Official Protocol Title:	A Phase Ib Clinical Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) in Combination with Cisplatin and Pemetrexed in Treatmentnaive Participants with Advanced Malignant Pleural Mesothelioma (KEYNOTE-A17).
NCT number:	NCT04153565
Document Date:	26-JUL-2022

Title Page

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Protocol Title: A Phase Ib Clinical Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) in Combination with Cisplatin and Pemetrexed in Treatment-naive Participants with Advanced Malignant Pleural Mesothelioma (KEYNOTE-A17).

Protocol Number: A17-02

Compound Number: MK-3475

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	Not applicable

Approval Date: 26 July 2022

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 02	26-JUL-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address. After approval of Protocol amendment 02, the study will end 90 days after the last dose of the last participant. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study and no further visits will be required.
Amendment 01	25-AUG-2021	To update the dose modification and toxicity management guidelines for irAEs and update some text to align with program standards. (English protocol only) To clarify some inclusion/exclusion criteria in line with the actual criteria.
Original Protocol	23-AUG-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendments:

Sponsor underwent an entity name change and update to the address.

After approval of Protocol amendment 02, the study will end 90 days after the last dose of the last participant. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study and no further visits will be required.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
1.1 Synopsis 1.3.2 Treatment Phase (pembrolizumab monotherapy) and Post Treatment Phase 4.1 Overall Design 8.10.4.2 Imaging Follow-up Visits 8.10.4.3 Survival Follow-up Visits	Add the following wordings: "After approval of Protocol amendment 02, the study will end 90 days after the last dose of the last participant. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study and no further visits will be required.”	To clarify the study completion.

Section # and Name	Description of Change	Brief Rationale
1.3.2 Treatment Phase (pembrolizumab monotherapy) and Post Treatment Phase	Add Notes to “Anti-cancer therapy status”	To clarify.
1.3.2 Treatment Phase (pembrolizumab monotherapy) and Post Treatment Phase 4.1 Overall Design 8.2.3 Tumor Imaging During the Study 8.10.4.2 Imaging Follow-up Visits	Add “pregnancy” and “the end of the study” (only added to section 8.2.3) to the definition of the end of imaging assessments	To align with the section 8.2.4.
4.4 Beginning and End of Study Definition	Add the following wordings: "The time point when the last participant completes the last observation (last study-related telephone-call or visit) will be 90 days after the last dose of the last participant."	To clarify when the last participant completes the last observation.
8.3.7 Submission of images for Interstitial Lung Disease (ILD)	Add the following wordings: "However, after approval of Protocol amendment 02, any imaging acquired more than 90 days after the last dose of the last participant need not be submitted."	No additional imaging submission is required due to the end of the study.
Minor grammatical, typographical and editorial changes have been made throughout the document.		

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase Ib Clinical Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) in Combination with Cisplatin and Pemetrexed in Treatment-naive Participants with Advanced Malignant Pleural Mesothelioma (KEYNOTE-A17).

Short Title: A Phase Ib Study of Pembrolizumab in Combination with Cisplatin and Pemetrexed in Advanced MPM

Acronym: MK-3475-A17

Hypotheses, Objectives, and Endpoints:

In males and females with advanced/unresectable malignant pleural mesothelioma (MPM) who are treatment naïve;

Primary Objectives	Primary Endpoints
To evaluate the safety and tolerability of treatment with pembrolizumab in combination with cisplatin and pemetrexed.	• Dose limiting toxicities (DLTs) rate • Adverse events (AEs) • Discontinuing study treatment due to AEs
Secondary Objectives	Secondary Endpoints
To evaluate the preliminary anti-tumor activity [objective response, disease control, and duration of response (DOR)] by modified Response Evaluation Criteria in Solid Tumors (modified RECIST) as assessed by the investigator of pembrolizumab in combination with cisplatin and pemetrexed.	• Objective response (OR): confirmed complete response (CR) or partial response (PR) • Disease control (DC): a response of confirmed CR or PR, or stable disease (SD) • DOR: the time from the first documented evidence of OR (CR or PR) to the earliest date of PD or death due to any cause, whichever comes first, for individuals with a confirmed CR or PR.

Tertiary/Exploratory	
• To evaluate the preliminary anti-tumor activity [progression free survival (PFS)] by modified RECIST as assessed by the investigator, and overall survival (OS) of pembrolizumab in combination with cisplatin and pemetrexed.	• PFS: the time from the first dose of study treatment to the first documented disease progression or death due to any cause, whichever occurs first. • OS: the time from the first dose of study treatment to death due to any cause.
• To explore the predictive effect of programmed cell death ligand 1 (PD-L1) expression at baseline in participants treated with pembrolizumab in combination with cisplatin and pemetrexed. (optional)	• OR • PFS • OS

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Advanced malignant pleural mesothelioma
Population	Treatment naïve participants with advanced malignant pleural mesothelioma
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study in Japan.
Type of Control	No treatment control
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 3 years from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 18 participants will be allocated.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Adminis-tration</th><th>Regimen/ Treatment Period</th><th>Use</th></tr>
<tr><td>Pembrolizumab</td><td>200 mg</td><td>Q3W</td><td>IV</td><td>Day 1 of each cycle for up to 35 cycles (approximately 2 years)</td><td>Experimental</td></tr>
<tr><td>Pemetrexed</td><td>500 mg/m^2</td><td>Q3W</td><td>IV</td><td>Day 1 of each cycle up to 4-6 cycles</td><td>Combination therapy</td></tr>
<tr><td>Cisplatin</td><td>75 mg/m^2</td><td>Q3W</td><td>IV</td><td>Day 1 of each cycle up to 4-6 cycles</td><td>Combination therapy</td></tr>
<tr><td colspan="6">Abbreviations: IV=intravenous, Q3W = every 3 weeks
Note:
・ Pembrolizumab should be administered prior to chemotherapies. Cisplatin should be administered after 30 minutes from pemetrexed administration.
・ Refer to the local institutional practice for replacement therapy of vitamin B_{12} and folic acid, and prophylaxis of corticosteroids for pemetrexed administration, and appropriate hydration for cisplatin administration.</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>Single Arm</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study from the time the participant signs the Informed Consent Form through the final protocol-specified contact.
After a screening phase of 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met.
After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy.
Participants who discontinue study intervention for reasons other than radiologic disease progression will have posttreatment follow-up imaging for disease status until any on the conditions for discontinuation of imaging are met.
All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.
After approval of Protocol amendment 02, the study will end 90 days after the last dose of the last participant. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study and no further visits will be required.</td></tr>
</table>

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

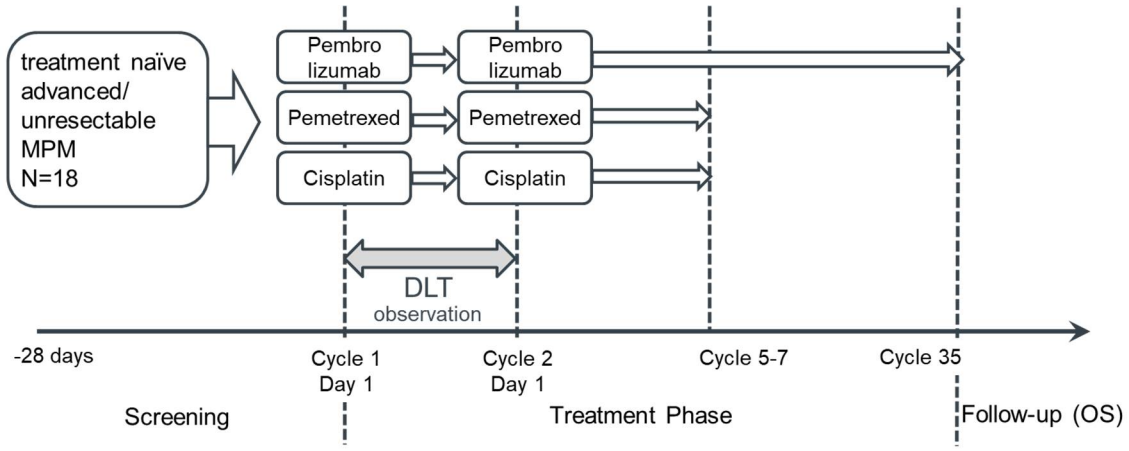

Figure 1 The study design

1.3 Schedule of Activities

1.3.1 Screening Phase and Treatment Phase (combination therapy)

Study Period:	Screening	Treatment phase (3-Week Cycles)					Notes
Treatment Cycle		1			2	3-6	
Treatment Days per Cycle:		1	8	15	1	1	
Visit Name/Number	1	2	3	4	5	6-9	
Scheduled Hour, Day, Week, etc., and Window:	-28 ~ -1	NA	NA	NA	-1 ~ +3	±3	
Administrative Procedures							
Informed Consent	X				X		Signed before any protocol-specific screening procedures are performed. Reconsent is required if a participant will receive the study treatments after Cycle 1 and beyond continuously.
Inclusion/Exclusion Criteria	X						
Participant Identification Card	X	X					Add allocation number at the Visit 2 (C1D1).
Demographic and Medical History	X						
Prior/Concomitant Medication Review	X	X	X	X	X	X	
Administration							
Pembrolizumab [a]		X			X	X	200 mg Q3W up to 35 cycles.
Pemetrexed [a]		X			X	X	500 mg/m^2 Q3W 4-6 cycles. Refer to the local institutional practice for replacement therapy of vitamin B_{12} and folic acid, and prophylaxis of corticosteroids.
Cisplatin [a]		X			X	X	75 mg/m^2 Q3W 4-6 cycles. Appropriate hydration should be performed based on the local institutional practice.
Tumor Tissue Collection							
Archival or Newly Obtained Tissue Collection for PD-L1 analysis (Optional)	X						An optional archival tumor tissue sample or newly obtained tumor sample will be submitted. Submission of an archival tumor sample <u>after</u> Screening period is acceptable.
Efficacy Procedures							
CT/MRI (Chest, abdomen and pars pelvis)	X					X	The same modality should be used for all scans. Perform at Screening (within 28 days prior to the first dose); Q6W (42 ± 7 days) from first dose during the treatment phase up to the first 24 weeks (i.e., W6, W12, W18, and W24). Subsequent tumor imaging should be continued as described in Section 8.2.3.

