figure 4 Kaplan-Meier Graph of Overall Survival (ITT Population) ..... 27  
Figure 5 Kaplan-Meier Graph of Time to Progression Per IMWG 2011 Based  
on Confirmed Investigator Review (Primary Censoring Rule) (ITT  
Population) ..... 28  
Figure 6 Kaplan-Meier Estimates of Overall Survival (ASaT Population)..... 29  
Figure 7 Dose Determination Schema ..... 64

## DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-3475-023-07	10-MAR-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-3475-023-06	05-APR-2018	<p>The treatment of subjects in Cohort 1 was discontinued based on a clinical hold placed on the study by the US FDA on 03-JUL-2017. 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 Cohort 1 of KN023 is closed effective immediately. All subjects stopped study treatment, completed the Discontinuation Visit, and moved into the long term safety and survival follow-up (every 12 weeks) per protocol.</p> <p>The enrollment of subjects into Cohort 2 was discontinued based on a partial clinical hold placed on the study by the US FDA on 15-SEP-2017. Enrollment was stopped and all subjects who derived clinical benefit from therapy are allowed to continue if reconsented. Those subjects who were already enrolled and deriving clinical benefit from therapy were allowed to continue if reconsented, and could continue on study until protocol-specific end of treatment, and then progress into long term safety and follow-up. Those subjects who were not deriving clinical benefit, stopped study treatment, completed the Discontinuation Visit, and moved into the long term safety and follow-up per protocol.</p>

Document	Date of Issue	Overall Rationale
MK-3475-023-05	28-NOV-2016	Removed biomarker bone marrow biopsy requirement for subjects enrolled to Dose Determination, Dose Confirmation and Cohort 1. Clarified that subjects in the US and Canada are to provide new bone marrow aspirate for biomarker analysis. Updated inclusion criteria to reflect this change and clarified bone marrow materials needed for disease assessment. PD-L1 testing using bone marrow core biopsies has been shown to be of limited utility due to its de-calcification impact on the PD-L1 antigen. Therefore, testing requirements were removed to reduce risk associated with this invasive procedure.
MK-3475-023-04	23-MAY-2016	Clarification to insure patients who may have a history of pneumonitis are excluded from the study (when applicable).
MK-3475-023-03	07-APR-2016	Removed Doublet arm of pembrolizumab in combination with lenalidomide in rMM, replaced with new triplet arm of pembrolizumab in combination with carfilzomib and dexamethasone in rMM (Cohort 2). This change was derived from need to explore other standard of care combinations in Multiple Myeloma to assess preliminary safety and efficacy. The title of the protocol was changed to include the new combination, and new rationale for the treatment and inclusion/exclusion criteria for Cohort 2 were added. Supportive care guidance for carfilzomib was added, and the study flowchart was updated to accommodate new treatment schedule and PK/antibodies testing for Cohort 2.

<b>Document</b>	<b>Date of Issue</b>	<b>Overall Rationale</b>
MK-3475-023-02	10-JUL-2014	<p>The 5 mg/kg and 10 mg/kg doses were removed from dose escalation. The “Dose Escalation” was changed to “Dose Determination”.</p> <p>Dose Confirmation was revised and 2 Expansion Arms (Doublet-MK+Len and Triplet-MK+Len+Dex) using a fixed dose MK-3475 were added. The statistical Section was also revised accordingly.</p>
MK-3475-023-01	08-JAN-2014	<p>First and second line patients were removed from the subject population. These changes were made based upon FDA comments</p>
MK-3475-023-00	02-OCT-2013	<p>Original protocol</p>

**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 early 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, which occurred in November of 2018. To date no subject remaining in follow-up has had a SCT.
5.10	Beginning and End of Trial	Updated criteria for end of the trial to include Sponsor decision to close.	To broaden the criteria for ending the trial.
7.1.5.3.1 7.1.5.4.1 7.1.5.4.2 7.2.3.2.1	Safety Follow-up Survival Follow-up Follow-up After Allogenic 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 Sponsor decision to close the trial.	To broaden the criteria for ending safety follow-up.



**ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:**

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
4.1.1.1	Pembrolizumab	Updated 2 reference citation DocIDs.	To allow proper linking at finalization.
4.2.3.5 7.1.1.1.2 12.2	Future Biomedical Research  Consent and Collection of Specimens for Future Biomedical Research  Collection and Management of Specimens for Future Biomedical Research	Removed references to Future Biomedical Research “sub-trial.”	Template update
7.1.5.4	Efficacy Follow-up Visits	Updated the heading name.	Template update for clarification.
7.1.5.4.2	Survival Follow-up	Added new template language on timing of survival follow-up	Template update for clarification.

## 1.0 TRIAL SUMMARY

Abbreviated Title	A Phase I Multi-Cohort Trial of Pembrolizumab (MK-3475) in Combination with Backbone Treatments for Subjects with Multiple Myeloma.
Trial Phase	I
Clinical Indication	Multiple Myeloma (MM)
Trial Type	Interventional
Type of control	No treatment control
Route of administration	IV, Oral
Trial Blinding	Unblinded Open-label
Treatment Groups	<b>Dose Determination:</b> pembrolizumab 2 mg/kg every 2 weeks (Days 1 and 15) in combination with 10 mg or 25 mg lenalidomide (Days 1-21) and dexamethasone 40 mg weekly of a 28-day cycle; <b>Dose Confirmation:</b> Pembrolizumab 200 mg every 2 weeks (Days 1 and 15) in combination with 10 mg or 25 mg lenalidomide (Days 1-21) and dexamethasone 40 mg weekly of a 28 day cycle. <b>Expansion Cohort:</b> Cohort 1 (rrMM): Pembrolizumab 200 mg every 2 weeks (Days 1 and 15) in combination with 25 mg lenalidomide (Days 1-21) and dexamethasone 40 mg weekly of a 28 day cycle. Cohort 2 (rMM): Pembrolizumab 200 mg every 3 weeks (Q3W) in combination with 56 mg/m <sup>2</sup> carfilzomib (Days 1, 2, 8, 9, 15, 16) and dexamethasone 20 mg (Days 1, 2, 8, 9, 15, 16, 22, 23) of a 28 day cycle.
Number of trial subjects	Approximately 115 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 66 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, eligible subjects will receive assigned treatment appropriate for the trial stage in which they are enrolled as described above. The assigned treatment will continue until documented confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or for administrative reasons. Subjects with confirmed disease progression according to response criteria whom the investigator considers are deriving clinical benefit may be considered to continue on treatment after consultation with the Sponsor. After the end of treatment, each subject will be followed for 30 days for the occurrence of adverse events and spontaneously reported pregnancy as described under Section 7.2 of the protocol (serious adverse events will be collected for 90 days following the cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier). Subjects who discontinue for reasons other than progressive disease will move into the Follow-Up Phase to monitor disease status and should be assessed every 4 weeks ( $\pm$ 14 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. Every

	<p>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 &amp; Disease Assessment Termination Form. Information regarding post-study anti-myeloma treatment will be collected if new treatment is initiated. After documented disease progression or the start of new antineoplastic therapy, each subject will be followed up by telephone every 12 weeks (<math>\pm</math> 7 days) 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.</p> <p>On 03-JUL-2017, the US FDA placed KN183 (pembrolizumab/pomalidomide/dexamethasone for Refractory or Relapsed and Refractory Multiple Myeloma), KN185 (pembrolizumab/lenalidomide/dexamethasone for treatment naïve multiple myeloma), and cohort 1 of KN023 on clinical hold based on safety data from KN183 and KN185 presented to the Data Monitoring Committee (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, KN185, and Cohort 1 of KN023 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 (every 12 weeks) per protocol.</p> <p>On 15-SEP-2017, the US FDA placed Cohort 2 of KN023 (pembrolizumab/carfilzomib/dexamethasone), on partial clinical hold. Enrollment was stopped and all subjects who derived clinical benefit from therapy are allowed to continue if reconsented, at least verbally. Enrollment will not be reopened by the sponsor after a full safety and efficacy evaluation did not demonstrate any significant difference from historical controls. Those subjects who are already enrolled and deriving clinical benefit from therapy were allowed to continue if reconsented, at least verbally, and will continue on study until protocol-specific end of treatment, and then progress into long term safety and follow-up. Those subjects who are not deriving clinical benefit, must stop study treatment, complete the Discontinuation Visit and move into the long term safety and follow-up per protocol.</p>
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A list of abbreviations used in this document can be found in Section 12.8.

## **2.0 TRIAL DESIGN**

### **2.1 Trial Design**

This is an open-label, Phase I, multicenter, multi-cohort trial of pembrolizumab (also referred to as MK-3475) in combination with lenalidomide and low-dose dexamethasone in subjects with refractory or relapsed and refractory Multiple Myeloma (rrMM), and in combination with carfilzomib and low-dose dexamethasone in subjects with relapsed or refractory Multiple Myeloma (rMM).

The trial will use a modified 3+3 design for Dose Determination followed by a toxicity probability interval (TPI) design for Dose Confirmation in subjects with rrMM. After the

MTD/MAD is defined the Expansion Cohort stage will be started. It is estimated that approximately up to 115 subjects (approximately 6-12 in Dose Determination, an additional 7-13 in Dose Confirmation and 60-90 in Expansion Cohorts) will be enrolled to evaluate safety, tolerability and efficacy in this trial. Dosing arms are described in [Table 3](#), Section 5.2.

During the Dose Determination stage, cohorts of approximately 3-6 subjects will be enrolled at 2 mg/kg of pembrolizumab in combination with 25 mg or 10 mg of lenalidomide and low-dose dexamethasone in rrMM subjects. In this stage, if Dose Level 1 is not tolerated, de-escalation to Dose Level -1A is permitted after the dose limiting toxicity (DLT) evaluation period of Dose Level 1 pembrolizumab 2 mg/kg in combination with lenalidomide 25 mg (Days 1-21) and weekly dexamethasone 40 mg. If Dose Level 1 is not tolerable, then the next cohort of subjects will be assigned to Dose Level -1A.

At a safety interim analysis in June 2015 a preliminary MTD/MAD was identified as pembrolizumab 2 mg/kg in combination with lenalidomide 10 mg (Days 1-21) and weekly dexamethasone 40 mg, additional subjects were enrolled in the Dose Confirmation stage at a fixed dose of 200 mg pembrolizumab in combination with lenalidomide and low-dose dexamethasone to determine the final MTD/MAD dose based on the TPI algorithm. The Dose Confirmation stage allowed for re-escalation of lenalidomide providing no additional toxicity was observed following the TPI algorithm. The final MTD/MAD was determined to be pembrolizumab 200 mg in combination with lenalidomide 25 mg (Days 1-21) and weekly dexamethasone 40 mg.

Once the final MTD/MAD was determined the Expansion Cohort stage started and encompasses:

- Cohort 1: Subjects with refractory or relapsed and refractory multiple myeloma (rrMM) who have undergone at least 2 lines of prior treatment, are refractory to their last line of treatment. Subjects must have been previously exposed to an immunomodulatory drug (IMiDs) such as lenalidomide, pomalidomide or thalidomide and a proteasome inhibitor such as bortezomib, ixazomib or carfilzomib and should be considered to be refractory or relapsed and refractory to an IMiD or a proteasome inhibitor or both. Subjects will receive pembrolizumab in combination with lenalidomide and dexamethasone.
- Cohort 2: Subjects with relapsed or refractory multiple myeloma (rMM) and have received 1 to 3 lines of prior treatment. Subjects will receive pembrolizumab in combination with carfilzomib and dexamethasone.

The Expansion Cohorts (Section 5.2.5.3) will further evaluate safety and characterize preliminary efficacy for pembrolizumab in combination with SOC for each cohort. A safety run in for Cohort 2 will be conducted after 6 subjects are enrolled and one cycle completed to assess overall safety before expanding this cohort to its specified sample size.

Study treatment with pembrolizumab in combination with SOC will continue until documented disease progression, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. However, in the setting where a subject assessment shows confirmed PD per IMWG 2006 criteria, by investigator assessment, study drug may be continued upon Sponsor consultation, if the investigator considers the subject is deriving clinical benefit.

After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events [SAEs] will be collected for 90 days following the cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier). Subjects who undergo allogeneic stem cell transplant (allo-SCT) within 24 months after their last dose of pembrolizumab will be followed for events of clinical interest (ECI) for up to 18 months post-transplant, or until the end of the trial. Subjects who discontinue for reasons other than progressive disease will move into the Follow-Up Phase to monitor disease status and should be assessed every 4 weeks ( $\pm$  14 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. 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. Information regarding post-study anti-myeloma treatment will be collected if new treatment is initiated. After documented disease progression or the start of new antineoplastic therapy, each subject will be followed by telephone every 12 weeks ( $\pm$  7 days) for at least 12 months following their discontinuation visit for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

The primary objectives of the trial are to establish an MTD or MAD in the Dose Determination and Dose Confirmation stages. The Expansion Cohorts will determine safety and tolerability of pembrolizumab in combination with SOC for each cohort. Secondary objectives include further evaluation of various efficacy parameters as objective response rate (ORR) and disease control rate (DCR) of pembrolizumab in combination with SOC. Exploratory objectives will include the evaluation of other efficacy parameters as duration of response (DOR), progression-free survival (PFS), time to progression (TTP) and overall survival (OS); pharmacokinetic (PK) properties of pembrolizumab in combination with lenalidomide and low-dose dexamethasone or carfilzomib and low-dose dexamethasone; the analysis of PD-L1 expression and corresponding efficacy in each subject population; and the relationship of candidate efficacy/resistance biomarkers and antitumor activity with SOC for each cohort activity.

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

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, KN185, and Cohort 1 of KN023 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 (every 12 weeks) per protocol.

On 15-SEP-2017, the US FDA placed Cohort 2 of KN023, on partial clinical hold. Enrollment was stopped and all subjects who derived clinical benefit from therapy are allowed to continue if reconsented, at least verbally. Enrollment will not be reopened by the sponsor after a full safety and efficacy evaluation did not demonstrate any significant difference from historical controls. Those subjects who are already enrolled and deriving clinical benefit from therapy were allowed to continue if reconsented, at least verbally, and will continue on study until protocol-specific end of treatment, and then progress into long term safety and follow-up. Those subjects who are not deriving clinical benefit, must stop study treatment, complete the Discontinuation Visit and move into the long term safety and 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.

No formal efficacy interim analyses are planned for this trial.

## 2.2 Trial Diagram

The trial design is depicted in [Figure 1](#).

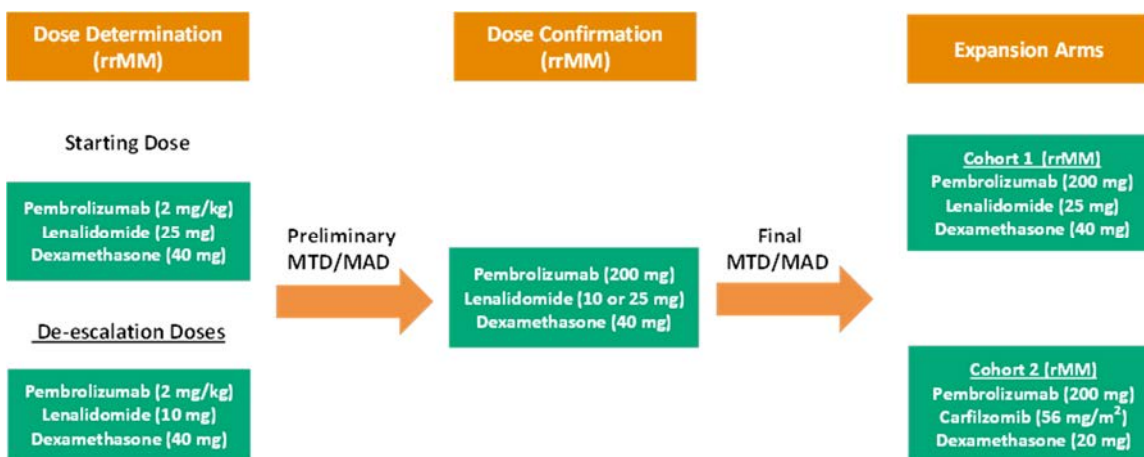


Figure 1 Trial Design

### 3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

#### 3.1 Primary Objective(s) & Hypothesis(es)

##### For Dose Determination and Dose Confirmation Stages:

- (1) **Objective:** To establish a maximum tolerated dose (MTD) or a maximum administered dose (MAD) of pembrolizumab when given in combination with lenalidomide and low-dose dexamethasone to subjects with refractory or relapsed and refractory multiple myeloma.

##### For Expansion Cohort Stage (Cohort 1 rrMM, Cohort 2 rMM):

- (2) **Objective:** To determine the safety and tolerability of pembrolizumab in combination with SOC in subjects with multiple myeloma.

#### 3.2 Secondary Objective(s) & Hypothesis(es)

The following secondary objective will be evaluated separately for Expansion Cohort 1 (rrMM) and for Expansion Cohort 2 (rMM):

**Objective:** To evaluate objective response rate (ORR) and disease control rate (DCR) of pembrolizumab in combination with SOC in subjects with MM by investigator assessment.

NOTE: The investigator assessment will be based on IMWG criteria (IMWG 2006) [1].

#### 3.3 Exploratory Objectives

The following objectives will be evaluated separately for Expansion Cohort 1 (rrMM) and for Expansion Cohort 2 (rMM):

- (1) **Objective:** To evaluate duration of response (DOR), progression-free survival (PFS) and time to progression (TTP) of pembrolizumab in combination with SOC in subjects with MM by investigator assessment.

NOTE: The investigator assessment will be based on IMWG criteria (IMWG 2006) [1].

- (2) **Objective:** To evaluate Overall Survival (OS) of pembrolizumab in combination with SOC in subjects with MM.

The following exploratory objectives will be evaluated for all subjects enrolled in the study:

- (3) **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.

(4) **Objective:** To explore the PK profile of pembrolizumab in combination with standard of care in each study cohort.

## **4.0 BACKGROUND & RATIONALE**

### **4.1 Background**

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. Refer to the Investigators Brochure (IB) for detailed background information on pembrolizumab.

#### **4.1.1 Pharmaceutical and Therapeutic Background**

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [2]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [3] [4] [5] [6] [7]. In particular, the presence of CD8<sup>+</sup> T-cells and the ratio of CD8<sup>+</sup> effector T-cells / FoxP3<sup>+</sup> 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) [8] [9]. The structure of murine PD-1 has been resolved [10]. 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 CD3 $\zeta$ , PKC $\theta$  and ZAP70 which are involved in the CD3 T-cell signaling cascade [8] [11] [12] [13]. 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 [14] [15]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4<sup>+</sup> and CD8<sup>+</sup> T-cells, B-cells, T regs, and Natural Killer cells [16] [17]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and



dendritic cells [18]. 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 [14] [19] [20] [21]. 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 [14]. 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) [22]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

#### **4.1.2 Pre-clinical and Clinical Trials**

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8<sup>+</sup> 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, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8<sup>+</sup> T-cell infiltration into the tumor and the presence of IFN- $\gamma$ , granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [23] [24] [25] [26] [27] [28]. 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 (see the Investigator's Brochure [IB]).

#### **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, triple negative breast cancer, gastric cancer, and hematologic malignancies. For trial details please refer to the Investigator's Brochure.

The external DMC met on 26-MAY-2017 and 09-JUN-2017 for a review of safety and survival data for all patients enrolled in KN183 and KN185 (cutoff date of 22-MAR-2017). Based on an imbalance of deaths in both studies, the eDMC recommended that Merck suspend enrollment and provide an updated complete safety and efficacy analysis. On 03-

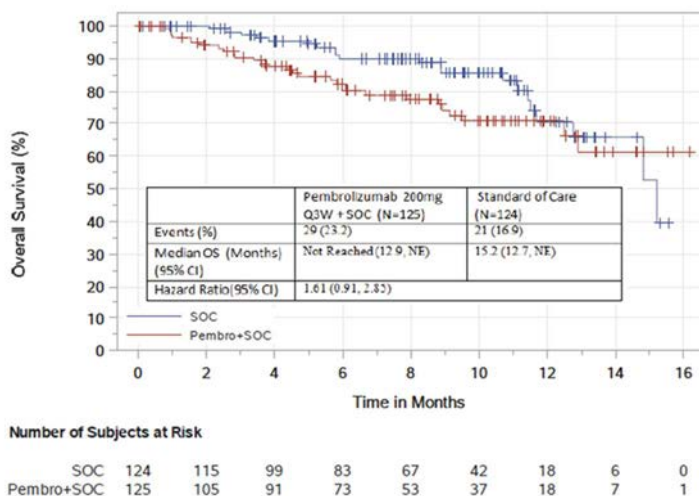
JUL-2017, after review of the data provided to the external DMC the US FDA placed studies KN183, KN185 and a cohort of KN023 on full clinical hold.

A full safety and efficacy analysis based on a 02-JUL-2017 data cutoff date was conducted for studies KEYNOTE-183 and KEYNOTE-185. A summary of these results is presented below.

KEYNOTE-183

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

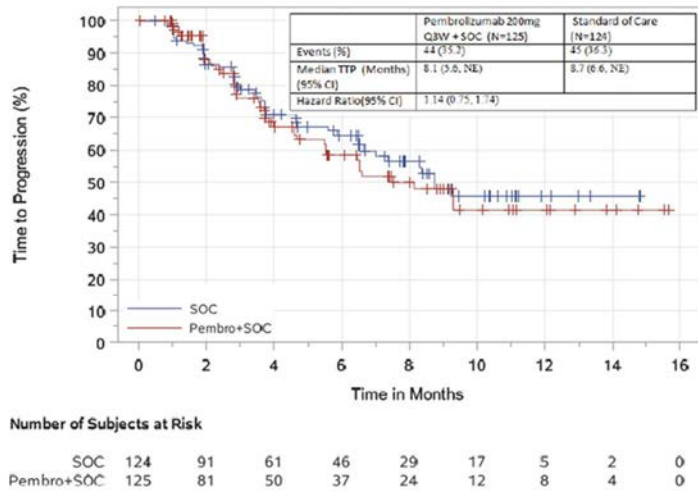
Using a data cutoff date of 02-JUN-2017, a complete evaluation of safety and efficacy was performed (Figure 2). There were 249 randomized patients included in the analysis. The median follow-up was 8.1 months. For overall survival, there were 29 deaths on the pembrolizumab-containing investigational arm and 21 deaths on the control arm. The hazard ratio of the pembrolizumab-containing investigational arm compared to the control arm was 1.61 (95% CI: 0.91, 2.85), increasing the relative risk of death by more than 50% compared to the control arm.



Standard of Care(SOC) is pomalidomide and low dose dexamethasone.  
 Database Cutoff Date: 02JUN2017.

Figure 2 Kaplan-Meier Graph of Overall Survival (ITT Population)

The objective response rate was 34% in the investigational arm compared to 40% in the control arm. In an exploratory time to progression analysis, a hazard ratio of 1.14 (95% CI: 0.75, 1.74) was observed (Figure 3).



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

Database Cutoff Date: 02JUN2017.