Study Period:	Screening	Treatment phase (3-Week Cycles)					Notes
Treatment Cycle		1			2	3-6	
Treatment Days per Cycle:		1	8	15	1	1	
Visit Name/Number	1	2	3	4	5	6-9	
Scheduled Hour, Day, Week, etc., and Window:	-28 ~ -1	NA	NA	NA	-1 ~ +3	±3	
MRI (Brain) (as needed)	X					X	Participants with previously treated brain metastases may participate provided they are stable (i.e., without evidence of progression) for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to the first dose of study intervention. Participants with carcinomatous meningitis are excluded regardless of clinical stability. After the start of the study medication, additional MRI will be performed based on the investigator's decision.
Safety Procedures							
Review Adverse Events	X	<--------				-------->	All adverse events that occur after the consent form is signed but before treatment allocation must be reported by the investigator if they cause the participant 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, or a procedure. Report AEs occurring within 30 days after the last dose of study intervention, regardless of initiation of new therapy. Report SAEs occurring within 90 days after the last dose of study intervention, or within 30 days after the last dose of study intervention if new anti-cancer therapy is initiated, whichever is earlier
Full Physical Examination	X						
Directed Physical Examination		X	X	X	X	X	Assessments should be performed prior to the study medication at each cycle.
Vital Signs (temperature, pulse, respiratory rate, height, weight and blood pressure)	X	X	X	X	X	X	Vital signs will be performed per local institutional practices. At Day 1 of each cycle, assessments should be performed prior to the study medication. Height will be measured at Screening only.
Peripheral Capillary Oxygen Saturation (SpO_2) Measurement	X	X	X	X	X	X	SpO_2 will be performed using local standard procedures once at Screening, prior to the study medication at each cycle, EOT and Safety FU.

Study Period:	Screening	Treatment phase (3-Week Cycles)					Notes
Treatment Cycle		1			2	3-6	
Treatment Days per Cycle:		1	8	15	1	1	
Visit Name/Number	1	2	3	4	5	6-9	
Scheduled Hour, Day, Week, etc., and Window:	-28 ~ -1	NA	NA	NA	-1 ~ +3	±3	
12-Lead ECG	X						12-Lead ECG will be performed per local institutional practices. An additional test may be performed if the investigator deems to be medically necessary.
Hematology	X	X	X	X	X	X	Within 7 days prior to the first dose in the Screening phase. Pre-dose laboratory safety tests for Cycle 2 should be conducted after Day 20 of Cycle 1. After Cycle 2, pre-dose laboratory safety tests can be conducted within 3 days prior to dosing for each cycle unless otherwise noted on the flow charts.
Chemistry	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	Within 7 days prior to the first dose in the Screening phase. Pre-dose tests for Cycle 2 should be conducted after Day 20 of Cycle 1. After Cycle 2, Pre-dose tests will be repeated every 6 cycles after beginning with Cycle 6 (i.e. Cycle 6, Cycle 12, and Cycle 18.).
Thyroid Function Testing (T3 or FT3, FT4, and TSH)	X					X	Test will be performed within 7 days prior to the first administration. After Cycle 1, the tests will be performed every other cycle within 3 days before the administration (i.e., Cycle 3, Cycle 5, Cycle 7…) starting with Cycle 3. Participants may be dosed while results are pending from Cycle 3.
CRP, KL-6 and SP-D	X				X	X	Test will be performed within 7 days prior to the first administration. After Cycle 1, the tests will be performed pre-dose at Day 1 within 3 days before the administration of each cycle. Participants may be dosed in subsequent cycles from Cycle 2 while results are pending.
Calculated CrCl	X	X			X	X	CrCl must be ≥45 mL/min prior to the administration of pemetrexed and/or cisplatin. CrCl should be calculated per institutional standard.
Pregnancy Test (WOCBP only)	X	X					Pregnancy test within 72 hours prior to the first dose is required for WOCBP only. Pregnancy test should be conducted at monthly intervals during intervention, and for the time required to eliminate systemic exposure after the last dose of each study interventions (Refer to Section 8.3.4.2 in details). Additional pregnancy test is performed if clinically warranted. If a urine test is positive or not evaluable, a serum test will be required.

Study Period:	Screening	Treatment phase (3-Week Cycles)					Notes
Treatment Cycle		1			2	3-6	
Treatment Days per Cycle:		1	8	15	1	1	
Visit Name/Number	1	2	3	4	5	6-9	
Scheduled Hour, Day, Week, etc., and Window:	-28 ~ -1	NA	NA	NA	-1 ~ +3	±3	
PT or INR and aPTT	X						Within 10 days of the first dose, PTT is acceptable if aPTT cannot be determined. Additional testing may be performed as clinically indicated.
ECOG Performance Status	X	X	X	X	X	X	At Screening, assess within 3 days before first treatment. After cycle 1, assess ECOG on Day 1 of each cycle prior to the dosing.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; CrCl = creatinine clearance; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT3 = free triiodothyronine; FT4 = free thyroxine; FU = follow-up; INR = international normalized ratio; KL-6 = Krebs von den Lungen-6; MRI = magnetic resonance imaging; NA = Not Applicable; PD-L1 = programmed death ligand 1; PT = prothrombin time; PTT = partial thromboplastin time; Q3W = every 3 weeks; Q6W = every 6 weeks; SAE = serious adverse event; SP-D = surfactant protein-D; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; W = week; WOCBP = women of childbearing potential;

a. All administrations of study intervention will begin on Day 1 of each cycle after all pre-dose study procedures and assessments have been completed. First study treatment should begin within 3 days of intervention allocation. The study intervention for Cycle 2 may be administered within 3 days after the scheduled Day 1 of Cycle 2. The following study intervention for Cycle 3 and beyond may be administered within 3 days before or after the scheduled Day 1 of each cycle.

1.3.2 Treatment Phase (pembrolizumab monotherapy) and Post Treatment Phase

Study Period:	Treatment Phase (3-Week Cycles)	End of Treatment	Post-Treatment Visits			Notes
Treatment Cycle	Up to 35					
Treatment Days per Cycle:	1					
Visit Name/Number	10-38	Discontinuation	Safety Follow-Up[a]	Imaging Follow-Up[b, c]	Survival Follow-Up[c]	
Scheduled Hour, Day, Week, etc., and Window:	±3	At the time of discontinuation	30 (+7) days Post Discon		Every 12 (±14 days) weeks Post Discon	
Administrative Procedures						
Pembrolizumab	X					200 mg Q3W up to 35 cycles.
Concomitant Medication Review	X	X	X	X		
Anti-cancer therapy status		X	X	X	X	Any changes in new treatment will be collected.
Vital Status		◄———	———	———	———►	Participants who experience radiologically confirmed disease progression or start a new anti-cancer therapy will move into the survival follow-up visit. Upon Sponsor request, participants may be contacted for survival status at any time during the study.
Efficacy Procedures						
CT/MRI (Chest, abdomen and pars pelvis)	X	X		X		The same modality should be used for all scans. Up to the first 24 weeks from the first dose, perform Q6W (42±7 days) (i.e., W6, W12, W18, and W24) and then Q9W (63±7 days) from the first dose until the end of first year (i.e. W33, W42, W51 and W60); and then Q12W (84±7 days) (i.e., W72, W84, etc.) thereafter. Schedule should be followed regardless of treatment delays. If imaging is obtained within 4 weeks before the end of treatment, an additional scan at the end of treatment is not mandatory.
MRI (Brain)	X	X		X		Additional MRI will be performed based on the investigator's decision.

Study Period:	Treatment Phase (3-Week Cycles)	End of Treatment	Post-Treatment Visits			Notes
Treatment Cycle	Up to 35					
Treatment Days per Cycle:	1					
Visit Name/Number	10-38	Discontinuation	Safety Follow-Up[a]	Imaging Follow-Up[b, c]	Survival Follow-Up[c]	
Scheduled Hour, Day, Week, etc., and Window:	±3	At the time of discontinuation	30 (+7) days Post Discon		Every 12 (±14 days) weeks Post Discon	
Safety Procedures						
Review Adverse Events	X	X	X	X		Report AEs occurring within 30 days after the last dose of study intervention, regardless of initiation of new therapy. Report SAEs occurring within 90 days after the last dose of study intervention, or within 30 days after the last dose of study intervention if new anti-cancer therapy is initiated, whichever is earlier.
Full Physical Examination		X				
Directed Physical Examination	X		X			During treatment phase, assessments should be performed prior to the study medication at each cycle.
Vital Signs (temperature, pulse, respiratory rate, weight and blood pressure)	X	X	X			Vital signs will be performed per local institutional practices. During treatment phase, assessments should be performed prior to the study medication at each cycle.
Peripheral Capillary Oxygen Saturation (SpO_2) Measurement	X	X	X			SpO_2 will be performed using local standard procedures once at Screening, prior to the study medication at each cycle, EOT and Safety FU.
12-Lead ECG		X				12-Lead ECG will be performed per local institutional practices. An additional test may be performed if the investigator deems to be medically necessary.
Hematology	X	X	X			Within 3 days before Day 1 of each cycle, EOT and Safety FU.
Chemistry	X	X	X			
Urinalysis	X	X	X			Within 3 days before Day 1 of every 6 cycles after beginning with Cycle 6 (i.e. Cycle 6, Cycle 12, Cycle 18.)., EOT and Safety FU.

Study Period:	Treatment Phase (3-Week Cycles)	End of Treatment	Post-Treatment Visits			Notes
Treatment Cycle	Up to 35					
Treatment Days per Cycle:	1					
Visit Name/Number	10-38	Discontinuation	Safety Follow-Up[a]	Imaging Follow-Up[b, c]	Survival Follow-Up[c]	
Scheduled Hour, Day, Week, etc., and Window:	±3	At the time of discontinuation	30 (+7) days Post Discon		Every 12 (±14 days) weeks Post Discon	
Thyroid Function Testing (T3, or FT3, FT4, and TSH)	X	X	X			Performs every other cycle (i.e., Cycle 5, Cycle 7…), EOT and Safety FU. Participants may be dosed in subsequent cycles after Cycle 1 while results are pending.
CRP, KL-6 and SP-D	X	X	X			Pre-dose at Day 1 of each cycle, EOT and Safety FU. Participants may be dosed in subsequent cycles after Cycle 1 while results are pending.
Calculated CrCl	X	X	X			CrCl should be calculated per institutional standard.
Urine Pregnancy Test (WOCBP only)	X	X	X			Pregnancy test should be conducted at monthly intervals during intervention, and for the time required to eliminate systemic exposure after the last dose of each study interventions (Refer to Section 8.3.4.2 in details). If a urine test is positive or not evaluable, a serum test will be required.
ECOG Performance Status	X	X				Obtain on Day 1 of each cycle prior to dosing and EOT.

Abbreviations: AE = adverse event; CrCl = creatinine clearance; CRP = C-reactive protein; CT = computed tomography; D/C = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT3 = free triiodothyronine; FT4 = free thyroxine; FU = follow-up; KL-6 = Krebs von den Lungen-6; MRI = magnetic resonance imaging; Q3W = every 3 weeks; Q6W = every 6 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SP-D = surfactant protein-D; T3 = triiodothyronine; TSH = thyroid-stimulating hormone; W = week; WOCBP = women of childbearing potential;

a. If the D/C visit takes place ≥30 days after the last dose of study intervention, a Safety FU visit is not required. In that event, all procedures required for both the D/C visit and the Safety FU visit will be performed at the D/C visit. The D/C date is the date when the decision was made to discontinue further study intervention(s).
b. Participants who discontinue study intervention for reasons other than radiologically verified disease progression by the investigator based on modified RECIST (Section 8.2.5) should continue with imaging assessments per the protocol-defined schedule until: (1) disease progression is radiologically verified by the investigator, (2) initiation of a new anti-cancer treatment, (3) death, (4) withdrawal of consent, (5) pregnancy, or (6) study conclusion or early termination, whichever occurs first.
c. After approval of Protocol amendment 02, the study will end 90 days after the last dose of the last participant. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study and no further visits will be required.

2 INTRODUCTION

This clinical study will evaluate safety and tolerability of pembrolizumab in combination with cisplatin and pemetrexed in treatment naïve participants with advanced MPM.

2.1 Study Rationale

Malignant mesothelioma is a malignant tumor that develops in the pleura, peritoneum, pericardium, testicular sheath membrane; 80% to 85% of pleura, 10% to 15% of peritoneum, and 1% or less of the other sites [Gemba K., et al 2012]. Malignant pleural mesothelioma (MPM) is a rare cancer and the disease has a poor prognosis. The main cause of MPM is exposure to asbestos. Still, even among asbestos-exposed people, the number of patients diagnosed as pleural mesothelioma is rare due to the long latency period (approximately 40 years) from initial exposure to asbestos and the presentation of MPM [Kishimoto T., et al 2010] [Wagner JC., et al 1960], it is predicted that the new cases of MPM will be increased.

Actually, in Japan, approximately 2000 new cases diagnosed as MPM and approximately 1550 death cases due to MPM were annually reported in 2017. Considering that approximately 870 death cases due to MPM was reported in 2003, the number was significantly increasing in recent years in Japan [Ministry of Health, Labour and Welfare (Internet)]. Given the fact that exposure to asbestos had been continued until 2006 when newly use of asbestos was finally prohibited by the Building Standards Act, and the lag time from the exposure to the development of MPM, the incidence of MPM will continue to rise also in Japan.

The treatment of malignant pleural mesothelioma is determined by the International Mesothelioma Interest Group (IMIG) TNM classification and the World Health Organization (WHO) classification comprehensively. In general, systemic chemotherapy treatment is used for subjects with clinically inoperable and post-operative recurrent cases [Baas P., et al 2015] [Kindler HL., et al 2018] [The Japan Lung Cancer Society. 2018]. Advanced MPM patients with good performance status and organ function treated with the combination of cisplatin and an antifolate (pemetrexed or raltitrexed) derive less than 3 months of OS benefit over cisplatin alone, resulting in a median OS of approximately 1 year [Vogelzang NJ., et al 2003] [van Meerbeeck JP., et al 2005]. More than decade, there is no new regulatory approved first line treatment for advanced MPM.

In 2016, phase III randomized trial compared adding bevacizumab to cisplatin and pemetrexed (with maintenance bevacizumab) versus cisplatin and pemetrexed in patients with unresectable MPM and Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2 who did not have bleeding or thrombosis was reported. Addition of bevacizumab to doublet chemotherapy improved OS compared with doublet chemotherapy arm [18.8 months (95%CI:15.9-22.6) vs 16.1 months (95%CI:14.0-17.9): HR=0.77 (95%CI:0.62-0.95), P=.0167] [Zalcman G., et al 2016] with expected manageable toxic effects. However, front-line patients with advanced MPM who would benefit from bevacizumab is limited and there are a still high unmet medical needs in treatment of advanced MPM.

In Japan, a phase II study of nivolumab: a multicenter, open-label, single-arm study in malignant pleural mesothelioma (MERIT) was conducted and 34 patients with advanced or metastatic Japanese MPM who had previously treated with up to two regimens of chemotherapy including pemetrexed-platinum doublet were treated with nivolumab 240 mg every 2 weeks (Q2W). Nivolumab showed durable efficacy and manageable safety profile in these patients [Nakano T., et al 2018]. Based on the results, nivolumab was approved in Japan for 2nd/3rd line MPM patients on Aug 2018. However, there is an unmet medical need for first line therapy for advanced MPM.

As for the clinical study with pembrolizumab in MPM, Alley EW, et al. reported the preliminary result of pembrolizumab at 10 mg/kg Q2W in previously treated MPM patients in a phase Ib study. As of June 20, 2016, 25 patients received pembrolizumab. Pembrolizumab appeared to be well tolerated and might confer anti-tumor activity in patients with PD-L1-positive malignant pleural mesothelioma [Alley EW., et al 2017].

Desai A, et al. reported the result of pembrolizumab at 200 mg Q3W in previously treated pleural or peritoneal malignant mesothelioma patients in a phase II study (ClinicalTrials.gov Identifier: NCT02399371). Pembrolizumab had robust activity in PD-L1 unselected, previously-treated mesothelioma. There were no unexpected toxicities. Although an optimal PD-L1 threshold could not be identified, a trend towards a higher response rate and more durable PFS with increasing PD-L1 expression was observed [Desai A., et al 2018].

Canadian Cancer Trials Group (CCTG) has been conducting a multi-center, randomized phase II/III study of pembrolizumab given alone or with standard chemotherapy (cisplatin and pemetrexed) vs. standard chemotherapy alone in patients with advanced MPM (ClinicalTrials.gov Identifier: NCT02784171).

With regards to the clinical study with the regimen of pembrolizumab plus chemotherapy, KEYNOTE-189 was the confirmatory Phase III study, with the treatments of pembrolizumab in combination with pemetrexed/platinum chemotherapy (cisplatin or carboplatin) provided a clinically meaningful and significant improvement in OS, PFS and ORR for previously untreated patients with metastatic non-squamous Non-Small Cell Lung Cancer (NSCLC) [Gandhi L., et al 2018]. In KEYNOTE-189, all subgroups benefited from pembrolizumab in combination with chemotherapy regardless of PD-L1 expression status. Regulatory agencies have approved pembrolizumab in combination with pemetrexed and platinum for non-squamous NSCLC globally including Japan.

Given the activity of pembrolizumab monotherapy on MPM described above and there are still high unmet medical needs in treatment of advanced MPM as a first line treatment, we plan to conduct a multi-center, phase Ib study of pembrolizumab in combination with the standard chemotherapy (cisplatin and pemetrexed) in Japanese participants with treatment naïve advanced MPM.

2.2 Background

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the IB.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Pembrolizumab (MK-3475) Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis ML. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley ME., et al 2005] [Hunder NN., et al 2008].

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 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald RJ., et al 2005] [Okazaki T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an IgV–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [Okazaki T., et al 2001] [Chemnitz JM., et al 2004] [Sheppard KA., et al 2004] [Riley JL. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry RV., et al 2005] [Francisco LM., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in MPM (refer to Section 2.1).

2.2.2 Preclinical and Clinical Studies

Refer to the respective IB for pembrolizumab for additional preclinical and clinical study data for pembrolizumab.

2.2.3 Ongoing Clinical Studies of Pembrolizumab

Ongoing clinical studies with pembrolizumab are being conducted in multiple solid tumors. In addition, multiple combinations with pembrolizumab are also being investigated. Refer to pembrolizumab IB for study details.