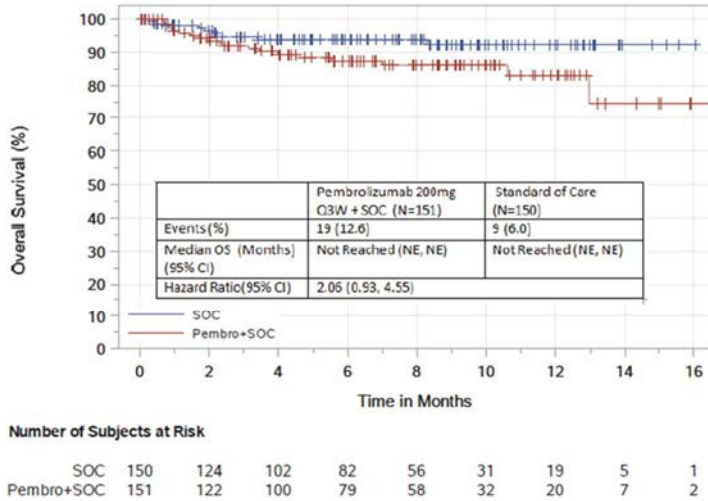
Figure 3 Kaplan-Meier Graph of Time to Progression Per IMWG 2011 Based on Confirmed Investigator Review (Primary Censoring Rule) (ITT Population)

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

### KEYNOTE-185

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

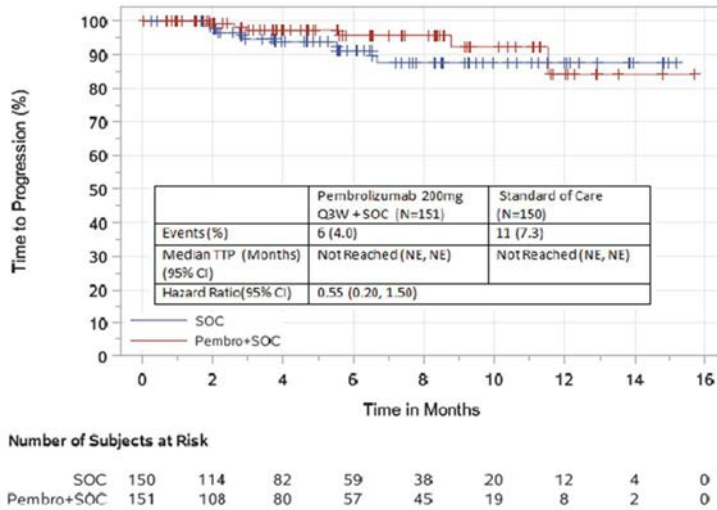
The data cutoff date of 02-JUN-2017 was used for these analyses (Figure 4). There were 301 randomized patients included in the analysis. The median follow-up was 6.6 months. For overall survival, there were 19 deaths on the pembrolizumab-containing investigational arm, and 9 deaths on the control arm. The hazard ratio of the pembrolizumab-containing investigational arm compared to the control arm was 2.06 (95% CI: 0.93, 4.55), more than doubling the relative risk of death compared to the control arm.



Standard of Care(SOC) is lenalidomide and low dose dexamethasone.  
 Database Cutoff Date: 02JUN2017.

Figure 4 Kaplan-Meier Graph of Overall Survival (ITT Population)

Additional efficacy analyses based on a 02-JUN-2017 data cutoff date demonstrated an objective response rate of 64% in the investigational arm compared to 62% in the control arm (Figure 5). In an exploratory time to progression analysis, a hazard ratio of 0.55 (95% CI: 0.20, 1.50) was observed.



Standard of Care(SOC) is lenalidomide and low dose dexamethasone.  
 Database Cutoff Date: 02JUN2017.

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

In conclusion, the benefit-risk profile for KEYNOTE 183 and 185 is unfavorable for:

- (1) the combination of pembrolizumab, pomalidomide and dexamethasone in relapsed refractory multiple myeloma, and
- (2) the combination of pembrolizumab, lenalidomide and dexamethasone in newly diagnosed treatment naive multiple myeloma.

KEYNOTE-023

Cohort 1: Based on a data cutoff of 10-MAR-2017, a total of 62 subjects were enrolled in this cohort, including dose determination, dose confirmation, and dose expansion. The follow-up was 18.9 months. The median overall survival (Figure 6) was not reached and there was a total of 16 deaths. Additional efficacy analysis in response evaluable population demonstrated an objective response rate of 44.0%.

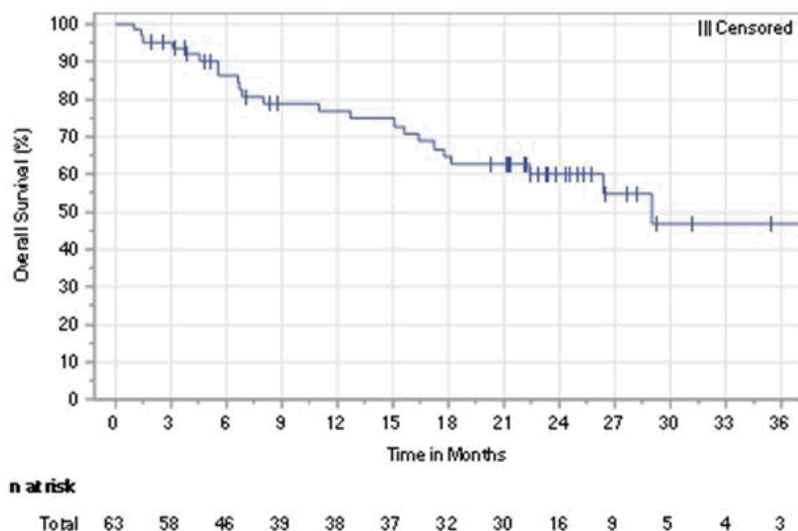


Figure 6 Kaplan-Meier Estimates of Overall Survival (ASaT Population)

Cohort 2: As of 2017-NOV-03 total of 10 subjects were enrolled in this cohort and no data has yet been published.

#### 4.1.4 Rationale for IMiDs as a Combination Agent:

IMiDs (thalidomide, lenalidomide, and pomalidomide) are a class of immunomodulatory agents, which are a mainstay in myeloma therapy and in the case of lenalidomide is currently under investigation in diffuse large B cell lymphoma, and could be rationally combined with anti-PD-1 therapy. IMiDs acquire their designation as “Immunomodulators” designed as therapeutic immune stimulators derived from the parent compound thalidomide. Lenalidomide, and now pomalidomide, are approved therapies for multiple myeloma. The immunostimulatory properties of IMiDs 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 result in clonal T-cell expansion and increased natural killer (NK) cell activity [29]. There is also evidence of increased IL-12 production in the setting of T-cell co-stimulation, which activates APCs [30].

#### 4.1.5 Rationale for Lenalidomide and Low-dose Dexamethasone in Multiple Myeloma

Lenalidomide is a good choice among the three available IMiDs due to its better safety profile compared to thalidomide and broader use in earlier lines of therapy compared to the newer pomalidomide in Multiple Myeloma. Clinical studies have shown that lenalidomide has single agent activity in relapsed or refractory MM, and synergistic effects when combined with dexamethasone [31] [32] [33] [34]. Two recent pivotal Phase III studies (MM-009 and MM-010) have robustly demonstrated the clinical benefit of lenalidomide plus high-dose dexamethasone over dexamethasone alone in subjects with relapsed or refractory MM [34] [35]. A combined analysis of the data from the two pivotal Phase III studies

demonstrated that lenalidomide plus high-dose dexamethasone achieved an OR in of approximately 60%, including 15% of patients achieving CR, a median OS of 38 months, and a median TTP of 13.4 months [36]. According to the National Cancer Institute Common Toxicity Criteria, the most common Grade 3–4 adverse events associated with the use of lenalidomide plus dexamethasone in clinical trials that included subjects with MM have been cytopenias, fatigue, muscle cramps, rash, infection, insomnia, and venous thromboembolism (VTE) [31] [32] [33] [34] [35] [37] [38]. Such events are largely manageable through subject evaluation and monitoring, dose adjustment, or prophylactic intervention.

Lenalidomide in combination with dexamethasone is indicated for the treatment of subjects with multiple myeloma across all lines of therapy. The initial Phase III registration studies of lenalidomide were done in combination with high-dose dexamethasone versus high-dose dexamethasone alone. The dose of dexamethasone (which was defined as high-dose dexamethasone) used for the initial approval by the FDA, in combination with lenalidomide in relapse or refractory multiple myeloma, was 40 mg QD PO on Days 1-4, 9-12, and 17-20 in the first 4 cycles, and on Days 1-4 in Cycle 5 and above in each 28-day treatment cycle.

However, two recent Phase III randomized studies in newly diagnosed multiple myeloma show that combining lenalidomide with low-dose dexamethasone as compared to combining with high-dose dexamethasone was safer and more effective. Low-dose dexamethasone was defined as 40 mg p.o. on Days 1, 8 15 and 22. These results led to the FDA final approval of lenalidomide in combination with low-dose dexamethasone in multiple myeloma.

The first randomized study (known as E4A03) sponsored by the US National Cancer Institute (NCI), and conducted by a network of researchers led by the Eastern Cooperative Oncology Group (ECOG), compared combination treatment of lenalidomide and either high- or low-dose dexamethasone in 445 patients with newly diagnosed multiple myeloma [39]. The dose of dexamethasone considered low-dose in this trial was 40 mg on Days 1, 8, 15, and 22 (i.e., once weekly) in each 28-day cycle. The study found that patients in the study who received low-dose dexamethasone and lenalidomide had a one-year survival of 96 percent compared to 87 percent for patients treated with the standard or high-dose of dexamethasone and lenalidomide. In addition, there were fewer side effects associated with the low-dose dexamethasone and lenalidomide.

In the second randomized Phase III study (FIRST trial), 1,623 patients were enrolled to compare the efficacy and safety of lenalidomide and low-dose dexamethasone (Rd) given continuously or for 18 cycles versus melphalan, prednisone, and thalidomide (MPT) in newly diagnosed multiple myeloma patients who were not candidates for stem cell transplant [40]. In the first arm of the study, lenalidomide plus low-dose dexamethasone were given continuously until progressive disease (Rd Continuous). In the second arm, lenalidomide plus low-dose dexamethasone were given for up to eighteen 28-day cycles. In the third arm, melphalan, prednisone, and thalidomide (MPT) were given for a maximum of twelve 42-day cycles. Patients in any of the lenalidomide arms received lenalidomide 25 mg once daily on Days 1 to 21 of 28-day cycles. Dexamethasone was administered at 40 mg once daily on Days 1, 8, 15, and 22 of each 28-day cycle. For patients over > 75 years old, the starting

dose of dexamethasone was 20 mg orally once daily on Days 1, 8, 15, and 22 of repeated 28-day cycles.

Progression-free survival (PFS) was significantly longer with Rd Continuous than MPT: HR 0.72 (95% CI: 0.61-0.85 p <0.0001). The improvement in median PFS time in the Rd Continuous arm compared with the MPT arm was 4.3 months. Objective response rate (ORR) was higher with Rd Continuous compared with MPT (75.1% versus 62.3%); with complete responses in 15.1% of Rd Continuous arm patients versus 9.3% in the MPT arm. The median time to first response was 1.8 months in the Rd Continuous arm versus 2.8 months in the MPT arm. For the interim OS analysis, the median follow-up time for all patients was 45.5 months and the observed OS HR was 0.75 for Rd Continuous versus MPT (95% CI = 0.62, 0.90).

#### **4.1.6 Rationale for Proteasome Inhibitors as a Combination Agent**

Proteasome inhibitors (bortezomib, carfilzomib and ixazomib) are a class of drugs widely used across all lines of therapy in multiple myeloma, which could be rationally combined with anti-PD-1 therapy. Several clinical studies indicate proteasome inhibitor activity is enhanced when combined with immune-modulatory drugs [41] [42] [43] [44] [45]. Moreover, in immunotherapy animal models involving low-avidity antigens [46] [47], the proteasome inhibitor bortezomib activated NF- $\kappa$ B p65 in CD8<sup>+</sup> T cells, stabilizing expression of T-cell receptor CD3 $\zeta$  and IL2 receptor- $\alpha$ , while maintaining IFN $\gamma$  secretion to improve FasL-mediated tumor lysis. Notably, bortezomib increased tumor cell surface expression of Fas in mice as well as human melanoma tissue from a responsive patient. In renal tumor-bearing immunodeficient *Rag2*<sup>-/-</sup> mice, bortezomib treatment after adoptive T-cell immunotherapy reduced lung metastases and enhanced host survival. Our findings highlight the potential of proteasome inhibitors to enhance antitumor T-cell function in the context of cancer immunotherapy.

#### **4.1.7 Rationale for Carfilzomib and Low-dose Dexamethasone in Multiple Myeloma**

Carfilzomib is a keto-epoxide tetrapeptide proteasome inhibitor recently approved for the treatment of relapsed or refractory MM in combination with lenalidomide and low-dose dexamethasone or with low-dose dexamethasone alone.

In the ASPIRE Phase 3 trial of 792 patients, carfilzomib in combination with lenalidomide and low-dose dexamethasone (KRd) was superior to lenalidomide and low-dose dexamethasone (Rd) in terms of response rates, PFS, and OS [48]. Progression-free survival was significantly longer for KRd than Rd (median, 26.3 months, vs. 17.6 months in the control group; HR 0.69; 95% CI: 0.57 to 0.83; p = 0.0001). The 2-year overall survival rates were 73.3% and 65.0% in the carfilzomib and control groups respectively (HR 0.79; 95% CI: 0.63 to 0.99; p = 0.04). Objective response rate (ORR) was higher with KRd compared with Rd (87.1% versus 66.7%, p <0.001)

Support for carfilzomib as a more potent proteasome inhibitor than bortezomib comes from a randomized Phase 3 trial (ENDEAVOR) in which carfilzomib-dexamethasone (Kd) was



compared with bortezomib-dexamethasone (Vd) in 929 subjects with relapsed MM [49]. Median progression-free survival was 18.7 months (95% CI: 15.6–not estimable) in the carfilzomib group versus 9.4 months (CI: 8.4–10.4) in the bortezomib group at a preplanned interim analysis (HR 0.53; 95% CI: 0.44–0.65;  $p < 0.0001$ ). Objective response rate (ORR) was higher with Kd compared with Vd (77 % versus 63%,  $p < 0.0001$ ). At the time of the analysis overall survival data was still immature and subjects continued on follow up.

This Phase I trial will establish the safety and tolerability of pembrolizumab in combination with lenalidomide and low-dose dexamethasone in subjects with refractory or relapsed and refractory MM or in combination with carfilzomib and low-dose dexamethasone in subjects with relapsed or refractory MM.

## **4.2 Rationale**

### **4.2.1 Rationale for the Trial and Selected Subject Population**

#### **4.2.1.1 Rationale for Evaluating anti-PD-1 Therapy in Multiple Myeloma**

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in the bone marrow leading to bone destruction and marrow failure. It accounts for 10% of all hematological malignancies, with an incidence of 5 cases per 100,000/year and a median age at onset of 65 to 70 years [50] [51] [52] [53]. The American Cancer Society has estimated 21,700 new cases of MM in the United States in 2012, with an estimated 10,710 deaths [54]. It is diagnosed by the presence of monoclonal plasma cell proliferation with more than 10% plasma cells in the bone marrow, presence of monoclonal proteins in serum, and/or in urine with one or more of end organ effects such as hypercalcemia, renal failure, anemia, or bone destruction (CRAB features) [55] [56]. Multiple myeloma is responsive to immunomodulatory drugs like lenalidomide. Although, improvements in overall survival have been achieved with newer therapies such as proteasome inhibitors and immunomodulatory drugs (IMiDs), myeloma remains an incurable disease. Relapsed and refractory MM patients have an overall survival of ~12 months, but only 3 months if they receive no therapy following relapse; thus reflecting the poor outcome among these patients [57] [58] [59].

In Multiple Myeloma, PD-L1 is expressed on most MM plasma cells [60], and PD-L1 overexpression enhanced MM invasiveness and rendered tumor cells less susceptible to cytotoxic T lymphocytes (CTLs). This effect was alleviated by anti-PD-L1 antibody treatment, demonstrating the importance of the PD-1/PD-L1 pathway in this process [61]. In addition, a recent report demonstrated increased levels of PD-L1 on MM cells together with enhanced PD-1 expression on T cells with an “exhausted” phenotype. The immunosuppressive effects of myeloma are overcome by PD-L1 blockade [62]. A Phase 1 clinical trial conducted in advanced hematologic malignancies using CT-011, a humanized antibody anti-PD-1, showed clinical responses in 6 of 17 subjects including HL and NHL while stable disease was observed in multiple myeloma patients [63].

#### **4.2.2 Rationale for Dose Selection/Regimen**

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

In KEYNOTE-001, an open-label Phase I study is being conducted to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD), and antitumor 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 dose expansion cohorts 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 addition, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg every 3 weeks (Q3W) is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been 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 population pharmacokinetic (PK) model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. 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. Pharmacokinetic properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed 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, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus the 200 mg fixed dose regimen is considered an appropriate fixed dose for other tumor indications as well.

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 as the appropriate dose for pembrolizumab.

### **4.2.3 Rationale for Endpoints**

#### **4.2.3.1 Safety Endpoints**

The primary objective of this trial is to characterize the safety and tolerability of pembrolizumab in combination with lenalidomide and low-dose dexamethasone or carfilzomib and low-dose dexamethasone in subjects with MM. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades of AEs experienced by subjects who have received pembrolizumab, including SAEs and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0 (Appendix 12.6). The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. Adverse events will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, the occurrence of specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 7.2.3.2.

#### **4.2.3.2 Efficacy Endpoints**

The efficacy objective of this trial is to evaluate the antitumor activity of pembrolizumab in combination with SOC for the different cohorts:

- **Dose Determination, Dose Confirmation, and Cohort 1:** In combination with lenalidomide and low-dose dexamethasone in subjects with rrMM
- **Cohort 2:** In combination with carfilzomib and low-dose dexamethasone in subjects with rMM

Efficacy will be assessed based on objective response rate (ORR) as assessed by the investigator per the International Myeloma Working Group criteria for multiple myeloma (IMWG 2006 Criteria) (Appendix 12.7) [1].

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. Although disease response assessment will be performed on day 1 of every 28-day treatment cycle for all cohorts, treatment

decisions will be based on the Week 12 response assessment. For subjects with biochemical progression two consecutive assessments are needed to confirm PD, according to IMWG 2006. In the setting where a subject's disease response assessment shows confirmed PD according to the IMWG criteria, the subject may continue on study treatment if the investigator considers the subject is deriving clinical benefit from study treatment upon consultation with the Sponsor.

#### **4.2.3.3 Biomarker Research**

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 AEs 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, we will also collect biospecimens (blood components, tumor material, etc.) 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 AEs, 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.

#### **Proteomics and immunohistochemistry (IHC) 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 melanoma, 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.

#### **4.2.3.4 Future Biomedical Research**

The Sponsor will conduct Future Biomedical Research on DNA, blood, and bone marrow specimens collected during this clinical trial. This research may include genetic analyses

(DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

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

## **5.0 METHODOLOGY**

### **5.1 Entry Criteria**

#### **5.1.1 Diagnosis/Condition for Entry into the Trial**

Male/Female subjects with multiple myeloma (MM) of at least 18 years of age will be enrolled in this trial.

#### **5.1.2 Subject Inclusion Criteria**

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

#### **Dose Determination Stage, Dose Confirmation Stage, Cohort 1:**

1. Be willing and able to provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical research.
2. Be  $\geq 18$  years of age on the day of signing informed consent.
3. Has a confirmed diagnosis of multiple myeloma based on standard criteria (see Durie 1986 for criteria [64]). See Appendix 12.4 for MM Diagnostic Criteria.

4. Currently has MM with measurable disease, defined as:
  - a monoclonal immunoglobulin spike on serum electrophoresis of at least 0.5 g/dL and/or
  - urine monoclonal protein levels of at least 200 mg/24 hours
  - for subjects without measurable serum and urine M-protein levels, an abnormal free light chain ratio (normal value: 0.26 - 1.65) with involved FLC level  $\geq 10$  mg/dL ( $\geq 100$  mg/L).
5. Must have undergone prior treatment with  $\geq 2$  treatment lines of anti-myeloma therapy and must have failed their last line of treatment defined as documented disease progression during or within 60 days of completing their last anti-myeloma therapy (refractory to last line of treatment).
6. Prior anti-myeloma treatments must have included an IMiD (lenalidomide, pomalidomide or thalidomide) AND proteasome inhibitor (bortezomib or carfilzomib) alone or in combination and subject must have failed therapy with an IMiD OR proteasome inhibitor defined as one of the following:
  - Refractory: Documented progressive disease on or within 60 days of completing treatment with an IMiD and/or proteasome inhibitor OR
  - Relapsed and refractory: In case of prior response [ $\geq$  partial response (PR)] to an IMiD or proteasome inhibitor, subjects must have relapsed within 6 months after stopping treatment with an IMiD and/or proteasome inhibitor containing regimen.
7. Be able to provide archival or newly obtained bone marrow material for disease assessment. In addition, for subjects in the US and Canada, be able to provide newly obtained bone marrow aspirate for biomarker analysis.
8. Has a performance status of 0 or 1 on the ECOG Performance Scale.
9. Demonstrate adequate organ function as defined by the following table (Table 1). All screening labs should be performed within 7 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

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

10. 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.).
11. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 10-14 days prior to and again within 24 hours prior to receiving the first dose of pembrolizumab, lenalidomide and dexamethasone. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Female subjects of childbearing potential should agree to ongoing pregnancy testing.
12. Female subjects of childbearing potential must be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.3). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for  $> 2$  years.

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



13. Male subjects must agree to use a latex condom during sexual contact with females of childbearing potential, even if they have had a successful vasectomy, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

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

**Cohort 2:**

1. Be willing and able to provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical research.
2. Be  $\geq 18$  years of age on the day of signing informed consent.
3. Multiple myeloma with relapsing or refractory disease at study entry.
4. Currently has MM with measurable disease, defined as:
  - a monoclonal immunoglobulin spike on serum electrophoresis of at least 0.5 g/dL and/or
  - urine monoclonal protein levels of at least 200 mg/24 hours or
  - for subjects without measurable serum and urine M-protein levels, an abnormal free light chain ratio (normal value: 0.26 - 1.65) with involved FLC level  $\geq 10$  mg/dL ( $\geq 100$  mg/L).
5. Received prior treatment with 1 to 3 lines for multiple myeloma. (Induction therapy followed by stem cell transplant and consolidation/maintenance therapy will be considered as one line of therapy.)
6. Achieved a partial response to at least one prior regimen (defined as  $\geq 50\%$  decrease in tumor burden).

**NOTE:** Prior treatment with carfilzomib is allowed if subject achieved at least a partial response to prior carfilzomib therapy, was not discontinued due to toxicity and had at least 6 months carfilzomib free treatment interval before entering the study.

**NOTE:** Prior treatment with bortezomib is allowed if subject achieved at least a partial response to prior bortezomib therapy, was not discontinued due to toxicity and had at least 6 months bortezomib free treatment interval before entering the study.

7. Be able to provide archival or newly obtained bone marrow material for disease assessment. In addition, for subjects in the US and Canada, be able to provide newly obtained bone marrow aspirate for biomarker analysis.
8. Has a performance status of 0 or 1 on the ECOG Performance Scale
9. Left ventricular ejection fraction of at least 40%.
10. Demonstrate adequate organ function as defined by the following table (Table 2). All screening labs should be performed within 7 days of treatment initiation.