2.2.4 Information on Other Study-related Therapy

As described in Section 2.1, the combination therapy of cisplatin and an antifolate (pemetrexed or raltitrexed) is widely used as a first line therapy for MPM globally. Also in Japan, cisplatin and pemetrexed combination provides promising activity and an acceptable safety profile for systemic chemotherapy naïve Japanese MPM patients with the same recommend dosage and schedule used in rest of the world (500 mg/m^2 pemetrexed Q3W and 75 mg/m^2 cisplatin Q3W) [Nakagawa K., et al 2008]. The combination therapy of cisplatin and pemetrexed is recommended for advanced MPM patients with ECOG performance status 0-2 in Guidelines for Diagnosis and Treatment of the Lung Cancer 2018 [The Japan Lung Cancer Society. 2018].

2.3 Benefit/Risk Assessment

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

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In males and females with advanced/unresectable MPM who are treatment naïve;

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of treatment with pembrolizumab in combination with cisplatin and pemetrexed.	• DLTs rate • AEs • Discontinuing study treatment due to AEs
Secondary	
• To evaluate the preliminary anti-tumor activity (objective response, disease control and DOR by modified RECIST as assessed by the investigator) of pembrolizumab in combination with cisplatin and pemetrexed.	• Objective response (OR): confirmed CR or PR • Disease control (DC): a response of confirmed CR or PR, or SD • DOR: the time from the first documented evidence of OR (CR or PR) to the earliest date of PD or death due to any cause, whichever comes first, for individuals with a confirmed CR or PR.
Tertiary/Exploratory	
• To evaluate the preliminary anti-tumor activity [progression free survival (PFS)] by modified RECIST as assessed by the investigator, and OS of pembrolizumab in combination with cisplatin and pemetrexed.	• PFS: the time from the first dose of study treatment to the first documented disease progression or death due to any cause, whichever occurs first. • OS: the time from the first dose of study treatment to death due to any cause.
• To explore the predictive effect of PD-L1 expression at baseline in participants treated with pembrolizumab in combination with cisplatin and pemetrexed. (optional)	• OR • PFS • OS

4 STUDY DESIGN

4.1 Overall Design

This is a multicenter, open-label, non-randomized, phase Ib study of pembrolizumab in combination with cisplatin and pemetrexed in treatment naïve participants with a histologically confirmed diagnosis of advanced MPM in Japanese. This study will evaluate the safety, tolerability, and preliminary efficacy of pembrolizumab in combination with cisplatin and pemetrexed.

The study design is shown in Figure 1. Approximately 18 participants will be enrolled. The details about the eligible criteria are described in Section 5.1 and 5.2.

In Treatment phase, participants will receive pembrolizumab in combination with the standard chemotherapy up to 4-6 cycles with reference to Figure 1. Pembrolizumab will be administered as fixed dose of 200 mg Q3W in combination with cisplatin 75 mg/m^2 Q3W and pemetrexed 500 mg/m^2 Q3W. The main objective of this study is to evaluate the tolerability of the study regimen by DLT observation rate as a part of safety endpoint. Cycle 1 is defined as an DLT assessment period and the number of participants experiencing a DLT will be evaluated. If ≤8 participants among 18 participants develop a DLT, the study regimen will be considered to be tolerated. Details of DLT assessment schedules and rules are described in Section 1.3 and 6.6.3. The definition of DLTs is outlined in Section 6.6.4. During DLT assessment period, participants will be basically hospitalized. There is no dose escalation/reduction of pembrolizumab in this study. When participants wish to receive consecutive study intervention after DLT assessment period (i.e. Cycle 2 and over), reconsent is required at the end of treatment in Cycle 1 and just before the starting Cycle 2.

Participants will receive pembrolizumab 200 mg Q3W up to 35 cycles from the first dose of the study, or until disease progression is radiographically documented by the investigator based on modified RECIST, or unacceptable AEs, or recurrent Grade 2 pneumonitis, or investigator's decision to discontinue treatment, or other reasons requiring cessation of treatment (Section 7.1).

Adverse event monitoring will be ongoing throughout the study and graded in severity according to the guidelines outlined in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 (Section 8.4). Adverse events will be reported by the investigator or delegate from the time of intervention allocation through 30 days following cessation of study intervention. Serious AEs (SAEs) will be reported by the investigator or delegate from first dose of the study through either 90 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anti-cancer therapy, whichever is earlier.

In addition, tumor sample (archival or fresh) will be obtained for the biomarker analysis of PD-L1 (optional). PD-L1 expression in tumor sample will be assessed using combined positive score (CPS). CPS is defined as number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) relative to the total number of viable tumor cells, multiplied by 100.

Participants who discontinue study intervention for reasons other than radiologically confirmed disease progression by the investigator based on modified RECIST (Section 8.2.5) should continue imaging follow-up visit per the protocol-defined schedule until: (1) disease progression is radiologically verified by the investigator, (2) initiation of a new anti-cancer treatment, (3) death, (4) withdrawal of consent, (5) pregnancy or (6) study conclusion or early termination, whichever occurs first.

Participants who experience radiologically confirmed disease progression or start a new anti-cancer therapy will move into the Survival Follow-up Phase and should be contacted by telephone approximately every 12 weeks (84 ±14 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. The Sponsor may request survival status be assessed at additional time points during the course of the study. For example, these additional time points may be requested prior to an efficacy analysis, and/or final analysis. All participants who are not known to have died prior to the request for these additional survival status time points will be contacted at that time.

After approval of Protocol amendment 02, the study will end 90 days after the last dose of the last participant. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study and no further visits will be required.

No interim analyses are planned in this study.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3 . Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

This is a phase Ⅰb study because primary endpoint is to evaluate the safety and tolerability of pembrolizumab in combination with cisplatin and pemetrexed. As mentioned in section 2.2.4, cisplatin and pemetrexed is the standard treatment of advanced MPM patients globally.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study will use OR, DC, DOR and PFS by the investigator based on modified RECIST (Section 8.2.5) and OS as the secondary or exploratory endpoints. OR, DC, DOR and PFS are acceptable measures of clinical benefit for a clinical study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile.

MPM most commonly grows as a ‘rind’ around the pleural surface, and the selection of measurement sites bidimensionally based on RECIST 1.1 is difficult on computed tomography (CT) scan. With this reason, modified RECIST criteria in MPM is commonly used to assess anti-tumor activity for malignant mesothelioma instead of RECIST 1.1. In this

study, the final determination of radiologic disease progression will be evaluated by the site investigator with radiological assessment based on modified RECIST.

OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in clinical studies.

4.2.1.2 Safety Endpoints

The primary objective of this study is to characterize the safety and tolerability of pembrolizumab as combination therapy with cisplatin and pemetrexed in treatment naïve Japanese participants with advanced MPM. The primary safety analysis will be based on participants who experience toxicities as defined by NCI CTCAE Version 5.0 criteria. Safety will be assessed by evaluating the DLT observation rate in Cycle 1 and quantifying the toxicities and grades of toxicities experienced by participants throughout the study.

For AEs, attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. Adverse events that will be analyzed include, but are not limited to, all AEs, SAEs, fatal AEs, and laboratory changes.

As mentioned in Section 2.1, in KEYNOTE-189, which is the confirmatory Phase III study for treatment naïve patients with metastatic non-squamous NSCLC, patients were treated with pembrolizumab in combination with pemetrexed/platinum chemotherapy (cisplatin or carboplatin). The clinical data of KEYNOTE-189 indicated that the study regimen was well tolerated and safe for these patients including Japanese.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

4.3.1.1 Rationale for Starting and Maximum Dose of MK-3475

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

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5 to 7.5 fold exposure range (refer to IB, Section 5.2.2)

- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W

- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and

- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W

4.3.1.2 Rationale for Cisplatin and Pemetrexed Dosing Regimen

This study will evaluate the safety, tolerability, and preliminary efficacy of pembrolizumab in addition to the standard chemotherapy (combination of cisplatin and pemetrexed) to advanced MPM, dose of cisplatin (75 mg/m^2 Q3W) and pemetrexed (500 mg/m^2 Q3W) are selected as per the approved local product label(s). These doses are approved globally for advanced MPM.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator). The time point when the last participant completes the last observation (last study-related telephone-call or visit) will be 90 days after the last dose of the last participant.

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

Male/Female participants with diagnosis of advanced malignant pleural mesothelioma at least 20 years of age will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Is male or female at least 20 years of age and has histologically confirmed diagnosis of advanced/unresectable MPM.

2. Have at least one measurable disease (one dimension as ≥10 mm or malignant lymph nodes ≥ 15 mm in the short axis), which is systemic therapy naïve, radiologically

assessed by the local site investigator per modified RECIST (refer to Section 8.2.5) using imaging scanned within 28 days prior to the first dose in this study.

3. Has a performance status of 0 or 1 on the ECOG Performance Scale within 3 days before the first administration.

4. Has a life expectancy of at least 3 months.

5. Demonstrate adequate organ function as defined in Table 1 Adequate Organ Function Laboratory Values.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1,500/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[a]
Renal	
Serum creatinine or creatinine clearance (CrCl) (measured or calculated)[b] or GFR in place of CrCl	≤1.5 X ULN or ≥60 mL/min for participants with creatinine levels >1.5 X ULN
Hepatic	
Total bilirubin (serum)	≤1.5 X ULN or Direct bilirubin <ULN for participants with total bilirubin levels >1.5 X ULN
AST (SGOT) and ALT (SGPT)	≤2.5 X ULN or ≤5 × ULN for participants with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT) [c]	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR = glomerular filtration rate; ULN = upper limit of normal.

[a] Criteria must be met without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months).

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

[c] If aPTT is not available, PTT may be tested.

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

Male Participants

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

6. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last dose of chemotherapy or 120 days after the last dose of pembrolizumab:

- Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

- Male participants must also agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex.

Female Participants

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

7. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a WOCBP

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix [5] during the intervention period and for at least 180 days after the last dose of chemotherapy or 120 days after the last dose of pembrolizumab after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period.