Table 2 Adequate Organ Function Laboratory Values

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

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

12. Female subjects of childbearing potential (Section 5.7.3) must be willing to use an adequate method of contraception as outlined in Section 5.7.3 – Contraception, for the course of the study through 120 days after the last dose of study medication.

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

13. Male subjects of childbearing potential (Section 5.7.3) must agree to use an adequate method of contraception as outlined in Section 5.7.3 – Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

### **5.1.3 Subject Exclusion Criteria**

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

#### **Dose Determination Stage, Dose Confirmation Stage, Cohort 1:**

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
2. Has history of repeated infections, primary amyloidosis, hyperviscosity, plasma cell leukemia, POEMS syndrome or Waldenström's macroglobulinemia.
3. Has a diagnosis of immunosuppressive disorder or is on any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
4. Has received a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e.,  $\leq$  Grade 1 or at baseline) from a baseline AE or a Grade 1 adverse event associated with agents administered more than 4 weeks earlier.
5. Has had prior anti-myeloma therapy (including dexamethasone), targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 who has not recovered (i.e.,  $\leq$  Grade 1 or at baseline) from adverse events due to a previously administered agent.

**NOTE:** Subjects with  $\leq$  Grade 2 neuropathy are an exception to this criterion and may qualify for the trial.

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

NOTE: Toxicity that has not recovered to  $\leq$  Grade 1 is allowed if it meets the inclusion requirements for laboratory parameters defined in [Table 1](#).

6. 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.
7. Has known clinically active CNS involvement.
8. Has an active autoimmune disease or a documented history of autoimmune disease/syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the trial.
9. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
10. Has an active infection requiring intravenous systemic therapy.
11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Is pregnant or breastfeeding, or is expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or Screening Visit through 120 days after the last dose of trial treatment.
13. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
14. Has a known Human Immunodeficiency Virus (HIV), or known active Hepatitis B (HBV), or known active Hepatitis C (HCV) infection.
15. Has a clinically significant coagulopathy per investigator's assessment.
16. Has known symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.
17. Has received or is planning for an allogeneic stem cell transplant.
18. Has received autologous stem cell transplant within 12 weeks before the first infusion.

19. Subjects with a prior history of Grade 4 rash associated with thalidomide treatment.
20. Has known hypersensitivity to thalidomide, lenalidomide or pomalidomide.
21. Has known gastrointestinal disease that may significantly alter the absorption of lenalidomide.
22. Is unable or unwilling to undergo antithrombotic prophylactic treatment.
23. Has received a live vaccine within 30 days prior to first dose.
24. Is or has an immediate family member (spouse or children) 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.

**Cohort 2:**

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
2. Subjects with smoldering multiple myeloma (SMM), monoclonal gammopathy of undetermined significance (MGUS), plasma cell leukemia or Waldenström's macroglobulinemia.
3. Has history of repeated infections, primary amyloidosis, hyperviscosity or POEMS syndrome.
4. 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.
5. Has received a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e.,  $\leq$  Grade 1 or at baseline) from a baseline AE or a Grade 1 adverse event associated with agents administered more than 4 weeks earlier.
6. Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 14 days prior to the first dose of treatment.

**NOTE:** Subjects with Grade 1 or Grade 2 (without pain) neuropathy are an exception to this criterion and may qualify for the trial.

7. Has had prior anti-myeloma therapy (including dexamethasone), targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 who has not recovered (i.e.,  $\leq$  Grade 1 or at baseline) from adverse events due to a previously administered agent.

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

**NOTE:** Toxicity that has not recovered to  $\leq$  Grade 1 is allowed if it meets the inclusion requirements for laboratory parameters defined in [Table 2](#).

8. 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.

9. Has an 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.
10. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
11. Has an active infection requiring intravenous systemic therapy, antiviral or antifungal agents within 14 days prior to the first dose of treatment.
12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
13. Is pregnant or breastfeeding, or is 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.
14. 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).
15. Has a known Human Immunodeficiency Virus (HIV), or known active Hepatitis B (HBV), or known active Hepatitis C (HCV) infection.
16. Has a clinically significant coagulopathy per investigator's assessment.

17. Myocardial infarction within 4 months prior to randomization, NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker.
18. Has received within the last 5 years or is planning for an allogeneic stem cell transplant.
19. Has received autologous stem cell transplant within 12 weeks before the first infusion.
20. Has received a live vaccine within 30 days prior to first dose.
21. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib).
22. Patients with hypersensitivity to carfilzomib, bortezomib, boron, or mannitol.
23. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to all anticoagulation and antiplatelet options, antiviral drugs, or intolerance to hydration due to pre-existing pulmonary or cardiac impairment.
24. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to the first dose of treatment.
25. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to the first dose of treatment.

## **5.2 Trial Treatment(s)**

Trial treatment should be administered starting with Day 1 of the first 28-day cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled day of administration due to administrative reasons. Subjects may continue on treatment until confirmed disease progression or until meeting other discontinuation criteria (Section 5.8). The treatments to be used in this trial are outlined below in [Table 3](#).

Table 3 Combination Trial Dosing Cohorts

Dose Level/Arm	Pembrolizumab	Lenalidomide	Dexamethasone	Carfilzomib
<b>Dose Determination Stage<sup>1,3</sup></b>				
1	2 mg/kg	25 mg	40 mg	NA
-1A Lenalidomide toxicity	2 mg/kg	10 mg	40 mg	NA
<b>Dose Confirmation Stage<sup>1,4</sup></b>				
1 (fixed dose)	200 mg	25 mg	40 mg	NA
-1A (fixed dose)	200 mg	10 mg	40 mg	NA
<b>Expansion Cohorts</b>				
Cohort 1 - rMM <sup>1</sup>	200 mg	25 mg	40 mg	NA
Cohort 2 - rMM <sup>2</sup>	200 mg	NA	20 mg	56 mg/m <sup>2</sup>
NA = Not Applicable				
<p><sup>1</sup> <b>Dose Determination, Dose Confirmation, and Expansion Cohort 1:</b> Pembrolizumab will be administered every two weeks (on Days 1 and 15) of each 28-day cycle. Lenalidomide will be dosed on Days 1 to 21 of each 28-day cycle. Dexamethasone will be dosed on Days 1, 8, 15, and 22 of each 28-day cycle. NOTE: A dexamethasone dose of 20 mg on Days 1, 8, 15, and 22 in subjects aged &gt; 75 years is recommended.</p> <p><sup>2</sup> <b>Expansion Cohort 2:</b> Pembrolizumab will be administered every three weeks. Carfilzomib will be dosed at 20 mg/m<sup>2</sup>/day on Days 1 and 2 of Cycle 1; if tolerated, the dose should be escalated to a target dose of 56 mg/m<sup>2</sup>/day starting on Day 8, and continuing on Day 9, 15, and 16 of Cycle 1, then on Days 1, 2, 8, 9, 15 and 16 of subsequent cycles, during a 28-day cycle. Dexamethasone will be dosed on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each 28-day cycle.</p> <p><sup>3</sup> <b>Dose Determination</b> stage will target returning to the standard dose of the lenalidomide/low-dose dexamethasone combo (SOC). If further dose escalation is permitted per <a href="#">Table 15</a> then DL 1 will be reevaluated.</p> <p><sup>4</sup> If pembrolizumab 2 mg/kg is determined to be the preliminary MAD/MTD in Dose Determination stage, then pembrolizumab 200 mg will be started as the fixed dose in <b>Dose Confirmation</b> stage. Preliminary lenalidomide dose started in <b>Dose Confirmation</b> stage will be determined during Dose Determination stage (e.g. 10 mg or 25 mg).</p>				

All trial treatments will be administered on an outpatient basis.

**Pembrolizumab [All Subjects]**

**Dose Determination, Dose Confirmation, and Cohort 1:** Pembrolizumab will be administered as a 30 minute IV infusion every two weeks (on Days 1 and 15) of a 28-day cycle (Q2W). Treatment dose may be modified as described in Section 5.2.1.2. 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 starting dose of pembrolizumab is 2 mg/kg.

**Cohort 2:** Pembrolizumab will be administered as a 30 minute IV infusion every three weeks (Q3W). Treatment dose may be modified as described in Section 5.2.1.2. 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). Pembrolizumab will be given as a fixed dose of 200 mg.

### **Lenalidomide [Dose Determination, Dose Confirmation, Cohort 1]**

The recommended starting dose of lenalidomide is 25 mg once daily on Days 1 through 21 of repeated 28-day cycles. If 25 mg dose of lenalidomide is not tolerated due to toxicity, the dose could be decreased according to Section 5.2.1.2.3 of this protocol. 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. Refer to local product label for more details.

### **Carfilzomib [Cohort 2]**

The recommended starting dose of carfilzomib is 20 mg/m<sup>2</sup>/day on Days 1 and 2 of Cycle 1. If tolerated, the dose should be escalated to a target dose of 56 mg/m<sup>2</sup>/day starting on Day 8, and continuing on Day 9, 15, and 16 of Cycle 1, then on Days 1, 2, 8, 9, 15 and 16 of subsequent cycles. Dose modifications and dose reductions are outlined in Section 5.2.1.2.5. Carfilzomib will be administered intravenously as a 30 minute infusion on two consecutive days each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28).

Treatment with carfilzomib requires pre-treatment medications; see Section 5.5.1.1 for specific details.

### **Dexamethasone [All Subjects]**

**Dose Determination, Dose Confirmation, and Cohort 1:** The recommended dose of dexamethasone is 40 mg once weekly on Days 1, 8, 15, and 22 of each 28-day cycle. A dexamethasone dose of 20 mg once weekly on Days 1, 8, 15, and 22 in subjects aged >75 years is recommended. Refer to local product label for more details.

**Cohort 2:** Dexamethasone 20 mg is taken by mouth or intravenously on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle. Administer dexamethasone 30 minutes to 4 hours before carfilzomib on the day of the infusion.

The Pharmacy Manual contains specific instructions for pembrolizumab dose calculation, reconstitution, preparation of the infusion fluid, and administration. The local product labels and institutional standards should be referenced for lenalidomide, carfilzomib and dexamethasone.

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

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, KN185, and Cohort 1 of KN023 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 (every 12 weeks) per protocol.

On 15-SEP-2017, the US FDA placed Cohort 2 of KN023, on partial clinical hold. Enrollment was stopped and all subjects who derived clinical benefit from therapy are allowed to continue if reconsented, at least verbally. Enrollment will not be reopened by the sponsor after a full safety and efficacy evaluation did not demonstrate any significant difference from historical controls. Those subjects who are already enrolled and deriving clinical benefit from therapy were allowed to continue if reconsented, at least verbally, and will continue on study until protocol-specific end of treatment, and then progress into long term safety and follow-up. Those subjects who are not deriving clinical benefit, must stop study treatment, complete the Discontinuation Visit and move into the long term safety and follow-up per protocol.

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**

The rationale for selection of doses to be used in this trial is provided in Section 4.2.2 – Background and Rationale.

The amount required to prepare the pembrolizumab infusion solution will be based on the subject's weight in kilograms (kg) for Dose Determination. During Dose Confirmation and Expansion Cohort 1, a fixed dose of pembrolizumab will be given Q2W. Subjects in Expansion Cohort 2 will receive pembrolizumab 200 mg Q3W. Details on the dose calculation, reconstitution, preparation of infusion fluid, and administration are provided in the Pharmacy Manual. Please refer to the local product label for dosing details of lenalidomide, carfilzomib and dexamethasone.

### **5.2.1.2 Dose Modification (Escalation/Titration/Other)**

#### **5.2.1.2.1 Guidelines for Dose Modification**

During Dose Determination, if dose modifications are necessary during the DLT observation period due to drug-related AEs that do not meet DLT criteria, then this would be considered a DLT. Following the DLT evaluation period, for Grade 3 and 4 toxicities, the dose of pembrolizumab, lenalidomide, and dexamethasone could be modified as outlined in [Table 4](#), [Table 5](#), [Table 7](#), [Table 8](#), [Table 9](#), [Table 10](#) and [Table 11](#).

In Cohort 2, for the initial 6 subjects in the safety run in, carfilzomib dose modifications are allowed in accordance with [Table 13](#) and [Table 14](#). During the safety run in, any drug-related AEs, which in the opinion of the investigator cannot be managed by the carfilzomib dose modifications outlined in [Table 13](#) and [Table 14](#), will be considered a DLT. After the safety run in for the initial 6 subjects have been completed, the dose of pembrolizumab, carfilzomib and dexamethasone can be modified as outlined in [Table 4](#), [Table 5](#), [Table 10](#), [Table 13](#) and [Table 14](#).

Subjects who discontinue lenalidomide, carfilzomib or dexamethasone due to toxicity, may continue receiving pembrolizumab until unacceptable toxicity or progression. Subjects who discontinue pembrolizumab due to untoward toxicities may not continue on the study receiving only lenalidomide or carfilzomib, and dexamethasone.

After any study medication has been held for any reason, it may be restarted when clinically indicated according to any applicable dose modification guidelines and the dosing schedule conforms to the schedule of the normal dosing cycle. Missed doses should be skipped, not delayed, if not given within the allowed window.

#### 5.2.1.2.2 Dose Modification Guidelines for Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events 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 4](#) and [Table 5](#) below. See Section 5.6.1 for supportive care guidelines, including use of corticosteroids.

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

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Hematological Toxicity	1, 2, 3	No	N/A	N/A
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	Toxicity does not resolve within 4 weeks of last infusion <i>Permanent discontinuation should be considered for any severe or life-threatening event</i>

**Dose modification and toxicity management for immune-related AEs associated with pembrolizumab**

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

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

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

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Myocarditis	Grade 1 or 2	Withhold	<ul style="list-style-type: none"> <li>Based on severity of AE administer corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>Ensure adequate evaluation to confirm etiology and/or exclude other causes</li> </ul>
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Intolerable/ Persistent Grade 2	Withhold	<ul style="list-style-type: none"> <li>Based on type and severity of AE administer corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>Ensure adequate evaluation to confirm etiology and/or exclude other causes</li> </ul>
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: GBS (Guillain-Barre Syndrome), SOTR (solid organ transplant rejection), encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
<p>1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.</p> <p><b>NOTE:</b>            For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).</p>				

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

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in [Table 6](#).

Table 6 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<u>Grade 1</u> 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
<u>Grade 2</u> Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	<b>Stop Infusion and monitor symptoms.</b> Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics  Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. <b>Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.</b>	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with:  Diphenhydramine 50 mg po (or equivalent dose of antihistamine).  Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
<u>Grades 3 or 4</u>  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	<b>Stop Infusion.</b> 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. <b>Subject is permanently discontinued from further trial treatment administration.</b>	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		



### **Other allowed dose interruption for pembrolizumab**

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

Subjects who experience a DLT in Cycle 1 should be discontinued from the study. However, the subject may be allowed to continue if it has been determined that the subject is deriving clinical benefit from the study therapy. It should be noted that if the dose of pembrolizumab is interrupted due to toxicity, the lenalidomide/low-dose dexamethasone or carfilzomib/low-dose dexamethasone may continue to be administered per standard of care based on investigator's assessment as appropriate.

#### **5.2.1.2.3 Dose Modification Guidelines for Lenalidomide (after DLT Evaluation Period)**

Dose modification guidelines are based on the recommendation provided by the myeloma expert panel review of the efficacy and toxicity of lenalidomide plus dexamethasone, and the guidance provided in the product label for lenalidomide [37] [65].

The criteria presented in this section below 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.

Lenalidomide is administered once daily from Day 1 through Day 21 in each 28-day cycle. The lowest dose of lenalidomide allowed in this trial is 5 mg. Therefore, if a subject receiving 5 mg of lenalidomide experiences an AE related to lenalidomide and is in need of dose modification, the subject should discontinue lenalidomide and continue only pembrolizumab and dexamethasone. A maximum of three dose reductions of lenalidomide will be allowed in the order indicated in [Table 9](#), where applicable. The duration of administration will remain the same.

A subject cannot be restarted on lenalidomide unless non-hematologic lenalidomide-related toxicities have returned to at least Grade 1 toxicity or baseline.

##### **5.2.1.2.3.1 Lenalidomide Dose Adjustments for Hematologic Toxicities during Multiple Myeloma Treatment**

Dose modification guidelines, as summarized below in [Table 7](#) and [Table 8](#), are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicities judged to be related to lenalidomide. Please refer to local product label for additional guidelines.

Table 7 Platelet Counts: Thrombocytopenia in MM

<b>When Platelets</b>	<b>Recommended Course</b>
Fall to <30,000/mcL	Interrupt lenalidomide treatment, follow CBC weekly
Return to $\geq$ 30,000/mcL	Restart lenalidomide at 15 mg daily
For each subsequent drop <30,000/mcL	Interrupt lenalidomide treatment
Return to $\geq$ 30,000/mcL	Resume lenalidomide at 5 mg less than the previous dose. Do not dose below 5 mg daily.

Table 8 Absolute Neutrophil Counts (ANC): Neutropenia in MM

<b>When Neutrophils</b>	<b>Recommended Course<sup>1</sup></b>
Fall to <1,000/mcL	Interrupt lenalidomide treatment, add G-CSF, and follow CBC weekly
Return to $\geq$ 1,000/mcL and neutropenia is the only toxicity	Resume lenalidomide at 25 mg daily
Return to $\geq$ 1,000/mcL and if other toxicity	Resume lenalidomide at 15 mg daily
For each subsequent drop <1,000/mcL	Interrupt lenalidomide treatment
Return to $\geq$ 1,000/mcL	Resume lenalidomide at 5 mg less than the previous dose. Do not dose below 5 mg daily.
<sup>1</sup> If the subject is receiving Len 10 mg, the subject may resume Len at 5 mg.	

#### 5.2.1.2.3.2 Other Grade 3 and 4 Lenalidomide Toxicities in MM

For other Grade 3 and 4 toxicities, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to  $\leq$  Grade 2 as outlined below in [Table 9](#).

Table 9 Lenalidomide Dose Reductions for Subjects with Other Grade 3 and 4 Toxicities

Modification	Dose <sup>1,2</sup>
Starting Dose	Lenalidomide 25 mg every day for 21 days, every 28 days
Dose Reduction 1	Lenalidomide 15 mg every day for 21 days, every 28 days
Dose Reduction 2	Lenalidomide 10 mg every day for 21 days, every 28 days
Dose Reduction 3	Lenalidomide 5 mg every day for 21 days, every 28 days
<sup>1</sup> Do not dose below 5 mg daily	
<sup>2</sup> If the subject is receiving Len 10 mg, the subject may resume Len at 5 mg.	

### 5.2.1.2.3.3 Recommended Lenalidomide Dose Adjustments for Subjects with Impaired Renal Function

Renal function may be impaired in subjects with MM by immunoglobulin light chains, amyloidosis. MM subjects with normal renal function may develop renal dysfunction or renal impairment during treatment with lenalidomide and dexamethasone. If renal toxicity occurs during study treatment, drug should not be restarted unless the toxicity resolved to ≤Grade 1.

### 5.2.1.2.4 Dose Modification Guidelines for Dexamethasone

Dose Determination, Dose Confirmation, and Cohort 1: Dexamethasone will be given at 40 mg QD PO on Days 1, 8, 15, and 22 (i.e., once weekly) in each 28-day cycle. If a subject experiences adverse events, up to two dose reductions of dexamethasone will be allowed. The duration of administration will remain the same; however, the weekly dose will be modified in the order indicated in [Table 10](#) and [Table 11](#). Additional supportive care guidelines specific to dexamethasone are indicated in [Table 12](#).

A subject cannot be restarted on dexamethasone unless non-hematologic dexamethasone-related toxicities have returned to at least Grade 1 toxicity or baseline.

Cohort 2: Dexamethasone will be given at 20 mg p.o. or IV on Days 1,2, 8, 9, 15, 16, 22, and 23 in each 28-day cycle. If a subject experiences dexamethasone-related adverse events, up to two dose reductions of dexamethasone will be allowed (in [Table 10](#)). At the investigator's discretion, dexamethasone could be tapered prior to complete discontinuation according to institutional practice. If the dexamethasone dose was reduced during the previous cycle, the reduced dose level will be continued on day 1 of the new cycle. If the reduced dose level was well tolerated for a complete cycle, the patient could, at the investigator's discretion, be rechallenged with the dose level prior to the reduction at the start of the next cycle.

Additional supportive care guidelines specific to dexamethasone are indicated in [Table 12](#).

A subject cannot be restarted on dexamethasone unless non-hematologic dexamethasone-related toxicities have returned to at least Grade 1 toxicity or baseline.

Table 10 Dexamethasone Dose Reductions for Subjects with Grade 3 and 4 Toxicities

<b>Dexamethasone: Dose Determination, Dose Confirmation, and Cohort 1</b>		
On Days 1, 8, 15, and 22 in each 28-day cycle		
<b>Starting Dose (mg)</b>	<b>Dose Reduction 1 (mg)</b>	<b>Dose Reduction 2 (mg)</b>
40	20	10
<b>Dexamethasone: Cohort 2</b>		
On Days 1, 2, 8, 9, 15, 16, 22, and 23 in each 28-day cycle		
<b>Starting Dose (mg)</b>	<b>Dose Reduction 1 (mg)</b>	<b>Dose Reduction 2 (mg)</b>
20	12	8

**5.2.1.2.4.1 Dose Modification Guidelines for Dexamethasone for Elderly Subjects > 75 Years of Age**

Table 11 Dexamethasone Dose Reductions for Elderly Subjects > 75 Years of Age with Grade 3 and 4 Toxicities

<b>Dexamethasone</b>		
Per Cohort Schedule		
<b>Starting Dose (mg)</b>	<b>Dose Reduction 1 (mg)</b>	<b>Dose Reduction 2 (mg)</b>
20	10	5

### 5.2.1.2.4.2 Supportive Care Guidelines Specific to Dexamethasone

Table 12 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 these measures, decrease dexamethasone dose by one dose level.
Gastrointestinal	> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms are 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 these 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 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 measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone by one dose level. If weakness persists despite 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 measures, decrease dose by one dose level until levels are satisfactory.

### 5.2.1.2.5 Cohort 2: Dose Modification Guidelines for Carfilzomib

In Cohort 2, for the initial 6 subjects in the safety run in, carfilzomib dose modifications are allowed in accordance with [Table 13](#) and [Table 14](#). During the safety run in, any drug-related AEs, which in the opinion of the investigator cannot be managed by the carfilzomib dose modifications outlined in [Table 13](#) and [Table 14](#), will be considered a DLT. After the safety run in for the initial 6 subjects have been completed, the dose of pembrolizumab, carfilzomib and dexamethasone can be modified as outlined in [Table 4](#), [Table 5](#), [Table 10](#), [Table 13](#) and [Table 14](#).

Table 13 Dose Modifications for Toxicity during Carfilzomib Treatment

<b>Hematologic Toxicity</b>	<b>Recommended Action</b>
ANC less than $0.5 \times 10^9/L$	Withhold dose. If recovered to greater than or equal to $0.5 \times 10^9/L$ , continue at the same dose level.  For subsequent drops to less than $0.5 \times 10^9/L$ , follow the same recommendations as above and consider 1 dose level reduction when restarting carfilzomib
Febrile neutropenia (ANC less than $0.5 \times 10^9/L$ and an oral temperature more than $38.5^\circ C$ or two consecutive readings of more than $38.0^\circ C$ for 2 hours)	Withhold dose. If ANC returns to baseline grade and fever resolves, resume at the same dose level.
Platelets less than $10 \times 10^9/L$ or evidence of bleeding with thrombocytopenia	Withhold dose. If recovered to greater than or equal to $10 \times 10^9/L$ and/or bleeding is controlled, continue at the same dose level.  For subsequent drops to less than $10 \times 10^9/L$ , follow the same recommendations as above and consider 1 dose level reduction when restarting carfilzomib
<b>Renal Toxicity</b>	<b>Recommended Action</b>
Serum creatinine greater than or equal to $2 \times$ baseline  OR  Creatinine clearance less than 15 mL/min, or creatinine clearance decreases to less than or equal to 50% of baseline, or need for dialysis	Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance) <ul style="list-style-type: none"> <li>• If attributable to carfilzomib, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction</li> <li>• If not attributable to carfilzomib, dosing may be resumed at the discretion of the physician</li> </ul> For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure
<b>Other Hon-hematologic Toxicity</b>	<b>Recommended Action</b>
All other severe or life-threatening non-hematological toxicities (CTCAE Grades 3 and 4)	Withhold until resolved or returned to baseline  Consider restarting the next scheduled treatment at 1 dose level reduction

Table 14 Dose Level Reductions for Carfilzomib

<b>Carfilzomib</b>			
<b>Nominal Dose</b>	<b>Dose -1</b>	<b>Dose -2</b>	<b>Dose -3</b>
20 mg/m <sup>2</sup>	15 mg/m <sup>2</sup>	11 mg/m <sup>2</sup>	-
56 mg/m <sup>2</sup>	45 mg/m <sup>2</sup>	36 mg/m <sup>2</sup>	27 mg/m <sup>2</sup>

### 5.2.2 Timing of Dose Administration

Trial treatment should be administered starting with Day 1 of the first 28-day cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled day of administration due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

### 5.2.3 Definition of Disease Progression

A subject with *unconfirmed* progression of disease may continue trial treatment until progression of disease is confirmed at the next scheduled assessment (refer to Section 7.1.2.6.1 for details). Subjects may only receive trial treatment while waiting for confirmation of PD if the following criteria are met:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

If a subject is noted to have *confirmed* progression of disease by the respective response criteria, the subject should not receive further treatment with trial treatment unless allowed after Sponsor consultation.

### 5.2.4 Guidelines for Study Drug Administration

The study starts with a 3+3 Dose Determination stage to identify a preliminary MTD (or MAD) of the combination. In this stage, pembrolizumab (2 mg/kg) will be evaluated in combination with lenalidomide and dexamethasone (Table 3).

After identification of a preliminary MTD/MAD, the dose confirmation stage will initiate based on the toxicity probability interval (TPI) [66] approach to further evaluate safety, define the final MTD/MAD and characterize preliminary efficacy. In this stage pembrolizumab will be given at a fixed dose in combination with lenalidomide and dexamethasone based on the preliminary MTD/MAD defined in the previous stage

Upon completion of the dose confirmation stage, 2 expansion cohorts will be initiated:

- Cohort 1: at the final MTD/MAD determined in the dose confirmation stage in combination with lenalidomide and dexamethasone;

- Cohort 2: 200 mg fixed dose pembrolizumab (Q3W) in combination with carfilzomib and dexamethasone.

Specific instructions for dose calculation, reconstitution, preparation of the infusion fluid, and administration of pembrolizumab as an IV infusion are provided in the Pharmacy Manual. Refer to the local product labels and institutional standards for the pertinent information on lenalidomide, carfilzomib and dexamethasone.

In the Dose Determination, Dose Confirmation, and Cohort 1 groups:

- For **the North America Sites**, lenalidomide must be prescribed through and in compliance with Celgene's Revlimid REMS<sup>®</sup> program for trial participants.
- For the **ex-North America Sites**, subjects will have lenalidomide dispensed from the investigational pharmacy at the site where they are enrolled in compliance with the country risk minimization plan.

## **5.2.5 Rules for Dose Determination and Confirmation**

### **5.2.5.1 Dose Determination**

Dose limiting toxicities (DLTs) observed in Cycle 1 will be used to determine the next dose level. The trial is using a modified 3+3 design based on the TPI method [66] and has 3 stages: a Dose Determination stage using a 3+3 design, a Dose Confirmation stage according to the TPI approach and an Expansion Cohort stage with two cohorts. The guidelines used for Dose Determination and Dose Confirmation are shown in [Figure 7](#) and [Table 15](#).

The following rules must be applied for the Dose Determination stage.

An initial cohort of 3 subjects is enrolled:

- If 0/3 subjects develop a DLT, no de-escalation will occur and the current dose will be considered the preliminary MTD.
- If 1/3 subjects develops a DLT:
  - Another 3 subjects will be enrolled at this dose level.
    - If 0 or 1 of the 3 new subjects develops a DLT (for a total of  $\leq 2/6$  subjects with a DLT at this dose level), the Dose Determination stage of the trial will be terminated, the current dose will be considered the preliminary MTD, and the trial will proceed to the Dose Confirmation stage.

If  $>1$  of the 3 new subjects develop a DLT (for a total of  $>2/6$  subjects with a DLT at this dose level), the Dose Determination stage of the trial will continue with dose de-escalation as outlined in [Table 3](#) until a preliminary MTD is identified. Then the trial will proceed to Dose Confirmation.

- If  $\geq 2/3$  subjects develop a DLT, dose de-escalation will occur.



It is conceptually acceptable to de-escalate to an intermediate, not pre-defined and not previously-studied dose, if evaluation of toxicity at such a dose is desired in lieu of proceeding directly to the Dose Confirmation stage of the trial. In addition, as specified in Table 3, it is possible to de-escalate to a lower dose of lenalidomide (Dose Level -1A) if lenalidomide toxicity is observed. If either approach is taken, 3 new subjects should be enrolled at the new intermediate dose, and the aforementioned rules should be used to determine further enrollment at this dose level.

The Dose Determination stage will terminate if the candidate dose of pembrolizumab (2 mg/kg) in combination with lenalidomide and dexamethasone is studied and 0/3 subjects or <2/6 subjects develop a DLT. Pembrolizumab 2 mg/kg in combination with lenalidomide and dexamethasone will be considered the preliminary MTD/MAD.

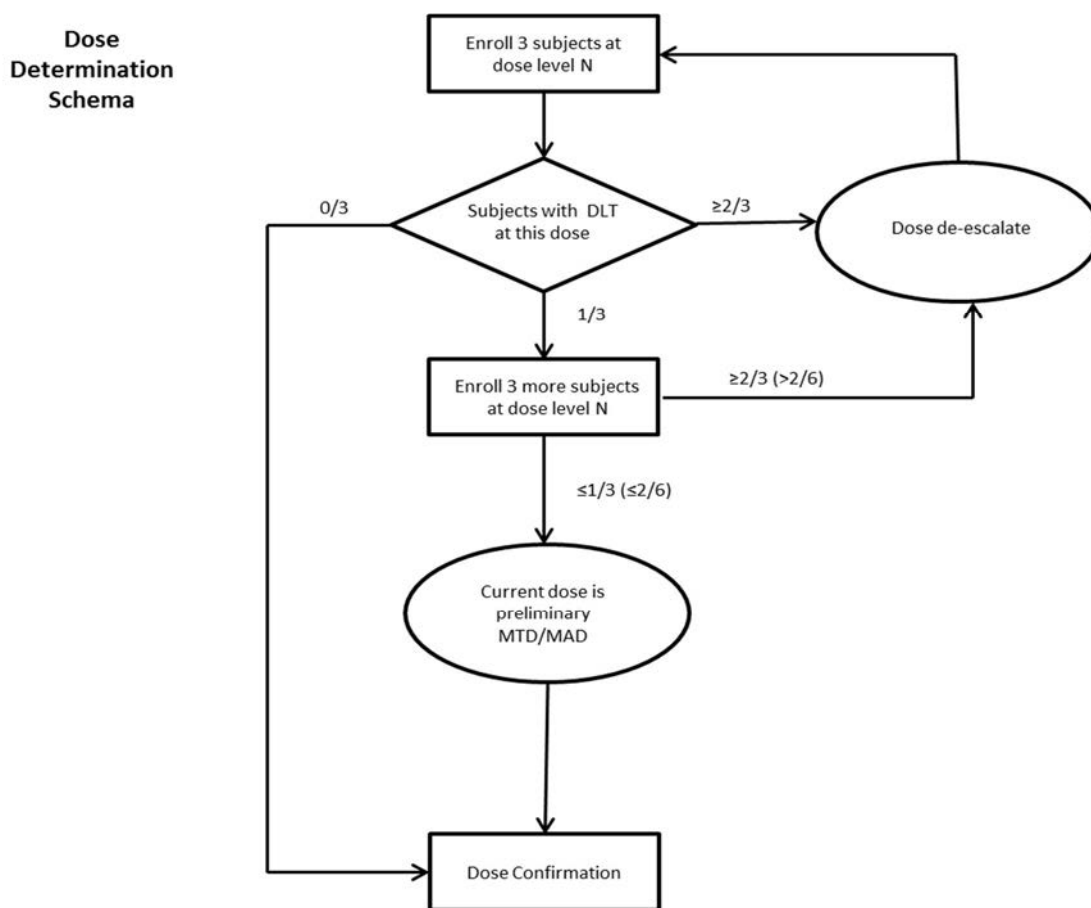


Figure 7 Dose Determination Schema

### 5.2.5.2 Dose Confirmation

The objective of the Dose Confirmation stage is to define final MTD/MAD in the pembrolizumab, lenalidomide, dexamethasone combination regimen.

Dose Confirmation will begin with the preliminary MTD identified in the Dose Determination stage described above which has been changed to a fixed dose depending on the results from the Dose Determination stage (i.e., if 2 mg/kg is determined as the MTD/MAD, then 200 mg will be the starting dose).

In this Dose Confirmation stage, an additional 7 subjects (or the number of additional subjects necessary to reach 13 in the MTD/MAD) will be enrolled in the pembrolizumab, lenalidomide, dexamethasone combination. The Dose Confirmation stage will continue until  $\leq 4$  of 13 subjects (combined from Dose Determination and Dose Confirmation) experience a DLT. As subjects become evaluable for DLT assessment, the number of subjects who are evaluable for DLT versus the number of subjects who developed a DLT will be continuously assessed as shown in Table 15. The DLTs observed during the Dose Determination stage will be included in the Dose Confirmation stage under the assumption of consistency between 2 mg/kg and 200 mg (see Section 4.2.2) as analogous.

In this stage, there will be no escalation above 200 mg; therefore, the decision to ‘escalate to a higher dose’ in the table below will be treated as ‘stay at the current dose’ for this situation, i.e. 200 mg. This table will be also used as a guide to determine the lenalidomide dose used for the expansion stage.

Table 15 Dose Confirmation Rules

		Number of subjects treated at current dose									
		4	5	6	7	8	9	10	11	12	13
Number of toxicities	0	E	E	E	E	E	E	E	E	E	E
	1	S	S	S	E	E	E	E	E	E	E
	2	D	S	S	S	S	S	S	E	E	E
	3	DU	DU	D	D	S	S	S	S	S	S
	4	DU	DU	DU	DU	DU	D	D	S	S	S
	5		DU	DU	DU	DU	DU	DU	D	D	D
	6			DU	DU	DU	DU	DU	DU	DU	DU
<p>E = Escalate to the next higher dose (taken as ‘stay at the current dose’ if current dose is 200 mg)                      S = Stay at the current dose                      D = De-escalate to the next lower dose                      DU = The current dose is unacceptably toxic                      Target DLT rate = 25%                      a=1; b=1; k1=1.5; k2=0.5; pow=1.1                      Source: Ji et al. (2007) [66]</p>											

Subjects may be enrolled continuously (i.e., without waiting for Cycle 1 completion of subjects who have received the first dose) unless a DLT is observed at the particular dose. Once a DLT is observed, the number of subjects who are enrolled at that dose, but are not yet fully evaluable for DLT assessment, may not exceed the number of remaining subjects who are at risk of developing a DLT before the dose would be considered unacceptably toxic (denoted as DU in [Table 15](#)). For example, if 2/7 subjects have experienced a DLT at a given dose level, no more than an additional 3 subjects should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 3 of the additional subjects experience a DLT (i.e., 5/10 subjects with DLT in [Table 15](#)).

If enrollment expands to 13 subjects for a dose level, and  $\leq 4$  of the 13 subjects develop a DLT, then the Dose Confirmation stage will stop. If 25 mg of lenalidomide is the starting dose in combination with pembrolizumab and enrollment expands to 13 subjects and  $>4/13$  subjects develop a DLT, then the 10 mg lenalidomide dose with pembrolizumab may be expanded to further explore the dose-response relationship. If 10 mg lenalidomide is the starting dose in combination with pembrolizumab, and  $>4/13$  subjects develop a DLT, then the Dose Confirmation stage will stop. Note that while 25% has been the target toxicity rate used to generate the guidelines in [Table 15](#), the observed rate of patients with DLT at the MTD may be slightly above or below 25%. [Table 16](#) below summarizes the operating characteristics of the TPI design.

Table 16 Operating Characteristics of Design Based on the Toxicity Probability Interval (TPI) Approach

True DLT Rate (DL1, DL2, DL3)	Probability of selecting dose as the MTD				Average Sample Size
	DL1	DL2	DL3	No Dose	
0.05, 0.05, 0.05	0.008	0.026	0.937	0.029	19.31
0.05, 0.10, 0.15	0.022	0.152	0.802	0.024	19.84
0.05, 0.10, 0.25	0.021	0.276	0.673	0.030	20.34
0.15, 0.25, 0.45	0.191	0.504	0.112	0.193	18.10
0.25, 0.35, 0.45	0.313	0.206	0.040	0.441	14.06
0.40, 0.45, 0.50	0.152	0.040	0.004	0.804	8.45
DL = dose level					

### 5.2.5.3 Expansion Cohort

After the definition of the final MTD/MAD from the dose confirmation stage around 30-45 subjects will be enrolled in each of the 2 cohorts of Expansion Cohort stage to assess safety and preliminary efficacy. The maximum number of subjects to be enrolled in the expansion arms is based on clinical rather than statistical consideration.

In the expansion cohorts, safety will be evaluated on a continuous basis but no formal rules for dose escalation or stopping are planned based on statistical considerations.

Since the combination of pembrolizumab with carfilzomib and dexamethasone (Cohort 2) was not evaluated during the Dose Determination and Dose Confirmation stages, Cohort 2 evaluation will commence with a 6 subject safety lead in and enrollment will be paused until completion of the first cycle of treatment for these subjects. In this safety lead in, any drug-related AEs, which in the opinion of the investigator cannot be managed by the carfilzomib dose modification rules outlined in [Table 13](#) and [Table 14](#) will be considered a DLT with the following decisions:

- If  $>2/6$  subjects develop a DLT during the first cycle of the safety lead in, Cohort 2 will be closed and no additional subjects will be enrolled.
- If  $\leq 2/6$  subjects develop a DLT during the first cycle, the safety lead in would be concluded and Cohort 2 will resume enrollment continuously (i.e. without waiting for Cycle one completion for the remaining subjects) as planned.

### **5.2.6 Definition of Dose Limiting Toxicities**

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.0 (Appendix 12.7).

#### Dose Determination and Dose Confirmation

The occurrence of any of the following toxicities during Cycle 1 during the Dose Determination and Dose Confirmation stages will be considered a DLT, if judged by the investigator to be possibly, probably or definitely related to pembrolizumab in combination with lenalidomide/dexamethasone. Please refer to Section 2.1 for dose level guidelines following DLT evaluation Cycle 1.

1. Grade 4 hematologic toxicity lasting  $\geq 7$  days.
2. Grade 4 non-hematologic toxicity (not laboratory).
3. Grade 3 non-hematologic toxicity (not laboratory) will be considered a DLT, except for inadequately treated nausea, hypersensitivity reactions, or fatigue lasting  $\leq 3$  days.
4. Any Grade 3 non-hematologic laboratory value if:
  1. Renal or liver function abnormality
  2. Medical intervention is required to treat the subject, or
  3. The abnormality leads to hospitalization, or
  4. The abnormality persists for  $>1$  week.

5. Febrile neutropenia Grade 3 or Grade 4:

- Grade 3 is defined as ANC  $<1000/\text{mm}^3$  with a single temperature of  $>38.3$  degrees C (101 degrees F) or a sustained temperature of  $\geq 38$  degrees C (100.4 degrees F) for more than one hour.
- Grade 4 is defined as ANC  $<500/\text{mm}^3$  with a single temperature of  $>38.3$  degrees C (101 degrees F) or a sustained temperature of  $\geq 38$  degrees C (100.4 degrees F) for more than one hour, with life-threatening consequences and urgent intervention indicated.

6. Thrombocytopenia  $<25,000/\text{mm}^3$  if associated with:

- A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
- A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit.

7. Grade 5 toxicity (i.e., death).

8. A delay of  $> 1$  week due to drug-related toxicity in initiating Cycle 2.

9. Unable to complete at least 80% of any of the three treatments during the first course of therapy due to treatment-related toxicity (even if not meeting above DLT criteria).

Cohort 2

For Cohort 2, during the first cycle of the safety lead in, a DLT will be defined as any drug-related AE (possibly, probably or definitely related to carfilzomib, pembrolizumab or the combination) which in the opinion of the investigator cannot be managed by the carfilzomib dose modification rules outlined in [Table 13](#) and [Table 14](#).

**5.2.7 Replacement of Subjects in DLT Evaluation Period**

In order to determine safety, all subjects selected must meet the evaluability criteria for Cycle 1.

1. Subjects will be considered non-evaluable and will be replaced if:

- they are allocated but not treated,
- they discontinue from the trial prior to completing all safety evaluations for reasons other than treatment-related adverse events,
- they received  $<90\%$  of the total pembrolizumab infusion in Cycle 1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a dose-hold or modification due to an adverse event,
- they received  $<80\%$  of lenalidomide, carfilzomib or dexamethasone intended for the trial for reasons other than treatment-related adverse events.

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

If a subject experiences a DLT in Cycle 1, trial treatment may be discontinued following discussion and agreement between the Sponsor and investigator. However, if it has been determined that the subject is deriving clinical benefit from the trial treatment, the subject may be allowed to continue at a lower dose. Please follow dose modification guidelines as described in Section 5.2.1.2.

### **5.2.8 Trial Blinding/Masking**

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

### **5.3 Randomization or Treatment Allocation**

Subjects will be allocated to assignment during the Dose Determination, Dose Confirmation and Expansion Cohort stages of the trial in accordance with Section 5.2.5. The Sponsor delegate will provide the allocation number to the site from the allocation schedules.

### **5.4 Stratification**

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

### **5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)**

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

#### **5.5.1 Acceptable Concomitant Medications**

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

Periodic monitoring of digoxin levels is recommended due to increased  $C_{max}$  and AUC with concomitant lenalidomide therapy. Subjects taking concomitant therapies such as

erythropoietin stimulating agents or estrogen containing therapies may have an increased risk of venous thromboembolism.

Refer to product label for lenalidomide, carfilzomib and dexamethasone for specific details about acceptable concomitant medications.

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

### **5.5.1.1 Concomitant Medications for Cohort 2 Carfilzomib**

The following pre-treatments are suggested for subjects receiving carfilzomib in Cohort 2, and should be incorporated per investigator discretion/local clinical practice:

- At least 48 hours before Cycle 1 Day 1, **oral hydration** should be given as follows: 30 mL/kg/day (approximately 6 to 8 cups of liquid per day, per local clinical practice) continuing up to the time of treatment. Subject compliance must be assessed before initiating treatment, which is to be delayed if oral hydration is not adequate. Oral hydration may be continued in Cycle 2 and beyond at the investigator's discretion
- At least 24 hours prior to Cycle 1 Day 1, the following treatments can be started:
  - **Ciprofloxacin** 500 mg PO QD to continue through Cycle 1 only (a similar fluoroquinolone, amoxicillin, or other appropriate prophylactic antibiotic may be used instead at the investigator's discretion).
  - **Valacyclovir** 500 mg PO QD (or equivalent antiviral), continuing for the duration of treatment (additional prophylaxis is at the investigator's discretion).
  - **Lansoprazole** 15 mg PO QD, or other oral proton-pump inhibitor to prevent peptic disease for the duration of treatment with dexamethasone.

### **5.5.2 Prohibited Concomitant Medications**

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

- Antineoplastic systemic chemotherapy or biological therapy
- G-CSF during Cycle 1, DLT evaluation period only
- GM-CSF
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol

- Investigational agents other than pembrolizumab
- Radiation therapy
  - Note: Radiation therapy to a symptomatic plasmacytoma, bone lesions or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed-virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist) are live attenuated vaccines, and are not allowed.
- Warfarin
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology.

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

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

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

## **5.6 Rescue Medications & Supportive Care**

### **5.6.1 Supportive Care Guidelines**

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. 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 does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1.2 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.

## 5.6.2 Supportive Care Guidelines Specific to Lenalidomide

### 5.6.2.1 Hematologic Toxicity

Lenalidomide can cause significant neutropenia, thrombocytopenia, and anemia. Subjects taking lenalidomide for MM should have complete blood counts repeated every two weeks (on Days 1 and 15 of each cycle) for all cycles. Subjects may require dose interruption and/or dose reduction [See Section 5.2.1.2.3]. Subjects may require use of blood product support and/or growth factors. See recommendations below for the management of cytopenias (Table 17).

Table 17 Recommendations for the Management of Cytopenias

	Recommendations
<b>Neutropenia</b>	If the ANC is $<1.0 \times 10^9/l$ on the first day of a new cycle, withhold lenalidomide treatment add G-CSF and follow CBC weekly until Grade 1 toxicity is reached. Reinitiate treatment at a lower dose (See Section 5.2.1.2.3.1, Table 8).
<b>Febrile neutropenia</b>	Antibiotic prophylaxis should be considered. Subjects should receive clear instructions to seek medical care within 3 hours if febrile while neutropenic. After an occurrence of a prior episode of febrile neutropenia, the use of antibiotic prophylaxis is recommended.
<b>Thrombocytopenia</b>	If the platelet count is $<75 \times 10^9/l$ on the first day of a new cycle, withhold treatment with lenalidomide until Grade 1 toxicity is reached. Reinitiate treatment at a lower dose (see Table 7). If the platelet count is $<25 \times 10^9$ – $50 \times 10^9/l$ during the cycle, withhold anticoagulation. Reinitiate treatment at the next cycle at a lower dose (See Section 5.2.1.2.3.1, Table 7).
<b>Anemia</b>	Erythropoiesis-stimulating agents <sup>1</sup> may be used in subjects with Hb counts of $<100$ g/l, and in symptomatic patients who present with Hb counts of $<120$ g/l, per investigator's discretion. The target level of treatment is an Hb count of 120 g/l, and this should not be exceeded.
Acronyms: ANC: absolute neutrophil count; Hb: hemoglobin. <sup>1</sup> Erythropoiesis-stimulating agents should not be used during Cycle 1 (DLT evaluation period). [56]	

### 5.6.2.2 Venous Thromboembolism

Venous thromboembolic events (VTE) (predominantly deep venous thrombosis and pulmonary embolism) have occurred in subjects with MM treated with lenalidomide combination therapy. See recommendations below for the management of venous thromboembolisms (Table 18).