The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine) within 72 hours before the first dose of study intervention.
- If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix [5].
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

8. The participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. A WOCBP who has a positive pregnancy test within 72 hours prior to treatment allocation (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

   Note: In the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study intervention, another pregnancy test (urine or serum) must be performed and must be negative in order for participant to start receiving study medication.

Prior/Concomitant Therapy

2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137).

3. Has previously received systemic anti-cancer therapy (including investigational agents) to MPM.

   Note: Participants who received (neo) adjuvant previously may be eligible, only if the last dose of chemotherapy was completed at least 6 months before registration. Such

participants must have recovered from all AEs due to previous (neo) adjuvant therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

4. Received radiation therapy to the lung that is > 30 Gy within 6 months of the first dose of trial treatment.

5. Completed palliative radiotherapy within 7 days of the first dose of trial treatment.

   Note: Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.

6. Had a major surgery within 3 months prior to the first administration in this study.

7. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection as killed virus vaccines are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

8. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.

   Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent.

Diagnostic Assessments

9. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug.

10. Has a known additional malignancy that is progressing or has required active treatment within the past 5 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

11. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (ie, without evidence of progression) for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically

stable and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention.

12. Has had a severe hypersensitivity reaction (≥Grade 3) to treatment a monoclonal antibody/components of the study intervention.

13. Is unable or unwilling to take folic acid or vitamin B_{12} supplementation.

14. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

15. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease. The definition of pneumonitis includes radiation pneumonitis.

16. Is being treated for pericardial effusion, or has symptomatic ascites or pleural effusion. A participant who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.

17. Has an active infection requiring systemic therapy.

18. Has a known history of HIV infection.

19. Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

    Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

20. Has a known history of active tuberculosis (TB; Bacillus tuberculosis).

21. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

22. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

23. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of pembrolizumab or 180 days after the last dose of chemotherapies.

24. Participants with a history of allogeneic tissue / organ transplantation

5.3 Lifestyle Considerations

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

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently allocated in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

In order to adequately evaluate DLT during Cycle 1 and the safety of the doses administered in this study, all participants enrolled must meet the criteria for evaluability for Cycle 1. Participants are considered non-evaluable and will be replaced if:

- They are allocated but not treated.
- They discontinue from the study prior to completing all the safety evaluations for reasons other than treatment-related AEs.
- They receive less than 90% of the total planned infusion of either drug (pembrolizumab, cisplatin or pemetrexed) in Cycle 1 and did not experience a DLT.

Non-evaluable participants will not be counted toward the total number of participants DLT evaluation.

If a participant experiences a DLT in Cycle 1, study intervention may be discontinued following discussion between the Sponsor and investigator. However, if the participant is deriving clinical benefit from the study intervention, the participant may be allowed to continue after discussion between the Sponsor and the investigator.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies study intervention(s) provided by the Sponsor will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement

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

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 2 Study Interventions.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
NA	Experi-mental	Pembrolizumab	Drug	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Q3W; Day 1 in each cycle up to 35 cycles	Experimental	IMP	Central
NA	Experi-mental	Pemetrexed	Drug	Solution for Infusion	500 mg/m2	500 mg/m2	IV Infusion	Q3W; Day 1 in each cycle up to 4-6 cycles	Background Treatment	IMP	Local Site
NA	Experi-mental	Cisplatin	Drug	Solution for Infusion	75 mg/m2	75 mg/m2	IV Infusion	Q3W; Day 1 in each cycle up to 4-6 cycles	Background Treatment	IMP	Local Site

IV = intravenous; NA = Not Applicable; Q3W = every 3 weeks

Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

The order of administration is that pembrolizumab is administered first, then pemetrexed is administered followed by a 30-minute interval once the infusion is completed. Cisplatin will be administered following a 30 minutes interval after the completion of pemetrexed infusion. Participants should take appropriate replacement therapy of vitamin B_{12} and folic acid, and prophylaxis of corticosteroids for pemetrexed treatment and receive appropriate hydration for cisplatin treatment based on the local institutional practice. Please see the Section 8.1.8 and refer to the pharmacy manual for more details.

All supplies indicated in Table 2 Study Interventions will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Concomitant chemotherapeutic agents will be prepared and administered based on the local institutional practice.

6.2.2 Dose Administration

Pembrolizumab 200 mg Q3W in combination with cisplatin 75 mg/m^2 Q3W and pemetrexed 500 mg/m^2 Q3W will be administered 4-6 cycles. After discontinuation of the combination therapy, pembrolizumab 200 mg Q3W will be treated as a monotherapy up to 35 cycles from the first dose.

Participants should take appropriate replacement therapy of vitamin B_{12} and folic acid, and prophylaxis of corticosteroids for pemetrexed treatment and receive appropriate hydration for cisplatin treatment based on the local institutional practice.

The order of administration is that pembrolizumab is administered first, then pemetrexed is administered followed by a 30-minute interval once the infusion is completed. Cisplatin will be administered following a 30 minutes interval after the completion of pemetrexed infusion.

Any variability in dosage, administration and time window from the protocol-specified dosing, pembrolizumab, cisplatin, or pemetrexed, should be documented in the participant's study record and recorded in the Case Report Form (eCRF)s.

First study treatment should begin within 3 days of intervention allocation. The study intervention for Cycle 2 may be administered within 3 days after the scheduled Day 1 of Cycle 2. The following study intervention for Cycle 3 and beyond may be administered within 3 days before or after the scheduled Day 1 of each cycle. All administrations of study intervention will begin on Day 1 of each cycle after all pre-dose study procedures and assessments have been completed as described in the SoA (Section 1.3).

6.2.3 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment.

6.3.2 Stratification

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

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule, the details of and reason for any interruption of study intervention will be documented in the participant's medical record.

Refer to Section 6.6.1 for dose modification and toxicity management for irAEs associated with pembrolizumab and for other allowed dose interruptions of pembrolizumab.

Interruptions from the protocol-specified treatment plan for more than 12 consecutive weeks between pembrolizumab doses or more than 6 consecutive weeks between chemotherapy (cisplatin or pemetrexed) for nondrug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

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

6.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care except for those that are prohibited as described in Section 6.5.2. All concomitant medication will be recorded on the CRF including all prescription, OTC, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or events of clinical interest (ECIs) are to be recorded. SAEs and ECIs are defined in Section 8.4.

6.5.2 Prohibited Concomitant Medications

The following medications and vaccinations are prohibited from the screening period to finishing the last dose in this study:

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

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion after the DLT observation period.

- Live or live attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study.

  Note: Killed virus vaccines are allowed.

- Systemic glucocorticoids except when used for the following purposes
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology.
  - For the prevention of emesis
  - To premedicate for IV contrast allergies
  - To treat chronic obstructive pulmonary disease (COPD) exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- Other glucocorticoid use except when used for the following purposes:
  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or COPD
- Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF) during DLT assessment period (Cycle 1) is NOT allowed.

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

6.5.3 Rescue Medications and supportive care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.1, Table 3 .

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 3 in Section 6.6.1 for guidelines regarding dose modification and supportive care.

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

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

6.6.1.1 Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. These 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 study 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.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 3.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

6.6.1.2 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 4.

Table 4 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention.	Participant may be premedicated 1.5 h (±30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab Monotherapy, Coformulations, or IO Combinations

Pembrolizumab monotherapy, coformulations, or IO combinations may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks (21 days) of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.1.3 Dose Modification and Toxicity Management AEs Associated with Chemotherapy

Dose modification of chemotherapy will not be permitted in DLT evaluation period (Cycle 1). Dose modification of cytotoxic chemotherapies due to AE except for creatinine clearance will conform to the site’s standards procedures (See below).

Creatinine clearance (CrCl):

CrCl must be ≥45 mL/min prior to the administration of chemotherapy. Pemetrexed and/or cisplatin may be delayed for up to 42 days to allow the subject time to recover from the toxicity. If CrCl value is not recovered and continues to record <45 mL/min over 42 days, consider discontinuing treatment with pemetrexed and/or cisplatin. CrCl should be calculated per institutional standard.

6.6.2 Dose Administration/Escalation

6.6.2.1 Dose Administration (Preparation)

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

6.6.3 Tolerability Evaluation Rules

DLT evaluation period is Cycle 1 (the first 3 weeks after the initiation of the study treatments). As a general rule, a participant should be hospitalized during the DLT evaluation period (Cycle 1).

The number of participants who are enrolled but are not yet fully evaluable for DLT assessment may not exceed the number of remaining participants who are at risk of developing a DLT (see Appendix 9). Enrollment will continue until 18 evaluable participants are enrolled, or a "DU (it means that the current dose is unacceptably toxic)" is reached. If a "DU" is reached, enrollment will be paused to consider next steps of this study (ex, alteration of the chemotherapy dosing regimen, or discontinuation of the study).

The total number of DLT observed participants will be used to determine the tolerability of pembrolizumab in combination with the standard chemotherapy regimen. The tolerability evaluation rules in this study are as follows:

- If ≤8 participants among 18 participants develop a DLT, the study regimen will be considered to be tolerated.
- If ≥9 participants among 18 participants develop a DLT, the study regimen will be considered to be NOT tolerated.

6.6.4 Definition of Dose-limiting Toxicity

All toxicities experienced during the DLT evaluation period (the first 3 weeks after initiation of study treatment, Cycle 1) will be graded using NCI-CTCAE Version 5.0 based on the investigator assessment in patients included in DLT evaluation. The DLT window of observation will be during Cycle 1. The occurrence of any of the following toxicities (Table 5) during Cycle 1 will be considered a DLT, if assessed by the investigator to be related to any of the study interventions in Table 2.

Table 5 Definition of DLT

Hematologic Toxicities: · Grade 4 hematologic toxicities (any period), except neutropenia and febrile neutropenia as below · Grade 4 neutropenia lasting >7 days despite appropriate supportive treatment · Grade 4 febrile neutropenia (any period) only if the event is considered as clinically significant for the participant deemed by investigator and sponsor.
Non-Hematologic Toxicities: · Any Grade 4 non-hematologic toxicity (except laboratory test abnormal including transient electrolyte abnormalities) · Any Grade 3 non-hematologic toxicity lasting >72 hours despite appropriate supportive treatment (not laboratory) · Any Grade 4 laboratory test value abnormality (refer to the hematologic toxicities for platelet count decreased and neutrophil count decreased) · Any Grade 3 laboratory test value abnormality lasting >7 days
General： · The start of the second course is delayed by more than 2 weeks (more than 35 days after the first dose) due to toxicity related to study procedures · Any Grade 5

The SPONSOR and the principal investigator will decide the appropriateness of the DLT, and enrollment of additional participants in consultation with the external Efficacy and Safety Evaluation Committee if needed.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-

up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.10.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant interrupts study administration of pembrolizumab for more than 12 consecutive weeks or administration of chemotherapy (cisplatin or pemetrexed) for more than 6 consecutive weeks.
- Clinical progression (without radiographic disease progression).
- Disease progression is radiographically documented by the investigator per modified RECIST outlined in Section 8.2.5.
- Any progression or recurrence of any malignancy, or occurrence of another malignancy that requires active treatment (new non-study anti-cancer therapy).
- Investigator's decision to discontinue treatment.
- The participant has a confirmed positive serum pregnancy test.
- Sponsor's decision.
- Discontinuation of treatment may be considered for participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks) receiving 2

cycles of the combination including 2 doses of pembrolizumab beyond the date when the initial CR was declared.

- Completion of 35 treatments (approximately 2 years) with pembrolizumab.

Note: The number of treatments is calculated starting with the first dose.

For participants who are discontinued from study intervention all applicable discontinuation activities will be performed according to Section 1.3.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, he/she shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

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

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

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

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant'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 participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. 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 participant's dated signature or by the participant's legally acceptable representative's dated signature.

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

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

8.1.1.2 Reconsent before the starting Cycle 2

When participants wish to receive consecutive study intervention after DLT period (i.e. Cycle 2 and over), reconsent is required at the end of treatment in Cycle 1 and just before the starting Cycle 2.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention allocation, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 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 important by the investigator.

Details regarding the disease for which the participant has enrolled in the study will be recorded separately and not listed as medical history.

If a medical condition is diagnosed at the time of Screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in).

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 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 participant within 28 days before the first dose of study medication.

Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

All medications related to reportable SAEs and ECIs should be recorded as defined in 8.4.

All new anti-cancer therapy initiated after the study start must be recorded in the eCRF. If a participant initiates another anti-cancer therapy other than the assigned study intervention(s), the study intervention(s) should be discontinued, and the participant will move into the survival follow-up phase; if a participant initiates a new anti-cancer therapy within 30 days after the last dose of the study intervention, the 30-day Safety Follow-up visit should occur before the first dose of the new therapy.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.10.1.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation. Once a

treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual. The total volume of study intervention infused will be compared to the total volume prepared to determine compliance with each dose administered.

8.1.8.1 Timing of Dose Administration

All study intervention should be administered on Day 1 of each cycle after all pre-dose procedures and assessments have been completed as described in Section 1.3.

First study treatment should begin within 3 days of intervention allocation. The study intervention for Cycle 2 may be administered within 3 days after the scheduled Day 1 of Cycle 2. The following study intervention for Cycle 3 and beyond may be administered within 3 days before or after the scheduled Day 1 of each cycle.

The administration order is that pembrolizumab is administered first, then pemetrexed is administered followed by a 30-minute interval once the infusion is completed, then cisplatin will be administered following a 30 minutes interval after the completion of pemetrexed infusion.

Pembrolizumab

Participants will be received pembrolizumab 200 mg on Day 1 of each cycle (every 3 weeks) as a 30 minute IV infusion (25-40 min) up to 35 cycles. The Pharmacy Manual contains specific instructions for pembrolizumab reconstitution, preparation of the infusion fluid, and administration.

Pemetrexed

Pemetrexed 500 mg/m^2 will be administered after pembrolizumab infusion on Day 1 of each cycle (every 3 weeks) up to 4-6 cycles an IV infusion. Subjects should also receive appropriate replacement therapy of vitamin B_{12} and folic acid, and prophylaxis of corticosteroids before and after the administration of pemetrexed to reduce the appearance of severe adverse events based on the local institutional practice.

Cisplatin

Cisplatin 75 mg/m^2 will be administered after pemetrexed infusion on Day 1 of each cycle (every 3 weeks) up to 4-6 cycles as an IV infusion. Appropriate hydration should be treated to reduce renal toxicities.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA (Section 1.3) and Section 8.10.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Domiciling

As a general rule, a participant should be hospitalized during the DLT evaluation period (the first 3 weeks after the initiation of study medications, Cycle 1).

8.1.12 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 study 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 are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

Tumor imaging should be acquired by CT (strongly preferred) and should include the chest, abdomen, and pelvis. MRI should be used when CT is contraindicated or for imaging in the brain. The same imaging technique regarding modality and use of contrast should be used in a participant throughout the study to optimize the visualization of existing and new tumor burden, per the local institutional practice.

8.2.2 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the first dose of study medication.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of the first treatment.

Brain imaging is not mandatory at the screening, but participants with previously treated brain metastases may participate provided they are stable (i.e., without evidence of progression) for at least 4 weeks by repeat imaging (note that the repeat imaging by the same imaging technique regarding modality should be performed during study screening).

Any neurologic symptoms must have returned to baseline and participants must have no evidence of new or enlarging brain metastases and have not used steroids for brain metastases for at least 14 days prior to study initiation per local site assessment. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.

8.2.3 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 6 weeks (42 days ±7 days) from the first dose. Subsequent tumor imaging should be performed every 6 weeks (Q6W) (42 days ±7 days) up to the first 24 weeks from the first dose (i.e., W12, W18, and W24). After 24 weeks, participants will have imaging performed every 9 weeks (Q9W) (63±7 days) from the first dose until the end of first year (i.e. W33, W42, W51, and W60), and then every 12 weeks (Q12W) (84±7 days) (i.e., W72, W84, etc.). Imaging assessment may be performed more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging are to be performed until radiological disease progression is identified by the investigator, or until the start of new anti-cancer treatment, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

PR and CR should be confirmed by a repeat imaging assessment. The imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

8.2.4 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study intervention, tumor imaging should be performed at the time of intervention discontinuation (±4 weeks window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at intervention discontinuation is not mandatory.

For participants who discontinue study intervention due to documented disease progression, this is the final required tumor imaging.

For participants who discontinue study intervention without documented radiological disease progression by the investigator based on modified RECIST (Section 8.2.5), every effort should be made to continue monitoring their disease status by tumor imaging on the same imaging schedule used while on treatment to monitor disease status until the start of a new

anti-cancer treatment, radiological disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.5 modified RECIST in Malignant Pleural Mesothelioma

All participants who have received at least one cycle should be assessed their response and progression using the modified RECIST in MPM by investigator's assessment.

8.2.5.1 Pleural Tumor Measurement

The method of pleural tumor measurement is followed by Byrne and Nowak [Byrne MJ., et al 2004]. The pleural tumor thickness should be measured perpendicular to the chest wall or mediastinum. It should be measured in 2 positions at 3 different levels ('cuts') on the thoracic CT scan. The transverse cuts should be at least 1 cm apart, and for ease of re-assessment, be related to anatomical landmarks in the thorax. Cuts should preferably be above the level of the main bronchi. At reassessment, the pleural thickness must be measured at the same level and position.

The pleural unidimensional measures are considered to be one organ.

8.2.5.2 Other Measurable Disease

Other measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). Malignant lymph nodes must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

8.2.5.3 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

8.2.5.4 Target Lesion

When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at

baseline. Note that the pleural unidimensional measures are considered to be one lesion of one organ.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

At baseline, the sum of the target lesions is to be recorded.

After baseline, a value should be provided on the eCRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

8.2.5.5 Non-target lesions

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”. Note: For this study, skin lesions will be considered as non-target lesions.

8.2.5.6 Response

After baseline, all participants will be assessed all selected site and “Overall Response” classified as outlined below and Table 6 at each assessment point. The assessment should be provided on the eCRF.

Complete Response (CR): disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases [Eisenhauer EA., et al 2009]) before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (pleural unidimensional measure, plus longest diameter of tumor lesions, plus short axis of lymph nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-PD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions and/or unequivocal progression in Non-target lesions will also constitute progressive disease (including lesions in previously unassessed areas).

Table 6 Integration of Target, non-Target and New Lesions into Response Assessment

Target Lesions	Non-Target Lesions	New Lesions[a]	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes[a]	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR / non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes[a]	PD	

[a] Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "clinical progression". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.
Confirmation of response (PR or CR) is required and the imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical exam during the Screening period as defined in the SoA (Section 1.3). Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in SoA (Section 1.3). After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.2 Directed Physical Examination

For cycles that do not required a full physical exam, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to study intervention administration as defined in the SoA (Section 1.3). New clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs at Screening, prior to the administration of each dose of study intervention and during the follow-up period as specified in the SoA (Section 1.3). Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at Screening only.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed using local standard procedures. The timing of ECGs is specified in the SoA (Section 1.3). Clinically significant abnormal findings should be recorded as medical history. Additional ECGs may be performed as clinically necessary.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

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

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

Laboratory tests for screening should be performed within 7 days prior to the first dose of study intervention. An exception is PT/INR and aPTT, which may be performed within 10 days prior to first dose. Pre-dose laboratory safety tests for Cycle 2 should be conducted after Day 20 of Cycle 1. After Cycle 2, pre-dose laboratory safety tests can be conducted within 3 days prior to dosing for each cycle unless otherwise noted on the flow charts.