Table 18 Recommendations for the Management of Venous Thromboembolism.

	Recommendations
<b>Screening</b>	Neither baseline coagulation studies, nor screening for VTE in asymptomatic subjects are recommended. In symptomatic subjects, sonography for the diagnosis of VTE is recommended.
<b>VTE Prophylaxis</b>	A 4 to 6 month course of prophylaxis is recommended in subjects with risk factors. The use of low-dose aspirin (81- 100 mg) is recommended for low VTE risk subjects and prophylactic doses of LMWH are recommended for high risk VTE subjects. <b>Warfarin is prohibited</b> (See Section 5.5.2).
<b>VTE Treatment</b>	The subject can be continued on treatment with lenalidomide plus dexamethasone or re-treated after stabilization depending on the severity of VTE. For therapeutic anticoagulation, subjects previously on aspirin should be switched to LMWH and subjects already on prophylactic doses of LMWH should receive therapeutic doses. Recommend 6 months of therapeutic-dose LMWH, after which prophylaxis can be restarted.
Acronyms: LMWH: low-molecular-weight heparin VTE: venous thromboembolism.	

### 5.6.2.3 Lactose Intolerance

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

### 5.6.2.4 Allergic Reactions

Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported for IMiDs. 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 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 if subject is discontinued for these reactions.

### 5.6.2.5 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.

### 5.6.2.6 Hepatotoxicity

Hepatic failure, including fatal cases, has occurred in subjects treated with lenalidomide in combination with dexamethasone. 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 upon evaluation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

### **5.6.2.7 Second Primary Malignancies**

Subjects with MM treated with lenalidomide in studies including melphalan and stem cell transplantation had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia (AML) and Hodgkin lymphoma, compared to subjects in the control arms who received similar therapy but did not receive lenalidomide. Monitor subjects for the development of second primary malignancies. Take into account both the potential benefit of the lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide.

### **5.6.3 Supportive Care Guidelines Specific for Carfilzomib [Cohort 2]**

#### **5.6.3.1 “First-Dose-Like Effect”**

A “first-dose-like effect” has been encountered in Phase 1 trials with carfilzomib, characterized by fever, chills, shortness of breath, and/or rigors occurring during the evening following the first day of infusion and an increase in creatinine on the subsequent day, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release. Should a “first dose effect” occur, glucocorticoids, IV fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted as medically indicated.

#### **5.6.3.2 Tumor Lysis Syndrome**

Tumor lysis syndrome (TLS), which may be associated with multi-organ failure, has been observed in treatment Cycles 1 and 2 in some subjects with multiple myeloma treated with carfilzomib. All subjects with multiple myeloma are considered to be at potential risk for TLS. In addition, multiple myeloma subjects with high tumor burden should be considered to be at greater risk for TLS. Hydration should be given to all subjects in Cohort 2 in Cycle 1 and at the investigator’s discretion in Cycle 2; premedication with allopurinol or other approved uric acid-lowering agent is optional. Subjects with laboratory abnormalities prior to dosing that are consistent with lysis of tumor cells (e.g., serum creatinine  $\geq$  50% increase, LDH  $\geq$  2-fold increase, uric acid  $\geq$  50% increase, phosphate  $\geq$  50% increase, potassium  $\geq$  30% increase, and calcium  $\geq$  20% decrease) should not receive the scheduled dose. Subjects with such abnormalities should be re-evaluated as clinically indicated. The Medical Monitor should be consulted if there are further delays.

Subjects should be informed of signs and symptoms that may be indicative of TLS, such as fever, chills/rigors, nausea, vomiting, muscle tetany, weakness, or cramping, seizures, and decreased urine output; subjects should be instructed to report such symptoms immediately and seek medical attention.

If TLS manifests, cardiac rhythm, fluid, and serial laboratory monitoring should be instituted. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer therapeutic and supportive care, including dialysis, as clinically indicated.

### **5.6.3.3 Renal Function**

Renal function, serum creatinine, and serum uric acid should be monitored closely. Carfilzomib has been evaluated in a Phase 2 trial in patients with normal renal function and those with mild, moderate, and severe renal impairment and patients on chronic dialysis. In this study, the pharmacokinetics of carfilzomib was not influenced by the degree of baseline renal impairment, including the patients on dialysis. Since dialysis clearance of carfilzomib concentrations has not been studied, the drug should be administered after any dialysis procedure.

Cases of acute renal failure have occurred in patients receiving carfilzomib. Renal insufficiency adverse events (including renal failure) have occurred in approximately 10% of patients treated with carfilzomib. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received carfilzomib monotherapy. This risk was greater in patients with a baseline reduced estimated creatinine clearance (calculated using Cockcroft and Gault equation). Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold carfilzomib doses as appropriate.

See [Table 13](#) for guidance regarding dose reduction in subjects with compromised renal function.

### **5.6.3.4 Hydration**

All subjects should be well hydrated. Subjects at risk of TLS should be hydrated as medically indicated. Those with a history of cardiac disease (such as congestive heart failure and cardiomyopathy) or pulmonary edema should be monitored closely for signs of fluid overload. Carfilzomib treatment can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of antiemetics or antidiarrheal agents. Fluid and electrolyte replacement should be administered as indicated.

## **5.6.4 Other Adverse Events on Combination Therapy**

**Atrial fibrillation:** Monitor on a regular basis.

**Constipation:** Does not require additional prophylaxis or therapy.

**Rash:** In case of rash, treat the subject with antihistamines. If rash is persistent, continuous low-dose prednisone (10–20 mg/day, for 14 days) should be added. Use of corticosteroids should be evaluated in the context of subjects receiving dexamethasone as part of trial treatment. Rash is mostly self-limiting with a duration of several days or weeks, but in some cases dose reduction or discontinuation of lenalidomide is necessary (See Section 5.2.1.2.3.2

Table 9 for dosing levels). Pembrolizumab could cause or exacerbate rash. Please refer to pembrolizumab dose modification guidelines under Section 5.2.1.2.2.

**Fatigue:** Other causes such as anemia, infection, depression, or hypothyroidism should be ruled out. Dose reduction may be considered for severe fatigue (See Section 5.2.1.2.3.2 Table 9 for dosing levels). Please refer to pembrolizumab dose modification guidelines under Section 5.2.1.2.2.

**Infection:** Routine antibiotic prophylaxis, for 3 months upon initiation of treatment, should be considered in all subjects, but is deemed mandatory in all subjects on high-dose dexamethasone, elderly subjects, and in those with a history of increased infection rate. In addition, vaccination against pneumococci, meningococci, and Haemophilus influenzae type b should be considered.

## **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 Blood Donation**

Subjects enrolled in the Dose Determination, Dose Confirmation, and Expansion Cohort 1 must not donate blood during treatment with lenalidomide (REVLIMID®) and for 120 days following discontinuation of lenalidomide because the blood might be given to a pregnant female whose fetus must not be exposed to lenalidomide (REVLIMID®).

### **5.7.3 Contraception**

#### **5.7.3.1 Dose Determination, Dose Confirmation, and Expansion Cohort 1**

Pembrolizumab, lenalidomide<sup>†</sup>, and dexamethasone may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab, lenalidomide, and dexamethasone have transient adverse effects on the composition of sperm. Non-pregnant, non-breastfeeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is  $\geq 45$  years of age and has not had menses for greater than 2 years will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either, two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide, as per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed

contraceptive agent that contains estrogen and/or progestin (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirements (described above) for the duration of the study and during the follow-up period defined in Section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

† Lenalidomide (REVLIMID®) is only available through a restricted distribution program called the REVLIMID REMS™ program in the US (formally known as the “RevAssist® program”).

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

- Prescribers must be certified with the REVLIMID REMS™ program by enrolling and complying with the REMS requirements. Study sites in the United States register with Celgene’s Revlimid REMS® Program prior to prescribing the Celgene Product in accordance with the Revlimid REMS® guidelines. Investigators at Study sites outside of the United States register with the appropriate Celgene risk minimization program in that country prior to prescribing the Celgene product.
- Study investigators must follow the Global Pregnancy Prevention Plan as presented by Revlimid REMS
- Subjects must sign a “Patient-Prescriber agreement form” and comply with the REMS requirements in the United States or the appropriate Celgene risk minimization program for countries outside of the United States. In particular, female subjects of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements. Refer to local product label.
- Pharmacies must be certified with the REVLIMID REMS™ program, must only dispense to subjects who are authorized to receive lenalidomide (REVLIMID®) and comply with REMS requirements. At the termination or conclusion of the study, sites shall direct all patients to return to Celgene any unused quantities of the Celgene product in accordance with the Celgene REMS® Program.
- Further information about the REVLIMID REMS™ program is available at PPD or by telephone at PPD.

Females of Reproductive Potential:

- Females of reproductive potential must avoid pregnancy for at least 4 weeks before beginning lenalidomide (REVLIMID®) therapy, during therapy, during dose interruptions, and for at least 4 weeks after completing therapy.
- Females must commit either to abstain continuously from heterosexual intercourse or to use two methods of reliable birth control, beginning 4 weeks prior to initiating treatment with lenalidomide (REVLIMID®), during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of REVLIMID® therapy.
- Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10 to 14 days and the second test within 24 hours prior to prescribing lenalidomide (REVLIMID) therapy; also, weekly during the first month and monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Refer to local product label for additional details.
- Pregnancy testing and counseling should be performed if a subject misses her period or if there is any abnormality in her menstrual bleeding. Lenalidomide (REVLIMID®) treatment must be discontinued during this evaluation.

Males of Reproductive Potential:

- Lenalidomide (REVLIMID®) is present in the semen of subjects receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide (REVLIMID) and for up to 28 days after discontinuing lenalidomide (REVLIMID®), even if they have undergone a successful vasectomy. Male subjects taking lenalidomide (REVLIMID®) must not donate sperm. Refer to local product label for additional details.

**5.7.3.2 Expansion Cohort 2**

Pembrolizumab and carfilzomib may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab or carfilzomib have transient adverse effects on the composition of sperm.

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

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

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

OR

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

OR

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

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

(1) practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

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



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

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

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

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

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

For women of reproductive potential, one negative pregnancy test must be obtained within 72 hours prior to initiating trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local trial site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated more frequently if required by local guidelines. Pregnancy testing and counseling should be performed if a subject misses her period or if there is any abnormality in her menstrual bleeding.

#### **5.7.4 Use in Pregnancy**

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, lenalidomide\* or carfilzomib, and dexamethasone, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document her status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported as a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn) to the Sponsor without delay and within 24 hours if the outcome. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately, the pregnancy reported to the Sponsor, and followed as described above and in Section 7.2.2.

**\*Lenalidomide (REVLIMID®) can cause fetal harm when administered to a pregnant female. If lenalidomide is used during pregnancy or if the subject becomes pregnant while taking lenalidomide, the subject should be apprised of the potential hazard to the fetus. Refer to local product label for further details.**

#### **5.7.5 Use in Nursing Women**

It is unknown whether pembrolizumab, lenalidomide, carfilzomib or dexamethasone is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment. Because of the potential for serious adverse reactions in nursing infants, breast feeding must be discontinued for the duration of therapy with pembrolizumab, lenalidomide or carfilzomib, and dexamethasone, if applicable. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of drug to the mother. Please refer to lenalidomide, carfilzomib, and dexamethasone local product labels for further information.

#### **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:

- Confirmed disease progression per respective response assessment criteria  
Note: For unconfirmed disease progression, please see Section 5.2.3.
- Unacceptable adverse experiences as described in Section 5.2.1.2.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis
- Intercurrent illness that prevents further administration of treatment.
- Investigator's decision to withdraw the subject.
- The subject has a confirmed positive serum pregnancy test.
- Noncompliance with trial treatment or procedure requirements.

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Trial Flow Chart) and Section 7.1.5 (Visit Requirements). After the End of Treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the End of Treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will move into the Follow-Up Phase to monitor disease status and should be assessed every 4 weeks ( $\pm$  14 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. 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. Information regarding post-study anti-myeloma treatment will be collected if new treatment is initiated. After documented disease progression or the start of new antineoplastic therapy each subject will be followed by telephone every 12 weeks ( $\pm$  7 days) for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

## **5.9 Subject Replacement Strategy**

Additional subjects may be enrolled in a given cohort to ensure that the required number of evaluable subjects in each cohort is achieved. A subject that discontinues treatment for a drug-related AE will not be replaced and will be counted in the evaluable population of subjects for the respective cohort (see also Section 5.2.7).

## **5.10 Beginning and End of the Trial**

The trial begins when the first subject signs the informed consent. The overall trial ends when the last subject completes the last trial visit, a minimum of 6 months have elapsed post last trial assessment, or the last subject either 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. If by the end of the trial, there remains at least 1 subject still on trial treatment for at least 6 months, the subject(s) may enter additional treatment cycles. At this point a database lock of the trial may occur to allow the analysis of the trial data. Any remaining subjects may continue to receive trial treatment and be seen by the investigator per usual standard of care for this subject population. In addition, the investigator will be expected to monitor for and report any serious adverse events, events of clinical interest, and pregnancies, as detailed in Section 7.2.3 (Serious Adverse Experiences). The subject is considered on trial until such time that he/she meets any of the discontinuation criteria and written notification is given to the Sponsor.

## **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 or regulatory requirements;
3. Incidence or severity of adverse drug reaction in this or other trials indicates a potential health hazard to subjects;
4. Plans to modify or discontinue the development of the trial drug.

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

## 6.0 TRIAL FLOW CHART

### 6.1 Trial Flow Chart Dose Determination, Dose Confirmation, and Cohort 1 (rrMM Subjects Allocated to Pembrolizumab Q2W, Lenalidomide and Low-dose Dexamethasone)

Trial Period:	Screening Phase	Treatment Cycles (every 28 days)				End of Treatment	Post-treatment			
		Cycle 1		Cycle 2 and Beyond			Discon <sup>6</sup>	Post-Treatment Safety Follow-up	Efficacy Follow-up Visits	Survival Follow-up
Treatment Cycle/Title:	Screening (Visit 1)									
Cycle Day (visit day) (± 3 days unless otherwise specified)	(-28 to -1 days)	1	15	1	15	At time of Discon	30 days post Discon	Every 4 weeks post Discon (± 14 days)	Every 12 weeks (± 7 days)	
<b>Administrative Procedures</b>										
Informed Consent	X									
Informed Consent for Future Biomedical Research	X									
Inclusion/Exclusion Criteria	X									
Subject Identification Card	X									
Demographics and Medical History	X									
Prior Multiple Myeloma treatment history	X									
International Staging System Criteria	X									
Prior and Concomitant Medication Review	X	X	X	X	X	X	X			
Register REVLAMID REMS™ program	X									
Trial Treatment Administration		See Section 6.1.1		See Section 6.1.1						
Post-study anticancer therapy status								X	X	
Survival Status <sup>7</sup>		←----->								X
<b>Clinical Procedures/Assessments</b>										
Review Adverse Events	X	X	X	X	X	X	X			
Full Physical Examination	X	X		X		X				
Directed Physical Examination			X		X					
Vital Signs and Weight	X	X	X	X	X	X				
12-Lead Electrocardiogram	X									
ECOG Performance Status	X	X	X	X	X	X				
Skeletal survey	X									
MRI /CT/PET	X	As clinically indicated, see Sections 7.1.2.7.2								
Disease Response Assessment by IMWG 2006 criteria [1]				X		X	X <sup>5</sup>	X <sup>5</sup>		

Trial Period:	Screening Phase	Treatment Cycles (every 28 days)				End of Treatment	Post-treatment		
		Cycle 1		Cycle 2 and Beyond			Discon <sup>6</sup>	Post-Treatment Safety Follow-up	Efficacy Follow-up Visits
Treatment Cycle/Title:	Screening (Visit 1)	1	15	1	15	At time of Discon	30 days post Discon	Every 4 weeks post Discon (± 14 days)	Every 12 weeks (± 7 days)
<b>Laboratory Procedures/Assessments: analysis performed by local laboratory</b>									
Pregnancy Test – Urine or Serum β-HCG <sup>1</sup>	X	X	X	X	X				
PT/INR and aPTT	X								
Serum or plasma viscosity	X								
CBC with Differential	X	X	X	X	X	X	X		
Comprehensive blood Chemistry Panel	X	X	X	X	X	X	X		
LDH	X	X		X		X	X		
Urinalysis	X			X			X		
T3 (or FT3 per local standard) FT4 and TSH	X			X			X		
Quantitative Serum Immunoglobulin	X	X		X		X	X <sup>5</sup>	X <sup>5</sup>	
Serum protein electrophoresis and serum immunofixation	X	X		X		X	X <sup>5</sup>	X <sup>5</sup>	
Serum free light chain assay	X	X		X		X	X <sup>5</sup>	X <sup>5</sup>	
24-hr urine protein electrophoresis and urine immunofixation	X	X		X		X	X <sup>5</sup>	X <sup>5</sup>	
M-protein quantitation (urine and/or serum)	X	X		X		X	X <sup>5</sup>	X <sup>5</sup>	
β2 microglobulin	X								
Bone Marrow Aspirate or Biopsy <sup>2</sup>	X								
<b>Laboratory Procedures/Assessments: analysis performed by central laboratory</b>									
Bone Marrow Aspirate <sup>3,4</sup>	X	X		X					
Correlative Studies Blood <sup>3,4</sup>	X	X		X					
Anti-pembrolizumab Antibodies		See Section 6.1.2		See Section 6.1.2			See Section 6.1.2		
Pharmacokinetics for pembrolizumab		See Section 6.1.2		See Section 6.1.2			See Section 6.1.2		
Blood for Future Biomedical Research <sup>4</sup>		X							

1. For women of reproductive potential, two negative pregnancy tests must be obtained prior to initiating trial treatment. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing lenalidomide and administering trial treatments; then weekly during the first month, and monthly (on Day 1 of each Cycle) thereafter in women with regular menstrual cycles or every 2 weeks (on Days 1 and 15) in women with irregular menstrual cycles. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local trial site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated more frequently if required by local guidelines. Pregnancy testing and counseling should be performed if a subject misses her period or if there is any abnormality in her menstrual bleeding. Lenalidomide (REVLIMID) treatment must be discontinued during this evaluation. ***Pharmacies must be certified with the REVLIMID REMS™ program, and must only dispense to subjects who are authorized to receive REVLIMID® and comply with REMS requirements. Refer to Local risk minimization programs for ex-US sites.***
2. Bone marrow analysis will include bone marrow morphology, IHC, and cytogenetics by FISH panel (if FISH not available, then do standard karyotyping). After baseline assessment, bone marrow biopsy or aspirate should be performed as clinically indicated.
3. Blood for correlative biomarker studies to be collected from all subjects at screening or C1D1 and at C2D1. In addition, subjects in the US and Canada only must provide a new bone marrow aspirate sample at screening or C1D1 and at C2D1. Cycle 2 Day 1 bone marrow aspirate is not required for subjects in Cohort 1. Refer to the Procedures Manual for collection and shipping details.
4. If the subject signs the Future Biomedical Research (FBR) consent, any leftover material 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.
5. Required for all subjects who discontinue trial treatment for a reason other than disease progression, until the start of new therapy, disease progression, death or end of study.
6. 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, KN185, and Cohort 1 of KN023 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 (every 12 weeks) per protocol.
7. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).

### 6.1.1 Trial Treatment Administration Schedule Dose Determination, Dose Confirmation, and Cohort 1

Trial Treatment/ Cycle Day (± 3 days window after C1D1)	Cycle Day (Cycle = 28 Days) <sup>5</sup>																											
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Pembrolizumab Q 2 Weeks <sup>1</sup>	X														X													
Lenalidomide <sup>2</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Dexamethasone <sup>3</sup>	X							X							X							X						
Pill count for lenalidomide and dexamethasone <sup>4</sup>	X																											
<sup>1</sup> Pembrolizumab will be administered as 2 mg/kg (Dose Determination) or as 200 mg (Dose Confirmation & Expansion Cohort 1) every two weeks (on Days 1 and 15) of each 28-day cycle as an IV infusion over 30 minutes. <sup>2</sup> Lenalidomide will be administered as 25 mg once daily orally on Days 1-21 of repeated 28-day cycles. <b><i>Lenalidomide must be prescribed through and in compliance with the REVLIMID REMS™ program.</i></b> Refer to local product label. <sup>3</sup> Dexamethasone will be administered as 40 mg once daily orally on Days 1, 8, 15, and 22 of each 28-day Cycle. A dexamethasone dose of 20 mg on Days 1, 8, 15, and 22 in subjects aged >75 years is recommended [56]. Refer to local product label. <sup>4</sup> Site should document drug accountability as per their institutional guidelines. <sup>5</sup> 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, KN185, and Cohort 1 of KN023 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 (every 12 weeks) per protocol.																												



**6.1.2 Pembrolizumab PK and Anti-pembrolizumab Antibodies Procedures during Dose Determination, Dose Confirmation and Cohort 1**

Treatment Cycle/Title:	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Every 3 Cycles through Cycle 24	Discon <sup>5</sup>	Follow-up Visits
Cycle Day	Day 1		Day 15	Day 15	NA	Day 1	Day 1	At time of Discon	30 Days post Discon
Hours		24 hours	96 hours					NA	
<b>Dose Determination:</b> Pharmacokinetics for pembrolizumab <sup>1,2</sup>									
Pre-Infusion	X		X	X		X	X		X
Post-Infusion	X	X	X						
<b>Dose Confirmation &amp; Cohort 1:</b> Pharmacokinetics for pembrolizumab <sup>1,3</sup>									
Pre-Infusion	X		X	X		X	X		X
Post-Infusion	X	X	X			X			
Anti-pembrolizumab Antibodies (ADA) <sup>4</sup>	X		X	X		X	X		X

1. Procedures for sample collection are described in the Procedures Manual.
2. **For the Dose Determination portion of the trial:** All pre-infusion pembrolizumab PK samples should be drawn within 24 hours before infusion. Pre-infusion pembrolizumab PK samples will be collected at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 15, Cycle 4 Day 1, and on Day 1 of each cycle every 3 Cycles thereafter. PK samples will also be collected 30 days after discontinuation of trial treatment (or until the subject starts new anti-cancer therapy). Post-infusion pembrolizumab PK samples will be collected at Cycle 1 Day 1 (within 30 minutes after the end of infusion), Cycle 1 Day 2 (24 hours post-infusion), Cycle 1 Day 5 (96 hours post-infusion) and Cycle 1 Day 15 within 30 minutes after the end of the second infusion.
3. **For the Dose Confirmation and Cohort 1 portion of the trial:** All pre-infusion pembrolizumab PK samples should be drawn within 24 hours before infusion. Pre-infusion pembrolizumab PK samples will be collected at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 15, Cycle 4 Day 1, and on Day 1 of each cycle every 3 Cycles thereafter. PK samples will also be collected 30 days after discontinuation of trial treatment. Post-infusion pembrolizumab PK samples will be collected at Cycle 1 Day 1 (within 30 minutes after the end of infusion), 1 sample between 24 and 96 hours post-infusion, and at Cycle 1 Day 15 (within 30 minutes after the end of the second infusion) and at Cycle 4 Day 1 (within 30 minutes after the end of infusion).
4. Anti-pembrolizumab antibodies should be drawn with all pre-infusion pembrolizumab PK samples (of both the Dose Determination as well as the Dose Confirmation portion of the trial), at 30 days after discontinuation of pembrolizumab.
5. 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, KN185, and Cohort 1 of KN023 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 (every 12 weeks) per protocol.