CrCl should be calculated per institutional standard prior to the administration of pemetrexed. Pemetrexed and/or cisplatin may be delayed for up to 42 days to allow the participant time to recover from the toxicity. If CrCl value is not recovered and continues to record <45 mL/min over 42 days, consider discontinuing treatment with pemetrexed and/or cisplatin.

Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of study intervention. Unresolved abnormal laboratory values that are drug-related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory results are within normal range.

8.3.4.2 Pregnancy Test

- Pregnancy testing requirements for study inclusion are described in Section 5.1.

- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.

- Pregnancy testing (urine or serum as required by local regulations) should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention(s) as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is as follows:

MK-3475: 120 days

Chemotherapy: 180 days

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.5 Performance Assessments

8.3.5.1 Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc.) with grades 0 to 5.

The investigator or qualified designee will assess ECOG status at Screening, prior to the administration of each dose of study intervention and during the follow-up period as specified in the SoA (Section 1.3).

8.3.6 Peripheral Capillary Oxygen Saturation (SpO_2)

SpO_2 will be performed using local standard procedures once at Screening, prior to the study medication at each cycle, end of treatment and Safety follow-up.

8.3.7 Submission of images for Interstitial Lung Disease (ILD)

In the case that pneumonitis/ILD occurs regardless of causality with study medication, an independent ILD evaluation committee will conduct adjudication of cases of the pneumonitis/ILD. For this purpose, relevant data such as chest imaging (from the baseline to the recovery of pneumonitis/ILD) will be submitted to MSD K.K. However, after approval of Protocol amendment 02, any imaging acquired more than 90 days after the last dose of the last participant need not be submitted.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation through 30 days following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation, through the time required to eliminate systemic exposure after cessation of study intervention as described in Section 5.1 and 8.3.4.2, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 7.

Table 7 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, 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.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

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

The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

8.4.7 Events of Clinical Interest

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

a. An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

b. 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 study site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose).

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study other than the optional PD-L1 analysis.

8.8.1 Planned Genetic Analysis Sample Collection

Planned genetic analysis samples will not be evaluated in this study.

8.9 Future Biomedical Research Sample Collection

Future biomedical research samples will not be collected in this study.

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.10.1 Screening

Approximately 28 days prior to the allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor.

Documented informed consent must be provided prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine 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 study intervention except for the following:

- Laboratory tests are to be performed within 7 days prior to the first dose of study intervention. An exception is PT or INR and aPTT testing, which may be done up to 10 days prior to the first dose of study intervention.
- Evaluation of ECOG is to be performed within 3 days prior to the first dose of study intervention.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- Archival or newly obtained tumor sample is not required to be obtained within 28 days prior to the first dose of study intervention (optional). Submission of an archival tumor sample after Screening period is acceptable.

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

8.10.2 Treatment Period

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided above in Section 8.

8.10.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in Section 1.3. Additional details regarding participant withdrawal and discontinuation are presented in Section 7.

8.10.4 Posttreatment Visit

8.10.4.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anti-cancer treatment, whichever comes first.

All AEs that occur prior to the Safety Follow-up Visit should be recorded (up to 30 days following end of treatment).

8.10.4.2 Imaging Follow-up Visits

Participants who discontinue study intervention for reasons other than radiologically verified PD should continue with imaging assessments per the protocol-defined schedule until: (1) PD is radiologically verified by the investigator, (2) initiation of a new anti-cancer treatment, (3) death, (4) withdrawal of consent, (5) pregnancy, or (6) study conclusion or early termination, whichever occurs first. The protocol-defined schedule is described in the SoA; up to the first 24 weeks from the first dose, perform Q6W (42±7 days) (i.e., W6, W12, W18, and W24) and then every 9 weeks (Q9W) (63±7 days) from the first dose until the end of first year (i.e., W33, W42, W51, and W60); and then every 12 weeks (Q12W) (84±7 days) (i.e., W72, W84, etc.) thereafter. After approval of Protocol amendment 02, the study will end 90 days after

the last dose of the last participant. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study and no further visits will be required.

8.10.4.3 Survival Follow-up Visits

Participants who experience disease progression or start a new anti-cancer therapy will move into the Survival Follow-up Phase and should be contacted by telephone every 12 weeks (84 ±14 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. After approval of Protocol amendment 02, the study will end 90 days after the last dose of the last participant. Participants in the Imaging Follow-up or Survival Follow-up phase will be discontinued from the study and no further visits will be required.

8.10.5 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the study by the Sponsor. For example, updated vital status may be requested before but not limited to, 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 vital status.

9 STATISTICAL ANALYSIS PLAN

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

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2-9.12.

Study Design Overview	A Phase Ib Clinical Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) in Combination with Cisplatin and Pemetrexed in Treatment-naive Participants with Advanced Malignant Pleural Mesothelioma (KEYNOTE-A17).
Intervention Assignment	This is a single arm, non-randomized and open-label study.
Analysis Populations	Safety (Primary): All-Participants-as-Treated (APaT) Efficacy (Secondary and exploratory): All-Participants-as-Treated (APaT)
Primary Endpoints	· Dose limiting toxicity (DLT) · Adverse event (AE) · Discontinuing study treatment due to an AE
Secondary Endpoints	Objective response (confirmed CR or PR), disease control (SD, or confirmed CR or PR) and duration of response by modified Response Evaluation Criteria in Solid Tumors (modified RECIST) for Malignant Pleural Mesothelioma (MPM).
Statistical Methods for Efficacy/Immunogenicity/ Pharmacokinetic Analyses	ORR and DCR will be estimated using an exact method based on the binomial distribution together with its 95% confidence interval (Clopper-Pearson interval). For DOR, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided, as appropriate.
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate. The estimate of the DLT rate among participants treated with pembrolizumab in combination with cisplatin and pemetrexed, and the 90% Bayesian credible intervals based on a prior distribution of Beta (1,1) for the estimate will be provided.
Interim Analyses	Data will be examined on a continuous basis to allow for dose confirmation decisions.
Multiplicity	No multiplicity adjustment is planned in this Phase Ib study.
Sample Size and Power	The sample size for this study is expected to be ~18.

9.2 Responsibility for Analyses/In-house Blinding

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

This study is being conducted as a non-randomized and open-label study, i.e., participants, investigators, and sponsor personnel will be aware of participant intervention assignment after each participant is enrolled and treatment is assigned.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are outlined in Section 3.

9.4 Analysis Endpoints

9.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

Efficacy endpoints are secondary and exploratory endpoints in this study.

Objective response in participants treated with pembrolizumab in combination with cisplatin and pemetrexed as assessed by investigator using modified RECIST criteria for Malignant Pleural Mesothelioma (MPM) is a secondary endpoint. Objective response is defined as a confirmed complete response (CR) or partial response (PR). ORR is the proportion of participants in the analysis population with objective response.

Disease control is defined as a response of confirmed CR or PR, or stable disease (SD). Disease control rate (DCR) is the proportion of participants in the analysis population with disease control.

Duration of response (DOR) is defined as the time from the first documented evidence of CR or PR to the earliest date of Progressive Disease (PD) or death due to any cause, whichever comes first, for individuals with a confirmed CR or PR.

Progression-free survival (PFS) and Overall survival (OS) are the exploratory endpoints.

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

OS is defined as the time from the first dose of study treatment to death due to any cause. Participants who do not die will be censored on the date of the last study assessment or contact.

A description of efficacy measures is provided in Section 4.2.1.1.

9.4.2 Safety Endpoints

The primary safety endpoints are DLTs, adverse events and discontinuing study treatment due to an AE. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, ECGs, vital signs.

A description of safety measures is provided in Section 4.2.1.2.

9.5 Analysis Populations

9.5.1 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all participants who received at least 1 dose of study intervention.

The DLT evaluable population includes APaT participants that meet the criteria for DLT evaluability (e.g., finished Cycle 1 without a DLT or experienced a DLT in Cycle 1). See Section 5.5, 6.6.3 and 6.6.4 for details.

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

9.5.2 Pharmacokinetic Analysis Populations

No pharmacokinetic analysis is planned in this study.

9.5.3 Efficacy Analysis Populations

The APaT population will be used for the analysis of efficacy data in this study. The APaT population consists of all participants who received at least 1 dose of study intervention.

In addition, Full Analysis Set (FAS) which consists of all participants who received at least 1 dose of study intervention and who had post-baseline scan for response evaluation will be used for supportive purposes. A patient who was lost to follow-up and didn't have any post baseline scan, resulting in a response of 'No Assessment' due to reasons other than patient disease status will be removed from the FAS population.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory endpoints will be described in the sSAP.

9.6.1 Statistical Methods for Efficacy Analysis

For ORR and DCR, the point estimate and 95% CI will be evaluated in participants treated with pembrolizumab in combination with cisplatin and pemetrexed, using an exact method based on the binomial distribution (Clopper-Pearson interval).

For DOR, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided, as appropriate. Participants who are alive, have not progressed, have not initiated new anti-cancer treatment, have not been determined to be lost to follow-up and have had a disease assessment within ~5 months of the data cutoff date are considered ongoing responders at the time of analysis. Censoring rules for DOR are summarized in Table 8.