**6.2 Trial Flow Chart Cohort 2 – (2L rMM Subjects Allocated to Triplet with Pembrolizumab Q3W, Carfilzomib and Low-dose Dexamethasone)**

Trial Period:	Screening Phase	Treatment Cycles (cycle = 28 days)									End of Treatment		Post-treatment			
		To be repeated beyond 3 cycles														
Treatment Cycle/Title: (28 days cycles)	Screening (Visit 1)	Cycle 1				Cycle 2			Cycle 3			Discon <sup>10</sup>	Post-Treatment Safety Follow-up	Efficacy Follow-up Visits	Survival Follow-up	
Cycle Day (visit day) (± 3 days unless otherwise specified)	(-28 to -1 days)	1	8	15	22	1	8	15	1	8	15	At time of Discon	30 days post Discon	Every 4 weeks post Discon (± 14 days)	Every 12 weeks (± 7 days)	
<b>Administrative Procedures</b>																
Informed Consent	X															
Informed Consent for Future Biomedical Research	X															
Inclusion/Exclusion Criteria	X															
Subject Identification Card	X															
Demographics and Medical History	X															
Prior Multiple Myeloma treatment history	X															
International Staging System Criteria	X															
Prior and Concomitant Medication Review	X	X		X	X	X		X	X	X	X	X	X			
Trial Treatment Administration		See Section 6.2.1														
Post-study anticancer therapy status															X	X
Survival Status <sup>9</sup>		←-----→														X
<b>Clinical Procedures/Assessments</b>																
Review Adverse Events	X	X		X	X	X		X	X	X	X	X	X	X		
Full Physical Examination	X					X			X				X			
Directed Physical Examination		X			X			X			X					
Vital Signs and Weight <sup>1</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram with QTc interval <sup>2</sup>	X									X						
ECHO	X															
ECOG Performance Status	X	X				X				X			X			
Skeletal survey	X															
MRI or CT or PET/CT	X	As clinically indicated, see Sections 7.1.2.7.2														
Disease Response Assessment by IMWG 2006 criteria [1]						X				X			X	X <sup>8</sup>	X <sup>8</sup>	

Trial Period:	Screening Phase	Treatment Cycles (cycle = 28 days)									End of Treatment		Post-treatment			
		To be repeated beyond 3 cycles														
Treatment Cycle/Title: (28 days cycles)	Screening (Visit 1)	Cycle 1				Cycle 2			Cycle 3			Discon <sup>10</sup>	Post-Treatment Safety Follow-up	Efficacy Follow-up Visits	Survival Follow-up	
Cycle Day (visit day) (± 3 days unless otherwise specified)	(-28 to -1 days)	1	8	15	22	1	8	15	1	8	15	At time of Discon	30 days post Discon	Every 4 weeks post Discon (± 14 days)	Every 12 weeks (± 7 days)	
<b>Laboratory Procedures/Assessments: analysis performed by local laboratory</b>																
Pregnancy Test – Urine or Serum β-HCG <sup>3</sup>	X	X				X			X							
PT/INR and aPTT	X															
Serum or plasma viscosity	X															
CBC with Differential	X	X		X	X	X		X	X	X	X	X	X			
Comprehensive Blood Chemistry Panel	X	X		X	X	X		X	X		X	X	X			
Abbreviated Blood Chemistry Panel <sup>4</sup>			X				X			X						
LDH	X								X			X	X			
Urinalysis	X								X				X			
T3 (or FT3 per local standard), FT4 and TSH	X								X				X			
Quantitative Serum Immunoglobulin	X	X				X			X			X	X <sup>8</sup>	X <sup>8</sup>		
Serum protein electrophoresis and serum immunofixation	X	X				X			X			X	X <sup>8</sup>	X <sup>8</sup>		
Serum free light chain assay	X	X				X			X			X	X <sup>8</sup>	X <sup>8</sup>		
24-hr urine protein electrophoresis and urine immunofixation	X	X				X			X			X	X <sup>8</sup>	X <sup>8</sup>		
M-protein quantitation (urine and/or serum)	X	X				X			X			X	X <sup>8</sup>	X <sup>8</sup>		
β2 microglobulin	X															
Bone Marrow Aspirate or Biopsy <sup>5</sup>	X															
<b>Laboratory Procedures/Assessments: analysis performed by central laboratory</b>																
Bone Marrow Aspirate <sup>6,7</sup>	X	X				X						X				
Correlative Studies Blood <sup>6,7</sup>	X	X				X						X				
Anti-MK- pembrolizumab Antibodies																See Section 6.2.2
Pharmacokinetics for pembrolizumab																See Section 6.2.2
Blood for Future Biomedical Research <sup>7</sup>		X														

Trial Period:	Screening Phase	Treatment Cycles (cycle = 28 days)									End of Treatment		Post-treatment		
		To be repeated beyond 3 cycles													
Treatment Cycle/Title: (28 days cycles)	Screening (Visit 1)	Cycle 1				Cycle 2			Cycle 3			Discon <sup>10</sup>	Post-Treatment Safety Follow-up	Efficacy Follow-up Visits	Survival Follow-up
Cycle Day (visit day) (± 3 days unless otherwise specified)	(-28 to -1 days)	1	8	15	22	1	8	15	1	8	15	At time of Discon	30 days post Discon	Every 4 weeks post Discon (± 14 days)	Every 12 weeks Follow-up (± 7 days)
<ol style="list-style-type: none"> <li>Vital signs should be collected as outlined in protocol Section 7.1.2.3 at screening, prior to the administration of each dose of trial treatment, including Carfilzomib (see Section 6.2.1), and at treatment discontinuation.</li> <li>12-Lead Electrocardiogram with QTc interval to be performed on Cycle 3, 6, 9, 12 and every 3 cycles thereafter.</li> <li>For women of reproductive potential, one negative pregnancy test must be obtained within 72 hours prior to initiating trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local trial site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated more frequently if required by local guidelines. Pregnancy testing and counseling should be performed if a subject misses her period or if there is any abnormality in her menstrual bleeding.</li> <li>Abbreviated Blood Chemistry Panel to be performed on Day 2, 8 and 9 of each cycle before Carfilzomib administration</li> <li>Bone marrow analysis will include bone marrow morphology, IHC, and cytogenetics by FISH panel (if FISH not available, then do standard karyotyping). After baseline assessment, bone marrow biopsy or aspirate should be performed as clinically indicated.</li> <li>Blood for correlative biomarker studies to be collected from all subjects at screening or C1D1, at C2D1, and at treatment discontinuation. In addition, subjects in the US and Canada only, must provide a new bone marrow aspirate sample at screening or C1D1, at C2D1, and at the time of discontinuation. Refer to the Procedures Manual for collection and shipping details.</li> <li>If the subject signs the Future Biomedical Research (FBR) consent, any leftover material 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.</li> <li>Required for all subjects who discontinue trial treatment for a reason other than disease progression, until the start of new therapy, disease progression, death or end of study.</li> <li>After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).</li> <li>On 15-SEP-2017, the US FDA placed Cohort 2 of KN023, on partial clinical hold. Enrollment was stopped and all subjects who derived clinical benefit from therapy are allowed to continue if reconsented, at least verbally. Enrollment will not be reopened by the sponsor after a full safety and efficacy evaluation did not demonstrate any significant difference from historical controls. Those subjects who are already enrolled and deriving clinical benefit from therapy were allowed to continue if reconsented, at least verbally, and will continue on study until protocol-specific end of treatment, and then progress into long term safety and follow-up. Those subjects who are not deriving clinical benefit, must stop study treatment, complete the Discontinuation Visit and move into the long term safety and follow-up per protocol.</li> </ol>															

### 6.2.1 Trial Treatment Administration Schedule Cohort 2

	Each Cycle = 28 Days (Cycles 1-3 to be repeated beyond 3 cycles) <sup>5</sup>											
	Cycle 1				Cycle 2				Cycle 3			
<b>Trial Treatment/ Day of Cycle</b> (± 3 days window after C1D1)	Days 1-7	Days 8-14	Days 15-21	Days 22-28	Days 1-7	Days 8-14	Days 15-21	Days 22-28	Days 1-7	Days 8-14	Days 15-21	Days 22-28
Pembrolizumab Q 3 Weeks <sup>1</sup>	1			22			15			8		
Carfilzomib <sup>2</sup>	1, 2	8, 9	15, 16		1, 2	8, 9	15, 16		1, 2	8, 9	15, 16	
Dexamethasone <sup>3</sup>	1,2	8,9	15,16	22,23	1,2	8,9	15,16	22,23	1,2	8,9	15,16	22,23
Pill count for dexamethasone <sup>4</sup>	1				1				1			

<sup>1</sup> Pembrolizumab (MK-3475) will be administered as 200 mg every 3 weeks as an IV infusion over 30 minutes

<sup>2</sup> Carfilzomib will be administered as a 30 minute IV infusion two consecutive days each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). The starting dose is 20 mg/m<sup>2</sup>/day in Cycle 1 on Days 1 and 2. If tolerated, the dose should be escalated to a target dose of 56 mg/m<sup>2</sup>/day starting on Day 8 of Cycle 1 and continuing on Day 9, 15, and 16 of Cycle 1, then on Days 1, 2, 8, 9, 15 and 16 of subsequent cycles.

<sup>3</sup> Dexamethasone will be administered as 20 mg orally or IV on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28 day Cycle.

<sup>4</sup> If applicable, site should document drug accountability as per their institutional guidelines.

<sup>5</sup> On 15-SEP-2017, the US FDA placed Cohort 2 of KN023, on partial clinical hold. Enrollment was stopped and all subjects who derived clinical benefit from therapy are allowed to continue if reconsented, at least verbally. Enrollment will not be reopened by the sponsor after a full safety and efficacy evaluation did not demonstrate any significant difference from historical controls. Those subjects who are already enrolled and deriving clinical benefit from therapy were allowed to continue if reconsented, at least verbally, and will continue on study until protocol-specific end of treatment, and then progress into long term safety and follow-up. Those subjects who are not deriving clinical benefit, must stop study treatment, complete the Discontinuation Visit and move into the long term safety and follow-up per protocol.

### 6.2.2 Pembrolizumab PK and Anti-pembrolizumab Antibodies Procedures during Cohort 2

Treatment Cycle/Title:	Cycle 1		Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Every 3 Cycles through Cycle 24	Discon <sup>4</sup>	Follow-up Visits
Cycle Day	1	22	NA	8	22	NA	8	8	NA	30 Days post Discon
<b>Laboratory Procedures/ Assessments:</b> <sup>1</sup>										
Pharmacokinetics for pembrolizumab <sup>2</sup>										
Pre-Infusion	X	X		X	X		X	X		X
Anti-pembrolizumab Antibodies <sup>3</sup>	X	X		X	X		X	X		X
<p>1. Procedures for sample collection are described in the Procedures Manual.</p> <p>2. All pre-infusion pembrolizumab PK samples should be drawn within 24 hours before infusion. Pre-infusion pembrolizumab PK samples will be collected at Cycle 1 Day 1 (Infusion 1), Cycle 1 Day 22 (Infusion 2), Cycle 3 Day 8 (Infusion 4), Cycle 4 Day 22 (Infusion 6), Cycle 6 Day 8 (Infusion 8), and Day 8 of every 3 cycles (every 4 infusions) thereafter. PK samples will also be collected 30 days after discontinuation of trial treatment (or until the subject starts new anti-cancer therapy).</p> <p>3. Anti-pembrolizumab antibodies should be drawn with all pre-infusion pembrolizumab PK samples, and at 30 days after discontinuation of pembrolizumab (or until the subject starts new anti-cancer therapy).</p> <p>4. On 15-SEP-2017, the US FDA placed Cohort 2 of KN023, on partial clinical hold. Enrollment was stopped and all subjects who derived clinical benefit from therapy are allowed to continue if reconsented, at least verbally. Enrollment will not be reopened by the sponsor after a full safety and efficacy evaluation did not demonstrate any significant difference from historical controls. Those subjects who are already enrolled and deriving clinical benefit from therapy were allowed to continue if reconsented, at least verbally, and will continue on study until protocol-specific end of treatment, and then progress into long term safety and follow-up. Those subjects who are not deriving clinical benefit, must stop study treatment, complete the Discontinuation Visit and move into the long term safety and follow-up per protocol.</p>										

## **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 after the subject provides written informed consent.

#### **7.1.1.4 Medical History**

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

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

#### **7.1.1.5 Prior and Concomitant Medications Review**

##### **7.1.1.5.1 Prior Medications**

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

##### **7.1.1.5.2 Concomitant Medications**

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

### **7.1.1.6 Disease Details and Treatments**

#### **7.1.1.6.1 Disease Details**

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

#### **7.1.1.6.2 Prior Treatment Details**

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation, and surgeries.

#### **7.1.1.6.3 Subsequent Antineoplastic Therapy Status**

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

#### **7.1.1.7 Assignment of Screening Number**

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

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

#### **7.1.1.8 Assignment of Randomization Number**

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

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

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

Interruptions from the protocol specified treatment plan for 4 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial treatment will be witnessed by the investigator and/or trial staff. The total volume of pembrolizumab or carfilzomib infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab or carfilzomib administered. The total daily dose of lenalidomide and dexamethasone will be compared to the number of doses a subject reports taking on the pill diary card.

### Medication Compliance

Subject compliance for lenalidomide and dexamethasone will be monitored by pill count. Sites should document drug accountability as per their institutional guidelines. Noncompliant subjects will be instructed about the importance of taking trial treatment as instructed.

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

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 Adverse Event (AE) Monitoring**

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the trial and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.6). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

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

This trial is a dose determination trial to establish the MTD/MAD of the combination therapy; therefore, each dose escalation will be based on the safety and tolerability of the combination therapy as experienced by subjects at each dose level. The safety and tolerability of each cohort will be reviewed prior to the start of the next cohort. The Sponsor and principal investigators will review the safety and tolerability of the trial treatment and communicate the appropriateness of dose escalation, when each cohort is completed and before the next cohort is opened for enrollment. Frequency of these communications will depend on the enrollment of each of the cohorts as well as any potential new information regarding a safety concern seen in this trial or other trials.

As a Phase I trial, there is no plan for an external safety reviewer. Data from individual subjects will be closely followed on an ongoing basis by the Principal Investigator and the Sponsor.

### **7.1.2.2 Physical Exam**

#### **7.1.2.2.1 Full Physical Exam**

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

#### **7.1.2.2.2 Directed Physical Exam**

For cycle days that do not require a full physical exam, the investigator or qualified designee will perform a directed physical exam per the Trial Flow Charts and as clinically indicated prior to trial treatment administration. New clinically significant abnormal findings should be recorded as AEs.

#### **7.1.2.3 Vital Signs**

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

#### **7.1.2.4 Electrocardiogram (ECG)**

In Dose Determination, Dose Confirmation and Cohort 1, a standard 12-lead ECG will be performed using local standard procedures at Screening. Clinically significant abnormal findings should be recorded as medical history.

In Cohort 2, a standard 12-lead ECG with QTc interval will be performed at Screening, Cycle 3, 6, 9, 12 and every 3 cycles thereafter. The QTc interval should be calculated and recorded.

#### **7.1.2.5 Assessment of LVEF using ECHO**

Subjects enrolling to Cohort 2 and receiving Carfilzomib must have a Left Ventricular Ejection Fraction (LVEF) of at least 40% at study entry. Therefore, a screening Echocardiogram (ECHO) must be performed to assess cardiac ejection fraction. Additional echocardiograms may be performed at investigator's discretion as clinically indicated.

### **7.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale**

The investigator or qualified designee will assess ECOG status (See Section 12.5) at Screening, prior to the administration of each dose of the trial treatment, and discontinuation of trial treatment as specified in the Trial Flow Charts (Section 6.0).

### **7.1.2.7 Assessment of Disease and Tumor Imaging**

#### **7.1.2.7.1 Criteria for Assessment of Disease**

The International Myeloma Working Group criteria (IMWG 2006) 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) [1].

#### **7.1.2.7.1.1 Myeloma Disease Measurements**

##### Primary Myeloma Panel

The Primary Myeloma Panel that the investigator followed for subject's disease status should be specified on the trial eCRF. Along with other Myeloma Markers, the clinical site should consistently record and follow the Primary Myeloma Panel throughout the trial.

##### Monoclonal Protein Considerations

Laboratory tests for measurement of Serum M-protein level are quantitated using densitometry on SPEP, except in cases where the SPEP is felt to be unreliable such as in patients with IgA monoclonal proteins migrating in the beta region. If SPEP is not available or is thought to be unreliable (e.g., in some cases of IgA myeloma) for routine M-protein quantitation during therapy, then quantitative immunoglobulin levels on nephelometry or turbidimetry can be accepted. However, this must be explicitly reported, and only nephelometry can be used for that patient to assess response; SPEP and nephelometric values cannot be used interchangeably.

Urine M-protein measurement is estimated using 24-h UPEP only. Random or 24-hr urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended.

See Appendix 12.7 for Myeloma Response Criteria.

#### **7.1.2.7.2 Imaging for Subjects with Myeloma Bone Disease**

Skeletal survey must be performed at baseline to determine the extent of the subject's myeloma bone disease. Skeletal survey should include a chest (PA or AP; lateral), skull (lateral), upper extremities (shoulder to elbow), lower extremities (hip to knee; AP), pelvis (AP), cervical/thoracic/lumbar spine (AP and lateral). A skeletal survey and/or an MRI or CT or PET/CT (according to subject's bone disease or plasmacytoma as clinically indicated)

performed as standard of care prior to signing consent can be used for screening if performed within 28 days of Day 1.

During the course of the trial, imaging should be performed as clinically indicated and, at the time of a complete response assessment, for all subjects without bone disease. For subjects with unmeasurable bone lesions, a skeletal survey should be performed as clinically indicated during the course of the study and at the time of a complete response assessment. Subjects with measurable plasmacytomas at baseline should have imaging performed as clinically indicated and at the time of a complete response assessment.

At any time a subject develops bone pain or there is a suspicion of new bone disease indicative of disease progression, appropriate imaging according to clinical practice should take place to confirm disease progression.

#### **7.1.2.7.3 Disease Assessment of Immunotherapeutic Agents**

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard response assessment criteria may not provide a complete response assessment of immunotherapeutic agents such as pembrolizumab. Therefore in the setting where a subject's assessment shows PD, study drug should not be discontinued unless progression is confirmed at least 4 weeks later, provided that the subject's clinical condition is stable.

#### **7.1.2.7.4 Timing of Disease Assessments**

Disease response will be assessed by the investigator per the International Myeloma Working Group criteria for multiple myeloma (IMWG 2006 Criteria) [1]. Disease response assessment will be performed on day 1 of every 28-day treatment cycle for all cohorts starting C2D1. For subjects with biochemical progression, two consecutive assessments are needed to confirm PD, according to IMWG 2006. In the setting where a subject's disease response assessment shows confirmed PD according to the IMWG 2006 criteria, the subject may continue on study treatment if the investigator considers the subject is deriving clinical benefit from study treatment upon consultation with the Sponsor.

#### **7.1.2.7.5 Initial Disease Assessment**

Initial, baseline 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 or 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.

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

#### **7.1.2.7.6 Disease Assessment During Trial**

Disease assessments should be performed per the frequency defined in Section 6.0 – Trial Flow Charts. There is a  $\pm 3$  day window for assessments performed after Day 1. Disease assessments should not be delayed for delays in cycle starts.

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. Additionally, disease assessments should be performed to confirm complete response or stringent CR or as clinically indicated. Prior to discontinuing patients from therapy, consult with Sponsor and submit the Treatment Termination & Disease Assessment Termination Form.

#### **7.1.2.7.7 Confirmation Assessments**

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.

In the setting where a subject's disease response assessment shows confirmed PD according to the IMWG criteria, the subject may continue on study treatment if the investigator considers the subject is deriving clinical benefit from study treatment upon consultation with the Sponsor. Subjects may only receive treatment after a PD assessment if the following criteria are met:

- Absence of signs and symptoms indicating disease progression;
- No decline in ECOG performance status;
- Absence of rapid progression of disease;
- Absence of progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention.

For any other subjects who have stable disease, minor response, partial response, very good partial response or complete response disease assessments should continue per the regular frequency.

In subjects who discontinue study therapy for reasons other than confirmed disease progression, a response assessment should be performed at the time of treatment discontinuation (i.e. date of discontinuation  $\pm 4$  week window), and then monthly in the follow up phase until disease progression is confirmed, withdraw of consent, initiation of a new anti-myeloma therapy or death, whichever occurs first.

### 7.1.2.7.8 Biopsy Collection and Correlative Studies Blood Collection

#### Dose Determination, Dose Confirmation, Cohort 1

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. Archival ( $\leq 60$  days) bone marrow biopsy or aspirate results, previously done for disease assessment as part of routine clinical management, will be acceptable for screening purposes. Bone marrow analysis will include bone marrow morphology, IHC, and cytogenetics by FISH panel. FISH panel should include del 1p, del 13, del 17p13, t(4;14), t(11;14), t(14;16), and 1q21 amplification. If FISH not available, then do standard karyotyping. Bone marrow biopsies or aspirate samples will be collected as per [Table 19](#).

Additionally, subjects in the US and Canada only must be willing to provide a newly obtained bone marrow aspirate sample at screening or C1D1 and C2D1 for biomarker characterization. However, subjects in Cohort 1 are not required to provide a C2D1 bone marrow aspirate for biomarker characterization.

Whole blood for correlative biomarker studies will be collected at screening or C1D1 and C2D1 for all subjects. These samples must be collected even if a bone marrow aspirate at the same time point is unable to be collected. All samples will be collected as indicated in [Table 19](#).

Table 19 Bone Marrow and Whole Blood Sample Collection (Dose Determination, Dose Confirmation, Cohort 1)

<b>Indication</b>	<b>Timing of Biopsy or Aspirate</b>
Bone marrow biopsy or aspirate for disease characterization at local institution.	<ul style="list-style-type: none"> <li>• Bone marrow biopsy archived material, or newly obtained biopsy or aspirate at Screening</li> <li>• As clinically indicated, or to confirm CR per IMWG.</li> </ul> <p>(See Section 6.0 for Trial Flow Chart and Procedures Manual for further details).</p>
Bone marrow aspirate (US and Canada sites only)	<ul style="list-style-type: none"> <li>• Screening or Cycle 1 Day 1               <ul style="list-style-type: none"> <li>○ For biomarker assessment</li> </ul> </li> <li>• Cycle 2 Day 1 (not required for Cohort 1)               <ul style="list-style-type: none"> <li>○ For biomarker assessment</li> </ul> </li> </ul> <p>(See Section 6.0 for Trial Flow Chart and Procedures Manual for further details).</p>
Whole blood	<ul style="list-style-type: none"> <li>• Screening or Cycle 1 Day 1               <ul style="list-style-type: none"> <li>○ For biomarker assessment</li> </ul> </li> <li>• Cycle 2 Day 1               <ul style="list-style-type: none"> <li>○ For biomarker assessment</li> </ul> </li> </ul> <p>(See Section 6.0 for Trial Flow Chart and Procedures Manual for further details).</p>



Cohort 2

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. Archival ( $\leq 60$  days) bone marrow biopsy or aspirate results previously done for disease assessment as part of routine clinical management will be acceptable for screening purposes. Bone marrow analysis will include bone marrow morphology, IHC, and cytogenetics by FISH panel. FISH panel should include del 1p, del 13, del 17p13, t(4;14), t(11;14), t(14;16), and 1q21 amplification. If FISH is not available, then do standard karyotyping.

Additionally, subjects in US and Canada only, must be willing to provide a newly obtained bone marrow aspirate sample at screening or C1D1, C2D1 and at the time of discontinuation for biomarker characterization.

Whole blood for correlative biomarker studies will be collected at screening or C1D1, C2D1 and at the time of discontinuation for all subjects. These samples must be collected even if a bone marrow aspirate at the same time point is unable to be collected. All samples will be collected as per [Table 20](#).

Table 20 Bone Marrow and Whole Blood Sample Collection (Cohort 2)

Indication	Timing of Biopsy or Aspirate
Bone marrow biopsy or aspirate for disease characterization at local institution.	<ul style="list-style-type: none"> <li>• Bone marrow biopsy archived material, or newly obtained biopsy or aspirate at Screening</li> <li>• As clinically indicated, or to confirm CR per IMWG.</li> </ul> <p>(See Section 6.0 for Trial Flow Chart and Procedures Manual for further details).</p>
Bone marrow aspirate (US and Canada sites only)	<ul style="list-style-type: none"> <li>• Screening or Cycle 1 Day 1               <ul style="list-style-type: none"> <li>○ For biomarker assessment</li> </ul> </li> <li>• Cycle 2 Day 1               <ul style="list-style-type: none"> <li>○ For biomarker assessment</li> </ul> </li> <li>• Treatment Discontinuation               <ul style="list-style-type: none"> <li>○ For biomarker assessment</li> </ul> </li> </ul> <p>(See Section 6.0 for Trial Flow Chart and Procedures Manual for further details).</p>
Whole blood	<ul style="list-style-type: none"> <li>• Screening or Cycle 1 Day 1               <ul style="list-style-type: none"> <li>○ For biomarker assessment</li> </ul> </li> <li>• Cycle 2 Day 1               <ul style="list-style-type: none"> <li>○ For biomarker assessment</li> </ul> </li> <li>• Treatment Discontinuation               <ul style="list-style-type: none"> <li>○ For biomarker assessment</li> </ul> </li> </ul> <p>(See Section 6.0 for Trial Flow Chart and Procedures Manual for further details).</p>

### **7.1.3 Laboratory Procedures/Assessments**

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

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

Laboratory tests for hematology, chemistry, and urinalysis are specified in [Table 21](#).

Table 21 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) <sup>a</sup>
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR) <sup>b</sup>
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT <sup>b</sup>
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total Triiodothyronine (T3) <sup>c</sup>
Red Blood Cell Count	Bicarbonate/Carbon Dioxide <sup>d</sup>	Microscopic exam, if abnormal results are noted	Free thyroxine (T4)
Absolute Neutrophil Count	Calcium	Urine pregnancy test <sup>a</sup>	Thyroid stimulating hormone (TSH)
	Chloride		Anti-pembrolizumab Antibodies
	Creatinine		PK
	GFR		Serum or plasma viscosity
	Uric Acid		
	Calcium		
	Glucose		
	LDH		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen/Urea <sup>e</sup>		

a. Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.  
b. 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.  
c. Free T3 may be performed in place of Total T3 per local standards.  
d. Test only if part of standard of care locally.  
e. Blood urea nitrogen is preferred; if not available, urea may be tested.

Laboratory tests for Screening should be performed within 7 days prior to the first dose of treatment. If laboratory tests for screening are performed within 3 days of Cycle 1 Day 1, the laboratory tests do not need to be repeated at the Cycle 1 Day 1 visit. After Cycle 1, predose 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.

In **Cohort 2**, an abbreviated panel of serum chemistries is performed per the Flow Chart on Day 2, 8, and 9 of each cycle before Carfilzomib administration. The analytes include: albumin, blood urea nitrogen, creatinine, creatinine clearance, glucose, uric acid, bicarbonate, calcium, chloride, phosphorus, potassium, sodium, and lactate dehydrogenase.

### **7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations**

#### **7.1.3.2.1 Blood Collection for Pembrolizumab**

Sample collection, storage, and shipment instructions for samples will be provided in the Procedure Manual.

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

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.

#### **7.1.3.2.2 Blood Collection for Anti-Pembrolizumab Antibodies**

Sample collection, storage and shipment instructions for blood samples will be provided in the Procedures Manual.

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

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 Future Biomedical Research**

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

- Blood for genomics use
- Leftover bone marrow aspirate samples
- Leftover correlative blood samples

## **7.1.4 Other Procedures**

### **7.1.4.1 Withdrawal/Discontinuation**

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 Period**

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

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

- Laboratory tests are to be performed within 7 days prior to the first dose of trial treatment.
- Archival ( $\leq 60$  days) bone marrow biopsy or aspirate results, previously done for disease assessment as part of routine clinical management, will be acceptable for screening purposes.
- For women of reproductive potential assigned to dose determination, dose confirmation or Cohort 1 treated with combination of pembrolizumab, lenalidomide, and dexamethasone, two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- For women of reproductive potential assigned to Cohort 2 treated with the combination of pembrolizumab, carfilzomib, and dexamethasone, one negative pregnancy test must be obtained within 72 hours of initiating therapy. 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 are met.

#### **7.1.5.2 Treatment Period**

Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

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, KN185, and Cohort 1 of KN023 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 (every 12 weeks) per protocol.

On 15-SEP-2017, the US FDA placed Cohort 2 of KN023, on partial clinical hold. Enrollment was stopped and all subjects who derived clinical benefit from therapy are allowed to continue if reconsented, at least verbally. Enrollment will not be reopened by the sponsor after a full safety and efficacy evaluation did not demonstrate any significant difference from historical controls. Those subjects who are already enrolled and deriving clinical benefit from therapy were allowed to continue if reconsented, at least verbally, and will continue on study until protocol-specific end of treatment, and then progress into long term safety and follow-up. Those subjects who are not deriving clinical benefit, must stop study treatment, complete the Discontinuation Visit and move into the long term safety and follow-up per protocol.

### **7.1.5.3 Post-Treatment Visits**

#### **7.1.5.3.1 Safety Follow-Up Visit**

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

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

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-allogeneic SCT, concomitant medications and/or laboratory results may also be reported. Additional medically important AEs may be submitted at the investigator's discretion.

### **7.1.5.4 Efficacy Follow-Up Visits**

Subjects who discontinue for reasons other than progressive disease will move into the Follow-Up Phase to monitor disease status and should be assessed every 4 weeks ( $\pm$  14 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. 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. Information regarding post-study anti-myeloma treatment will be collected if new treatment is initiated.

#### **7.1.5.4.1 Survival Follow-Up**

Once a subject experiences confirmed disease progression or starts a new antineoplastic therapy, the subject moves into the Survival Follow-up phase and should be contacted by telephone approximately every 12 weeks for at least 12 months following their discontinuation visit to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. The first survival follow-up assessment should be scheduled as described below:

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

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

#### **7.1.5.4.2 Follow-up After 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.

Post-allogeneic-stem cell transplant events of clinical interest (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.

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

#### **7.1.5.5 Survival Status**

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor



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

## **7.2 Assessing and Recording Adverse Events**

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

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

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

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

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

All adverse events that occur after the consent form is signed but before 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).

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

For purposes of this trial, an overdose of pembrolizumab (MK-3475) will be defined as any dose of 1,000 mg or greater. No specific information is available on the treatment of overdose of pembrolizumab (MK-3475). In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. An overdose for all other trial treatments will be defined as any dose exceeding the prescribed dose by 20%. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information 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 that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations 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, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious

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

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

### **7.2.3 Immediate Reporting of Adverse Events to the Sponsor**

#### **7.2.3.1 Serious Adverse Events**

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

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

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

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

Refer to [Table 22](#) for additional details regarding each of the above criteria.

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

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

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

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

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

### **7.2.3.2 Events of Clinical Interest**

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

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

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

Events of clinical interest for this trial include:

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

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

### **7.2.3.2.1 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.

Post-allogeneic-stem cell transplant events of clinical interest (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.

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

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

### **7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting**

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3- Immediate Reporting of Adverse Events to the Sponsor. Any such event will be submitted to the Sponsor within 24 hours either by electronic or paper media.

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

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

#### **7.2.4 Evaluating Adverse Events**

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

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

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 22 Evaluating Adverse Events

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

<b>V4.0 CTCAE Grading</b>	<b>Grade 1</b>	<b>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</b>
	<b>Grade 2</b>	<b>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.</b>
	<b>Grade 3</b>	<b>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.</b>
	<b>Grade 4</b>	<b>Life threatening consequences; urgent intervention indicated.</b>
	<b>Grade 5</b>	<b>Death related to AE</b>
<b>Seriousness</b>	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	† <b>Results in death</b> ; or	
	† <b>Is life threatening</b> ; 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	
	† <b>Results in a persistent or significant disability/incapacity</b> (substantial disruption of one's ability to conduct normal life functions); or	
	† <b>Results in or prolongs an existing inpatient hospitalization</b> (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	† <b>Is a congenital anomaly/birth defect</b> (in offspring of subject taking the product regardless of time to diagnosis); or	
	<b>Is a new cancer</b> ; (that is not a condition of the study) or	
	<b>Is an overdose</b> (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. 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.	
	<b>Other important medical events</b> 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 †).	
<b>Duration</b>	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
<b>Action taken</b>	Did the adverse event cause the Sponsor's product to be discontinued?	
<b>Relationship to test drug</b>	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. <b>The following components are to be used to assess the relationship between the Sponsor's product and the AE</b> ; 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):	
	<b>Exposure</b>	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?
	<b>Time Course</b>	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)?
	<b>Likely Cause</b>	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

<b>Relationship to Sponsor's Product (continued)</b>	<b>The following components are to be used to assess the relationship between the test drug and the AE: (continued)</b>	
	<b>Dechallenge</b>	<p>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.)</p>
	<b>Rechallenge</b>	<p>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.</p>
	<b>Consistency with Trial Treatment Profile</b>	<p>Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?</p>
<p>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.</p>		
<b>Record one of the following</b>		<b>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).</b>
<b>Yes, there is a reasonable possibility of Sponsor's product relationship.</b>		<p>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.</p>
<b>No, there is not a reasonable possibility of Sponsor's product relationship</b>		<p>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 there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)</p>



### **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.

## **8.0 STATISTICAL ANALYSIS PLAN**

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are 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, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

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, KN185, and Cohort 1 of KN023 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 (every 12 weeks) per protocol.

On 15-SEP-2017, the US FDA placed Cohort 2 of KN023, on partial clinical hold. Enrollment was stopped and all subjects who derived clinical benefit from therapy are allowed to continue if reconsented, at least verbally. Enrollment will not be reopened by the sponsor after a full safety and efficacy evaluation did not demonstrate any significant difference from historical controls. Those subjects who are already enrolled and deriving clinical benefit from therapy were allowed to continue if reconsented, at least verbally, and will continue on study until protocol-specific end of treatment, and then progress into long term safety and follow-up. Those subjects who are not deriving clinical benefit, must stop study treatment, complete the Discontinuation Visit and move into the long term safety and 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**

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

### 8.1.1 Efficacy Analyses

The primary and key secondary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in [Table 23](#) below.

The objective response rate (ORR) per 2006 International Myeloma Working Group criteria (IMWG 2006) based on investigator assessment will be conducted in the All-Subjects-as-Treated (ASaT) population. No multiplicity adjustment is planned.

Table 23 Summary of Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time point)	Statistical Method	Analysis Population	Missing Data Approach
ORR and DCR per IMWG 2006 criteria based on investigator assessment	Point estimate, Clopper-Pearson 95% CI	ASaT	Subjects with missing data are considered as non-responders

### 8.1.2 Safety Analyses

The All-Subjects-as-Treated (ASaT) population will be employed for safety analyses. DLT will be summarized by dose level for the Dose Determination stage and Dose Confirmation stage. Descriptive tables that summarize the number and percentage of subjects that experience adverse events as categorized in the NCI CTCAE Version 4 will be generated by dose level.

### 8.1.3 Power and Sample Size

The sample size of the Dose Determination stage of the study depends primarily on clinical considerations rather than on statistical considerations. Specifically, the final number of subjects enrolled in the trial will depend on empirical safety (DLT) observations. However, it is estimated that a maximum of 12 subjects evaluable for safety and tolerability will be enrolled in the Dose Determination portion of this trial to adequately assess the toxicity of pembrolizumab in combination with lenalidomide and low-dose dexamethasone. If lenalidomide toxicity is observed, then 6 to 12 additional subjects may be enrolled to further evaluate pembrolizumab and lenalidomide/low-dose dexamethasone with a lower dose of lenalidomide.

The Dose Confirmation stage will enroll a small cohort of subjects (approximately 7-13) to establish the MTD/MAD fixed dose evaluated for efficacy; and the Expansion Cohort stage of the study will enroll approximately up to 45 subjects in each cohort.

## 8.2 Statistical Analysis Plan

### 8.2.1 Responsibility for Analyses

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

The preliminary Dose Determination stage, the Dose Confirmation stage and the Expansion Cohort stage of the study will be conducted as an open-label study.

The Clinical Biostatistics department will generate an allocation schedule for all enrolled subjects.

### 8.2.2 Hypotheses/Estimation

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

### 8.2.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated by dosing schedules, dose levels and disease-specific cohorts are listed below.

#### 8.2.3.1 Efficacy Endpoints

Key efficacy endpoints for the trial are listed below.

- ORR: defined as the proportion of subjects who have achieved a response (Partial Response or better) by investigator assessment. Subjects with missing outcome on objective response will be considered non-responders.
- DCR: defined as the proportion of subjects who have achieved a response (Partial Response or better) or have demonstrated stable disease for at least 12 weeks prior to any evidence of progression.

Exploratory endpoints include:

- DOR: for subjects who demonstrate a response (Partial response or better), duration of response is defined as the time from first documented evidence of a response until disease progression or death due to any cause, whichever occurs earlier. The censoring rules for DOR are summarized in [Table 24](#).
- PFS: defined as the time from first day of study treatment to first documented progressive disease (PD) or death due to any course, whichever occurs earlier. Subjects without documented PD/death will be censored at the last disease assessment date.
- TTP: defined as the time from first dose to first documented progressive disease (PD). Subjects without documented PD will be censored at the last disease assessment date.

In addition, overall survival (OS) and change from baseline in bone marrow/aspirate PD-L1 expression will also be evaluated.

### **8.2.3.2 Safety Endpoints**

The primary safety endpoints of the study include the DLT rate and AEs graded using CTCAE (Version 4.0) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including serious AEs and events of clinical interest (ECIs). Other safety endpoints include laboratory safety assessments, vital signs and physical examinations. Safety measurements are described in Section 7.

## **8.2.4 Analysis Populations**

### **8.2.4.1 Efficacy Analysis Populations**

The All Subjects as Treated (ASaT) population will be used for the analysis of efficacy data in this trial. The ASaT population consists of all subjects who received at least one dose of trial treatment. Subjects will be analyzed according to the assigned dose level. The analysis of response duration is based on all responders. Details on the approach to handling missing data are provided in Section 8.2.5 Statistical Methods. In addition, a response evaluable population will be used for supportive analyses for the primary efficacy endpoints (ORR and DCR) and will consist of all treated subjects who have at least two post-baseline efficacy assessments and did not have a significant major protocol violation at study entry as defined by the Sponsor.

### **8.2.4.2 Safety Analysis Populations**

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this trial. The ASaT population consists of all subjects who received at least one dose of trial treatment. Subjects will be analyzed according to the assigned dose level. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

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

For safety analysis related to DLT rate, the DLT evaluable population will be used. The DLT evaluable population consists of all DLT evaluable subjects. In order to be considered evaluable, the subject must complete the first cycle of combination therapy or discontinue from the trial due to a drug-related adverse event. Subjects who discontinue prematurely due to a non drug-related cause are not included in the DLT evaluable population.

## 8.2.5 Statistical Methods

### 8.2.5.1 Statistical Methods for Efficacy Analyses

Efficacy analyses will be performed separately by treatment and by Cohort. The pembrolizumab 2 mg/kg dose and 200 mg fixed dose will be combined for the same lenalidomide dose level. Subjects from the Dose Determination and Dose Confirmation stages who were treated with the same study treatment as Expansion Cohort 1 will be combined with subjects from Expansion Cohort 1. For other subjects who were enrolled during the Dose Determination and Dose Confirmation stages, given the small number of subjects in each treatment group, efficacy results, such as objective response, PFS and OS, will be listed only.

For the efficacy endpoints ORR and DCR, the point estimate and 95% confidence intervals will be provided using the Clopper-Pearson methods. There is no plan for any formal comparison between any two treatment regimens of the Expansion Cohort stage.

Since subjects who have progressed by investigator assessment may continue study treatment, supportive analyses (point estimate and 95% confidence intervals) will be conducted for ORR to consider these subjects who later achieve partial response or better post-progression as responders.

Kaplan-Meier estimates of time to event endpoints, including DOR, PFS, TTP and OS, will be provided for each treatment.

For DOR, the censoring rules are summarized in [Table 24](#). Subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, and have not been determined to be lost to follow-up are considered responders at the time of analysis.

Table 24 Censoring Rules for the Analysis of DOR

Situation	Date of progression or censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate assessment before new anti-cancer therapy initiated	Censor (non-event)
≥ 2 consecutive missed adequate disease assessments at any time prior to progression or death	Last adequate assessment prior to ≥ 2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤ 1 missed adequate disease assessments	Death or progression	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response. Subjects are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anti-cancer therapy, have not had ≥ 2 consecutive missed disease assessments, and have not been determined to be lost to follow-up.		

For PFS, subjects without documented PD/death will be censored at the last disease assessment date. For OS, subjects without documented death at the time of analysis will be censored at the last known alive date. For TTP, subjects without documented PD will be censored at the last disease assessment date. [Table 25](#) summarizes the primary efficacy analyses; supportive analyses for the primary efficacy endpoints (ORR and DCR) will also be conducted in the response evaluable population defined in Section 8.2.4.1.

Table 25 Analysis Strategy for Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Analysis Population	Statistical Method	Missing Data Approach
ORR and DCR per IMWG 2006 criteria based on investigator assessment	P	ASaT	Point estimate, Clopper-Pearson 95% CI	Subjects with missing data are considered as non-responders
DOR per IMWG 2006 criteria based on investigator assessment	P	All responders	Summary statistics using Kaplan-Meier method	Non-responders are excluded in analysis
PFS per IMWG 2006 criteria based on investigator assessment	P	ASaT	Summary statistics using Kaplan-Meier method	Censored at last disease assessment date
OS	P	ASaT	Summary statistics using Kaplan-Meier method	Censored at the last date known to be alive
TTP per IMWG 2006 criteria based on investigator assessment	P	ASaT	Summary statistics using Kaplan-Meier method	Censored at the last non-PD assessment date
P=Primary approach; ASaT = All Subjects as Treated; CI = Confidence interval				

### 8.2.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), ECOG, laboratory tests, vital signs, and ECG measurements, and will be performed separately by treatment. The pembrolizumab 2 mg/kg dose and 200 mg fixed dose will be combined for the same lenalidomide dose level.

Dose limiting toxicities will be summarized and listed for the Dose Determination stage and Dose Confirmation stage.

Summary statistics (median and range) for time to first Grade 3-5 AE, which is defined as the time from the first day of study treatment to the first event of Grade 3-5 AE, will be provided. Adverse experiences will be summarized as counts, frequencies and grade by NCI CTCAE version 4.0 for each dose level of each combination regimen. Laboratory values will

be graded by NCI CTCAE version 4.0. The percentage of subjects with laboratory abnormalities by grades will be tabulated. The change of grades during the study will be summarized by a lab shift table. In this analysis, the percentage of subjects who improve or worsen from baseline for each laboratory test will be summarized. A clinically meaningful worsening in CTCAE grade was defined as a shift from less than Grade 3 at baseline to Grade 3 or above, or a shift from Grade 0 to Grade 2. Summary statistics for baseline, on treatment, and change from baseline values of continuous measures such as changes from baseline in laboratory and vital signs will be provided by dose level in table format. Immune-related AEs (irAEs) that are designated as events of special interest will be summarized separately from other AEs.

### **8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses**

#### Demographic and Baseline Characteristics

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 screened, the primary reasons for screening failure, 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.

#### Other Analyses

Change from baseline in bone marrow aspirate/biopsy PD-L1 expression will be summarized by dosing schedules using descriptive statistics.

### **8.2.6 Multiplicity**

There is no multiplicity adjustment planned for this study.

### **8.2.7 Sample Size and Power Calculations**

The sample size of the study depends primarily on clinical considerations rather than on statistical considerations; see Section 5.2.5 for details

### **Stage 1: Dose Determination (Cohort 1)**

The final number of subjects enrolled in the Dose Determination stage of the trial will depend on empirical safety (DLT) observations. A standard 3+3 dose scheme will be applied in the preliminary dose finding portion of the study for each regimen. A maximum of 12 subjects (6 subjects per dose level) will be enrolled in each dosing schedule of pembrolizumab in combination with lenalidomide and dexamethasone. If lenalidomide toxicity is observed during Dose Determination, then 6-12 additional subjects may be enrolled to further evaluate the triplet with a lower dose of lenalidomide.

### Stage 2: Dose Confirmation (Cohort 1)

The Dose Confirmation stage will enroll 7-13 subjects for a total of 13 in all when combined with subjects in the Dose Determination stage. Table 16 summarizes the operating characteristics the TPI design.

### Stage 3: Expansion Cohort (Cohorts 1 and 2)

The Expansion Cohort stage of the study will enroll approximately up to 45 treated subjects, allowing for subjects who are not response evaluable in each cohort, to further assess safety and preliminary efficacy. Table 26 displays the two-sided 95% CIs of ORR with the sample size of 30 response evaluable subjects for different observed response rates based on the method of Clopper and Pearson (1934) [67] with a maximum half-width of 19%. For a sample size of 45 subjects, the precision of the CI is greater, with a maximum half-width of 15%.

Table 26 Two-sided 95% Confidence Intervals of ORR with 30 Subjects

Number of Observed Responders	ORR Estimates (%)	95% CI of ORR (%)
10	33.3	(17.3, 52.8)
15	50.0	(31.3, 68.7)
20	66.7	(47.2, 82.7)
25	83.3	(65.3, 94.4)

### 8.2.8 Subgroup Analyses and Effect of Baseline Factors

There is no formal subgroup analysis for this study.

### 8.2.9 Interim Analysis

There is no planned interim analysis for this study.