Table 8 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated.	Last adequate disease assessment.	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated.	Last adequate disease assessment before new anti-cancer therapy initiated.	Censor (non-event)
Death or progression after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any.	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anti-cancer therapy, if any.	Censor (non-event)
Death or progression after ≤1 missed adequate disease assessment and before new anti-cancer therapy, if any.	PD or death.	End of response (Event)

The key efficacy analyses are summarized in Table 9.

Table 9 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Secondary Objectives			
ORR based on modified RECIST	Exact method based on binomial distribution	APaT	Participants with missing data are considered non-responders
DCR based on modified RECIST	Exact method based on binomial distribution	APaT	Participants with missing data are considered non-responders
DOR based on modified RECIST	Summary statistics using Kaplan-Meier method	All responders	Censoring rules follow Table 8.

9.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory tests, vital signs, ECG measurements, and physical examinations. Adverse events will be summarized by counts and frequencies. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

Dose limiting toxicities will be listed and summarized. The estimate of the DLT rate among participants treated with pembrolizumab in combination with cisplatin and pemetrexed, and the 90% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided.

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.3.1 Demographic and Baseline Characteristics

Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized.

9.6.3.2 Pharmacokinetic and Pharmacodynamic Modeling Analysis

No pharmacokinetic analysis is planned in this study.

9.7 Interim Analyses

Data will be examined on a continuous basis to allow for dose confirmation decisions.

9.8 Multiplicity

There will be no multiplicity control in this study.

9.9 Sample Size and Power Calculations

The sample size for this study is expected to be ~18.

Precision of the DLT Rate

The estimated DLT rate, and its 90% Bayesian credible interval will be calculated from the posterior distribution of the DLT rate. If 18 participants are dosed, the estimated DLT rate and its 90% credible interval should be similar to one of the rows in Table 10.

Table 10 Precision of the Estimated DLT Rates (N=18)

Number of participants with DLT	Estimated DLT rate (%)	90% credible interval (%)†
1	5.6	(1.9, 22.6)
2	11.1	(4.4, 29.6)
3	16.7	(7.5, 35.9)
4	22.2	(10.9, 41.9)
5	27.8	(14.7, 47.6)
6	33.3	(18.8, 53.0)
7	38.9	(23.0, 58.2)
8	44.4	(27.4, 63.2)
9	50.0	(32.0, 68.0)
†A prior distribution of Beta (1,1) is assumed.		

Precision of the ORR/DCR

Table 11 shows the ORR/DCR estimate and the 95% CI (Clopper-Pearson interval) for N=18.

Table 11 Precision of the Estimated ORR/DCR (N=18)

Number of Responses	Observed ORR/DCR (%)	95%CI for ORR/DCR (%)
1	5.6	(0.1, 27.3)
2	11.1	(1.4, 34.7)
3	16.7	(3.6, 41.4)
4	22.2	(6.4, 47.6)
5	27.8	(9.7, 53.5)
6	33.3	(13.3, 59.0)
7	38.9	(17.3, 64.3)
8	44.4	(21.5, 69.2)
9	50.0	(26.0, 74.0)

9.10 Subgroup Analyses

Subgroup analyses of the efficacy endpoints of OR, PFS and OS may be conducted by baseline PD-L1 status as appropriate.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, 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 participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD 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 that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

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 MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

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

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud,

scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. 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 such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). 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. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants 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.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD 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

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

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

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 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 IRB, IEC, 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 study 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.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant 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 participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. 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.

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with

standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study 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 study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

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

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

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

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

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study 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 or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during

the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 12 will be performed by the local laboratory.
- All on-treatment samples will be collected prior to administration of study intervention.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing:

  Pregnancy testing requirements for study inclusion are described in Section 5.1.

  Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of treatment and 30 days follow-up after the last dose of study intervention.

  Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

  Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention, and for the time required to eliminate systemic exposure after the last dose of each study intervention(s) (Refer to Section 8.3.4.2 in details).

Table 12 Protocol-required Safety Laboratory Assessments

Hematology	**Comprehensive Chemistry Panel**	**Urinalysis**	**Other**
Hematocrit	Albumin	Blood	β-hCG Pregnancy test (serum or urine) [a]
Hemoglobin	Alkaline phosphatase	Glucose	Prothrombin Time (PT) or International Normalized Ratio (INR)
Platelet count	Alanine aminotransferase	Protein	Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT) [b]
WBC (total and differential [d])	Aspartate aminotransferase	Specific gravity	Total triiodothyronine T3 (or Free T3 [FT3][c]) [e]
RBC count	Calcium	Microscopic exam (if blood or protein is abnormal)	Free thyroxine (FT4) [e]
Absolute lymphocyte count	Chloride		Thyroid-stimulating hormone (TSH) [e]
Absolute neutrophil count	Creatinine		Surfactant protein-D (SP-D) [e]
	Glucose		Krebs von den Lungen-6 (KL-6) [e]
	Lactate dehydrogenase (LDH)		C-Reactive Protein (CRP)
	Magnesium		Creatinine clearance
	Phosphorus		
	Potassium		
	Sodium		
	Total bilirubin		
	Direct bilirubin (if total bilirubin is elevated above the upper limit of normal)		
	Total protein		
	Blood urea nitrogen (BUN)		
	Amylase [e]		
	Lipase [e]		

[a] Perform on women of childbearing potential within 72 hours prior to Day 1 of Cycle 1.
[b] If aPTT is not available, PTT may be tested.
[c] T3 is preferred; if not available, Free T3 (FT3) may be tested.
[d] Report % of Neutrophil, Lymphocyte, Monocyte, Eosinophil and Basophil.
[e] Participants may be dosed while any lab results are pending in after Cycle 1.

Investigators must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**
- **Is life-threatening**
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

  - In offspring of participant taking the product regardless of time to diagnosis.

- **Other important medical events**

  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

    Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame 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

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4: Life threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE 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 product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**

Exposure: Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

Time Course: Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

Likely Cause: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

Dechallenge: Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

If yes, did the AE resolve or improve?

If yes, this is a positive dechallenge.

If no, this is a negative dechallenge.

(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

Rechallenge: Was the participant 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 study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

Yes, there is a reasonable possibility of Sponsor's product relationship:

> There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

No, there is not a reasonable possibility of Sponsor's product relationship:

> Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, 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 AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
    - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not Applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:

  Documented hysterectomy

  Documented bilateral salpingectomy

  Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

  - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female with 1 of the following:

  Documented hysterectomy

  Documented bilateral salpingectomy

  Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

  - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol-defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

- The following are not acceptable methods of contraception:
  - Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM.
  - Male condom with cap, diaphragm, or sponge with spermicide.
  - Male and female condom cannot be used together.

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to consistent and correct use of a highly effective method of contraception as described in below during the protocol-defined time frame in Section 5.1.

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b] • IUS[c] • IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. Male condom with cap, diaphragm, or sponge with spermicide. Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.7 Appendix 7: Country-specific Requirements

Study Intervention

Definition of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

SPONSOR does not deal with background treatment (s) as IMP in Japan in clinical trials in which the investigational drug and the background treatment (s) are used in combination.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
APaT	All-Participants-as-Treated
BCG	Bacillus Calmette–Guérin
β-hCG	β-human chorionic gonadotropin
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CR	complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAEv5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DILI	drug-induced liver injury
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
EMA	European Medicines Agency
FDAAA	Food and Drug Administration Amendments Act
FAS	Full Analysis Set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
INR	International Normalized Ratio

Abbreviation	Expanded Term
IMP	Investigational Medicinal Product
IO	immuno-oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LAM	lactational amenorrhea method
mAb	monoclonal antibody
MRI	magnetic resonance imaging
mTPI	modified Toxicity Probability Interval
NIMP	Non-Investigational Medicinal Product
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	Progressive Disease
PD-1	programmed cell-death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression free survival
PK	Pharmacokinetic
PKCθ	protein kinase C-theta
PP	per-protocol
PR	partial response
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
Q9W	every 9 weeks
Q12W	every 12 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TMDD	target-mediated drug disposition
WBC	white blood cell
WOCBP	woman/women of childbearing potential
ZAP70	zeta-chain-associated protein kinase

10.9 Appendix 9: Dose Limiting Toxicity evaluation

The total number of DLT observed participants during the DLT evaluation period (Cycle 1) will be used to determine the tolerability of pembrolizumab in combination with the standard chemotherapy regimen using a modified Toxicity Probability Interval (mTPI) design (target DLT rate: 30%) [Ji Y., et al 2007]. In this study, it will be considered the decision of "E (Escalation)" or "S (Stay)" based on the modified TPI design as "tolerated" for further investigation.

Table 13 Dose-finding Rules per modified Toxicity Probability Interval Design

		Number of patients treated at current dose												
		6	7	8	9	10	11	12	13	14	15	16	17	18
Number of toxicities	0	E	E	E	E	E	E	E	E	E	E	E	E	E
	1	E	E	E	E	E	E	E	E	E	E	E	E	E
	2	S	S	S	S	S	E	E	E	E	E	E	E	E
	3	S	S	S	S	S	S	S	S	S	S	E	E	E
	4	DU	D	D	S	S	S	S	S	S	S	S	S	S
	5	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S
	6	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S
	7		DU	DU	DU	DU	DU	DU	DU	D	D	S	S	S
	8			DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S
	9				DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
	10					DU	DU	DU	DU	DU	DU	DU	DU	DU
	11						DU	DU	DU	DU	DU	DU	DU	DU
	12							DU	DU	DU	DU	DU	DU	DU
	13								DU	DU	DU	DU	DU	DU
	14									DU	DU	DU	DU	DU
	15										DU	DU	DU	DU
	16											DU	DU	DU
	17												DU	DU
	18													DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
DU = The current dose is unacceptably toxic
Target DLT = 30%, N = 18, ε1 = ε2 = 0.03, prior distribution = Beta (1,1)

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