### 8.2.10 Compliance (Medication Adherence)

For IV drugs, drug accountability data for trial treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

Compliance with oral drugs will be assessed using the prime therapy records provided in the electronic Case Report Forms (eCRFs). Compliance will be defined as the percentage of the “Number of Days on Therapy” over the “Number of Days Should be on Therapy”. A day within the study will be considered an “On-Therapy” day if the subject takes study drug on a scheduled day for treatment administration without dose variation or with dose variation, including dose reduction and dose interruption, for reasons other than noncompliance. For each subject, the “Number of Days Should be on Therapy” is the total number of scheduled days for treatment administration from entry to the study to the date of discontinuation.



For each subject, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100.$$

Summary statistics will be provided on percent compliance by treatment group for the ASaT population.

### 8.2.11 Extent of Exposure

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

## 9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

### 9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in [Table 27](#).

Table 27 Product Descriptions

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

All other supplies not indicated in [Table 27](#) 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 for recording 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.

Pembrolizumab vials will be provided in an open label fashion for subject dosing.

## **9.3 Clinical Supplies Disclosure**

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. 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 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.

## **10.0 ADMINISTRATIVE AND REGULATORY DETAILS**

### **10.1 Confidentiality**

#### **10.1.1 Confidentiality of Data**

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

### **10.1.2 Confidentiality of Subject Records**

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

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

### **10.1.3 Confidentiality of Investigator Information**

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

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

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

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

### **10.1.4 Confidentiality of IRB/IEC Information**

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

## **10.2 Compliance with Financial Disclosure Requirements**

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

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

## **10.3 Compliance with Law, Audit and Debarment**

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

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

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

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

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

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

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

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

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

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

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national

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

#### **10.4 Compliance with Trial Registration and Results Posting Requirements**

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

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

#### **10.5 Quality Management System**

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

## 10.6 Data Management

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

Detailed information regarding Data Management procedures for this protocol will be provided by the Sponsor.

## 10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on [www.clinicaltrials.gov](http://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](http://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.<sup>1</sup>
- b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.<sup>2</sup>
- c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.<sup>2</sup>
- d. DNA: Deoxyribonucleic acid.
- e. RNA: Ribonucleic acid.

### **2. Scope of Future Biomedical Research**

The DNA, blood, and bone marrow specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug/vaccine. The DNA, blood, and bone marrow specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

### **3. Summary of Procedures for Future Biomedical Research**

#### **a. Subjects for Enrollment**

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

#### **b. Informed Consent**

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

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

Subjects are not required to participate in Future Biomedical Research in order to participate in the main trial. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main trial.

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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

#### 4. Confidential Subject Information for Future Biomedical Research

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

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

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

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

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

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

## **5. Biorepository Specimen Usage**

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

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens.

Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in the FBR contract. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

## **6. Withdrawal From Future Biomedical Research**

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

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

## **7. Retention of Specimens**

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

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

## **8. Data Security**

Separate databases for specimen information and for results from Future Biomedical Research will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research

personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only and will not be used for any other purpose.

## **9. Reporting of Future Biomedical Research Data to Subjects**

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

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

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

## **10. Gender, Ethnicity and Minorities**

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

## **11. Risks Versus Benefits of Future Biomedical Research**

For future biomedical research risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time routine blood specimens are drawn in the main trial.

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

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

## **12. Self-Reported Ethnicity**

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

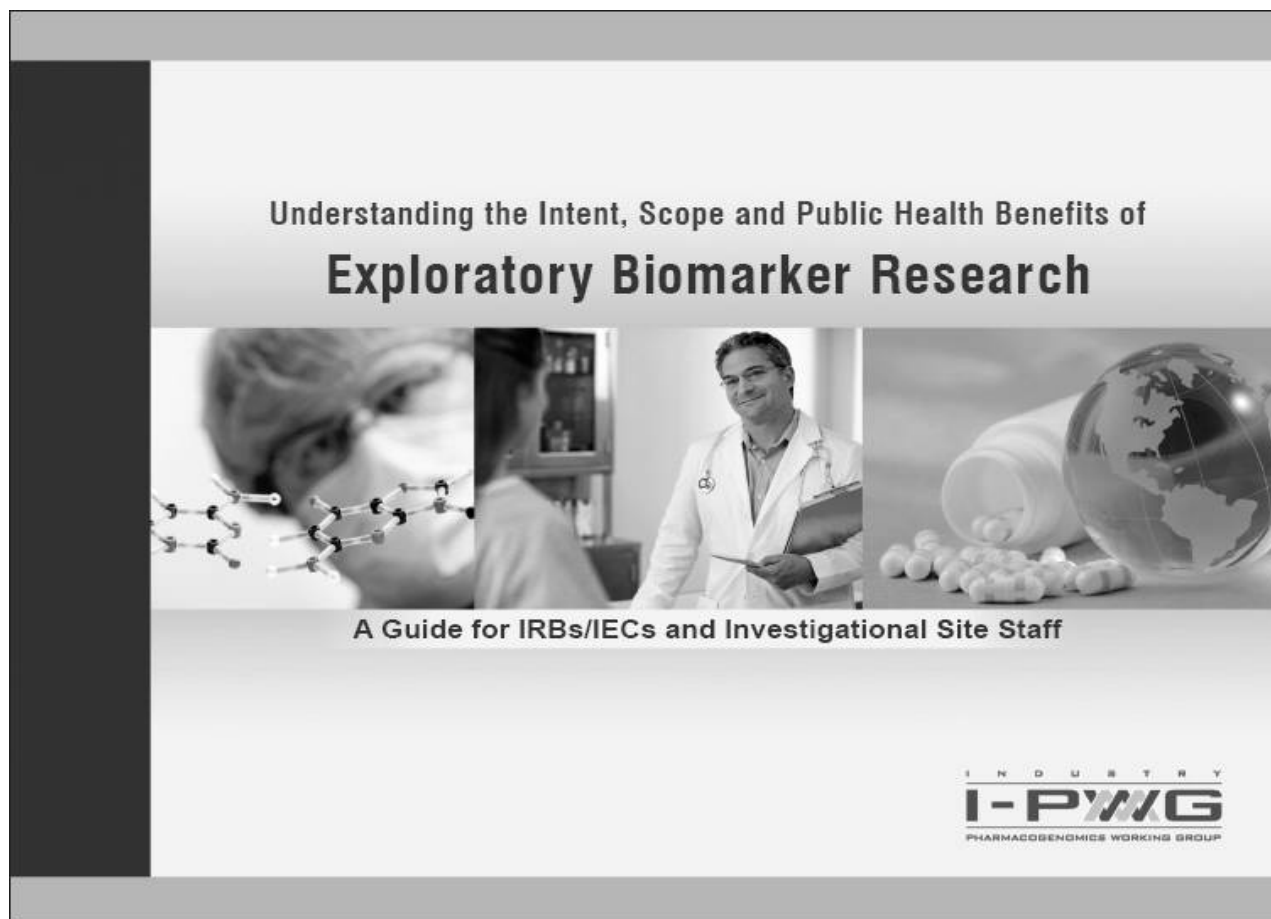
## **13. Questions**

Any questions related to the future biomedical research should be e-mailed directly to [clinical.specimen.management@merck.com](mailto:clinical.specimen.management@merck.com).

## **14. References**

1. National Cancer Institute: <http://www.cancer.gov/dictionary/?searchTxt=biomarker>
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html>

### 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](http://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".<sup>1</sup>

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<sup>2</sup> and ICH Guidance E15<sup>3</sup> 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.<sup>4</sup> 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/](http://www.fda.gov/oc/initiatives/criticalpath/); in the EU: [www.imi.europa.eu/index\\_en.html](http://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).<sup>5</sup> 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](http://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.<sup>3, 6-24</sup>

### 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.<sup>7</sup> Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.

## 5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.<sup>25</sup> 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<sup>®</sup>) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec<sup>®</sup>) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix<sup>®</sup>) or cetuximab (Erbix<sup>®</sup>) 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<sup>®</sup>) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B\*57:01* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen<sup>®</sup>).

**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<sup>®</sup>), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as sur-

rogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

**Prognostic biomarkers** – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch<sup>™</sup> 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.<sup>26-27</sup>

## 7. Informed Consent for Collection & Banking of Biomarker Samples

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

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.<sup>29-31</sup>

#### 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

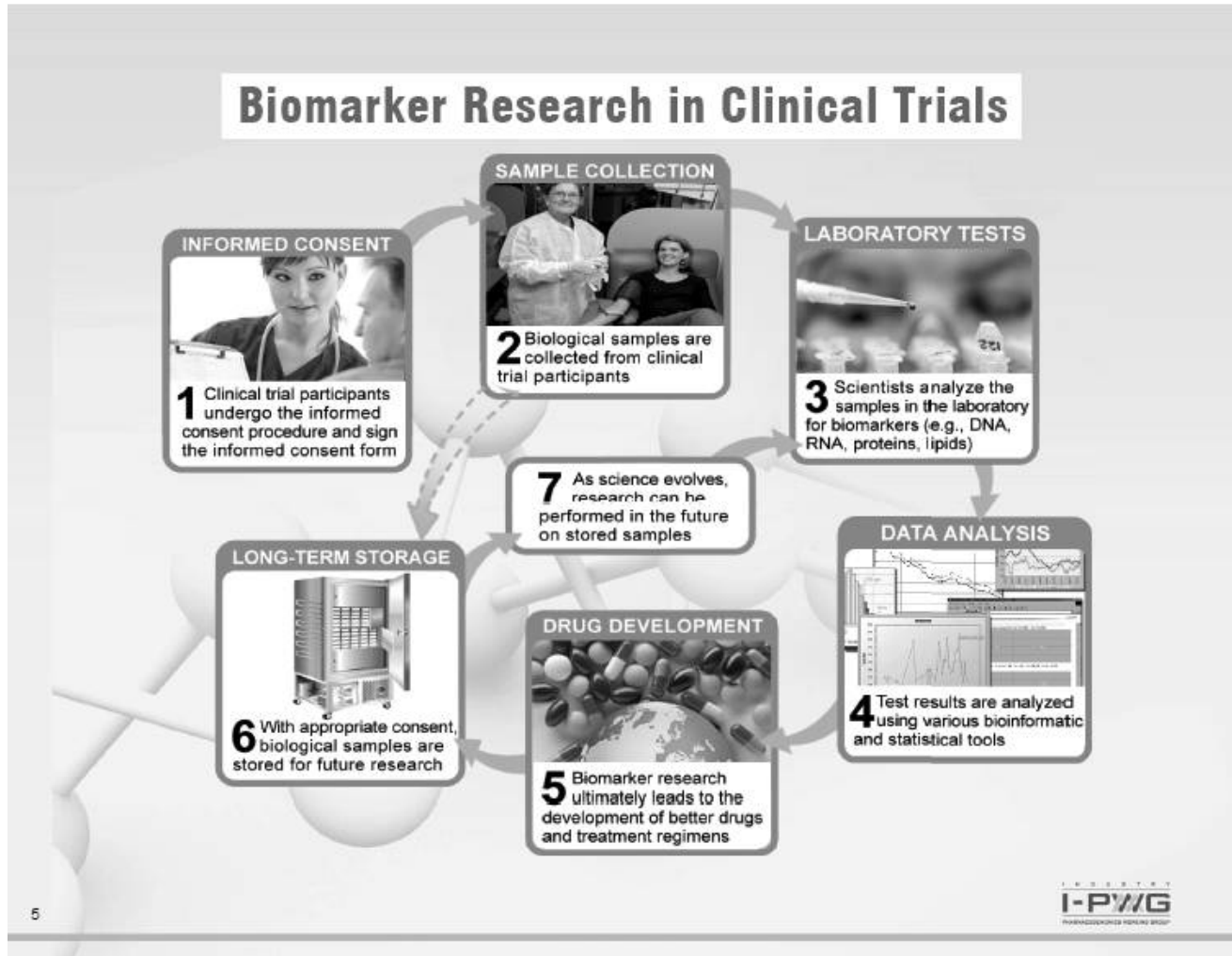
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants 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.<sup>3, 31</sup> 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:<sup>30</sup>

**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.<sup>3</sup> 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.<sup>38</sup>

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



## 8. Biomarker Sample Collection in Different Countries

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

## 9. Return of Research Results to Study Participants

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

- i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)
- ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable
- iii) whether genetic counseling is recommended (for genetic results)
- iv) the ability to accurately link the result to the individual from whom the sample was collected
- v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

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

## 10. Benefits and Risks Associated with Biomarker Research

### Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbix<sup>®</sup>) and panitumumab (Vectibix<sup>®</sup>) 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.<sup>28,33</sup> 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.<sup>28,32</sup>

### Risks

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

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

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

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

### 11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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).<sup>36-37</sup>

### 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](http://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-

ities and policy groups to ensure alignment. More information about the I-PWG is available at: [www.i-pwg.org](http://www.i-pwg.org).

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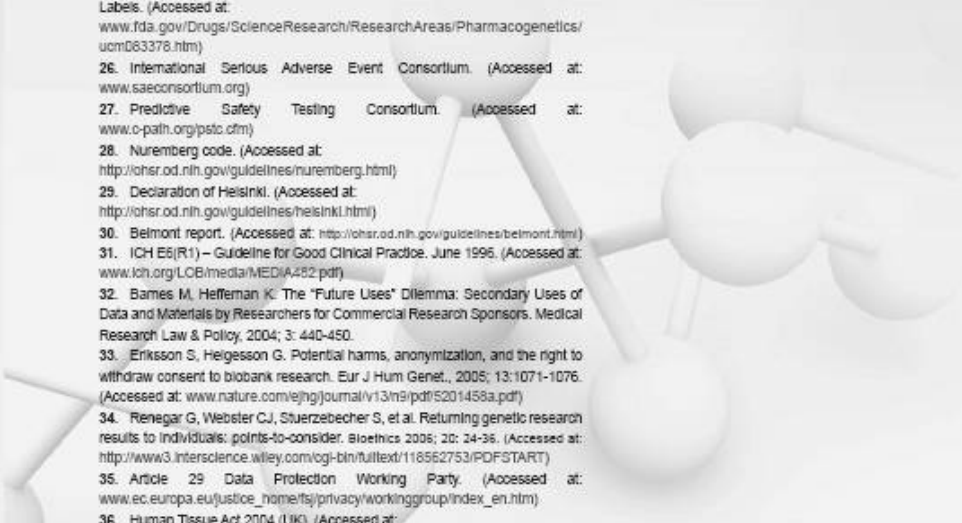
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9





## 12.4 Multiple Myeloma Diagnostic Criteria

Durie, Seminars in Oncology, Vol 13, No 3 (September), 1986: pp300-309:

1. Criteria for Diagnosis of Multiple Myeloma
  - Major criteria
    - I. Plasmacytoma on tissue biopsy.
    - II. Bone marrow plasmacytosis with >30% plasma cells.
    - III. Monoclonal globulin spike on serum electrophoresis exceeding 3.5 g/dL for IgG peaks or 2.0 g for IgA peaks,  $\geq 1.0$  g/24 h of  $\kappa$  or  $\lambda$  light chain excretion on urine electrophoresis in the absence of amyloidosis.
  - Minor criteria
    - a. Bone marrow plasmacytosis with 10% to 30% plasma cells.
    - b. Monoclonal globulin spike present, but less than the levels defined above.
    - c. Lytic bone lesions.
    - d. Normal IgM <50 mg, IgA <100 mg, or IgG <600 mg/dL.

Diagnosis will be confirmed when any of the following features are documented in symptomatic patients with clearly progressive disease. The diagnosis of myeloma requires a minimum of one major + one minor criterion or three minor criteria that must include a + b

  1. I + b, I + c, I + d (I + a not sufficient)
  2. II + b, II + c, II + d.
  3. III + a, III + c, III + d.
  4. a + b + c, a + b + d.
2. Criteria for Monoclonal Gammopathy of Undetermined Significance (MGUS), Indolent Myeloma and Smoldering Myeloma (Stage I or IIA)
  - i. MGUS
    - I. Monoclonal gammopathy
    - II. M component level  
IgG  $\leq 3.5$  g/dL  
IgA  $\leq 2.0$  g/dL  
BJ  $\leq 1.0$  g/24 h
    - III. Bone marrow plasma cells <10%
    - IV. No bone lesions
    - V. No symptoms
  - ii. Indolent myeloma: Criteria as for myeloma (I above) with the following limitations:
    - I. No bone lesions or only limited bone lesions ( $\leq 3$  lytic lesions); no compression fractures
    - II. M component levels
      - a. IgG <7 g/dL
      - b. IgA <5 g/dL
    - III. No symptoms or associated disease features
      - a. Performance status >70%\*
      - b. Hemoglobin >10 g/dL
      - c. Serum calcium: normal
      - d. Serum creatinine <2.0 mg/dL
      - e. No infections

Smoldering Myeloma: Criteria as for indolent myeloma with additional constraints:

  - I. There must be no demonstrable bone lesions
  - II. Bone marrow plasma cells  $\geq 10\% \leq 30\%$

### 12.5 ECOG Performance Status

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

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

## **12.6 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)**

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (<http://ctep.cancer.gov>)

## 12.7 MM Disease Response Criteria

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

Criteria for multiple myeloma disease assessment:

<i>Response subcategory</i>	<i>Response criteria<sup>a</sup></i>
sCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow <sup>b</sup> by immunohistochemistry or immunofluorescence <sup>c</sup>
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow <sup>b</sup>
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h If the serum and urine M-protein are unmeasurable, <sup>d</sup> a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

<sup>a</sup>All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

<sup>b</sup>Confirmation with repeat bone marrow biopsy not needed.

<sup>c</sup>Presence/absence of clonal cells is based upon the  $k/\lambda$  ratio. An abnormal  $k/\lambda$  ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is  $k/\lambda$  of >4:1 or <1:2.

<sup>d</sup>Refer to Table 4 for definitions of measurable disease.

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

<i>Relapse subcategory</i>	<i>Relapse criteria</i>
<p>Progressive disease<sup>a</sup>                      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)</p>	<p>Progressive Disease: requires any one or more of the following:</p> <p>Increase of <math>\geq 25\%</math> from baseline in                      Serum M-component and/or (the absolute increase must be <math>\geq 0.5</math> g/dl)<sup>b</sup>                      Urine M-component and/or (the absolute increase must be <math>\geq 200</math> 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 <math>&gt; 10</math> mg/dl.                      Bone marrow plasma cell percentage: the absolute % must be <math>\geq 10\%</math><sup>c</sup>                      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 <math>&gt; 11.5</math> mg/dl or <math>2.65</math> mmol/l) that can be attributed solely to the plasma cell proliferative disorder</p>
<p>Clinical relapse<sup>a</sup></p>	<p>Clinical relapse requires one or more of:                      Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)<sup>b</sup> 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</p> <ol style="list-style-type: none"> <li>1. Development of new soft tissue plasmacytomas or bone lesions</li> <li>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</li> <li>3. Hypercalcemia (<math>&gt; 11.5</math> mg/dl) [<math>2.65</math> mmol/l]</li> <li>4. Decrease in hemoglobin of <math>\geq 2</math> g/dl [<math>1.25</math> mmol/l] (see Table 3 for further details)</li> <li>5. Rise in serum creatinine by 2 mg/dl or more [<math>177</math> <math>\mu</math>mol/l or more]</li> </ol>
<p>Relapse from CR<sup>a</sup>(To be used only if the end point studied is DFS)<sup>d</sup></p>	<p>Any one or more of the following:                      Reappearance of serum or urine M-protein by immunofixation or electrophoresis                      Development of <math>\geq 5\%</math> plasma cells in the bone marrow<sup>c</sup>                      Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see below)</p>

Abbreviations: CR, complete response; DFS, disease-free survival.

<sup>a</sup>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.

<sup>b</sup>For progressive disease, serum M-component increases of  $\geq 1$  gm/dl are sufficient to define relapse if starting M-component is  $\geq 5$  g/dl.

<sup>c</sup>Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

<sup>d</sup>For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

Durie et al. Corrigendum: International uniform response criteria for multiple myeloma. *Leukemia*. 2007; 21:1134.

Correction to the above tables of criteria for multiple myeloma disease assessment:

Table 5: Bone marrow criteria for CR should be '<5% plasma cells' and not ' $\leq 5\%$  plasma cells'.

Table 6: Relapse criteria for progressive disease should state 'Increase of  $\geq 25\%$  from lowest response level' and not 'Increase of  $\geq 25\%$  from baseline'.

## 12.8 List of Abbreviations

Abbreviation/Term	Definition
AE	Adverse event
ADA	Anti-Drug/pembrolizumab Antibodies
ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
ALT	Alanine aminotransferase
AML	Acute Myelogenous Leukemia
ANC	Absolute neutrophil count
APC	Antigen Presenting Cells
aPTT	Activated partial thromboplastin time
ASaT	All Subjects as Treated
AUC	Area Under Curve
AST	Aspartate aminotransferase
β-HCG	Beta human chorionic gonadotropin
CBC	Complete blood count
CDC	Complement-Dependent Cytotoxicity
CNS	Central nervous system
CR	Complete response
CrCl	Calculated creatinine clearance
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	Cytotoxic T Lymphocytes
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
Dex	Dexamethasone
DL	Dose Level
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of Response
ECI	Events of clinical interest
ECI-ie	Events of clinical interest with a potential immunologic etiology
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERC	Ethics review committee
FAS	Full analysis set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FLC	Free Light Chain



Abbreviation/Term	Definition
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
Hb	Hemoglobin
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IMiD	Immunomodulatory
IMWG	International Myeloma Working Group
INR	International normalized ratio
irAEs	Immune-related adverse events
IRB	Institutional Review Board
ISS	International Staging System
ITIM	Immunoreceptor tyrosine-based switch motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
IV	Intravenous
K	Carfilzomib (Kyprolis®)
Kg	kilogram
LDH	lactate dehydrogenase
Len	Lenalidomide
LMWH	Low-molecular weight heparin
mAb	Monoclonal antibody
MAD	Maximum administered dose
mcL	Millimeters
MEL	Melanoma
MG	Milligram
Mg/kg	Milligram per kilogram
ML	milliliter
MM	Multiple Myeloma
MRI	Magnetic resonance imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MTD	Maximum tolerated dose
NA or N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	Natural Killer
NSAID	Non-steroidal anti-inflammatory drug
ORR	Overall response rate
OS	Overall survival
OTC	Over-the-counter

Abbreviation/Term	Definition
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
PGt	Pharmacogenetic
PK	Pharmacokinetic
PK-PD	Pharmacokinetic-Pharmacodynamic
PO	Oral administration
PR	Partial response
PT	Prothrombin time
rMM	Refractory or relapsed multiple myeloma
rrMM	Refractory or relapsed and refractory multiple myeloma
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
RR	Response rate
Q2W	Every 2 weeks
SAE	Serious adverse events
SAP	Statistical Analysis Plan
sCR	Stringent Complete Response
SFU	Survival follow-up
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SoC	Standard of Care
SJS	Stevens-Johnson Syndrome
SOP	Standard Operating Procedures
SPEP	serum protein electrophoresis
TEN	Toxic Epidermal Necrolysis
TIL	Tumor-infiltrating lymphocytes
TLS	Tumor lysis syndrome
TPI	Toxicity Probability Interval
TSH	Thyroid stimulating hormone
TTP	Time To Progression
ULN	Upper limit of normal
UPEP	urinary protein electrophoresis
VTE	Venous Thromboembolism
WHO	World Health Organization

### 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	