NCT02784171
IND227: A Phase II/III Randomized Study of Pembrolizumab in Patients with Advanced Malignant Pleural Mesothelioma
Date: 2022.Sept.30

STATISTICAL ANALYSIS PLAN

for Phase III Component of

A PHASE II/III RANDOMIZED STUDY OF PEMBROLIZUMAB IN PATIENTS WITH ADVANCED MALIGNANT PLEURAL MESOTHELIOMA

Protocol CCTG IND.227
EudraCT Protocol Number: 2016-002286-60

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ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
AE	Adverse Event
ALK	Anaplastic lymphoma kinase
ALT	Alanine Aminotransferase
Arm A	Standard chemotherapy alone
Arm B	Pembrolizumab with standard chemotherapy
Arm C	Pembrolizumab alone
AST	Serum Glutamic Oxaloacetic Transaminase
AUC	Area under the curve
BSA	Body Surface Area
CCTG	Canadian Cancer Trials Group
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Cancer Group
ECG	Electrocardiography
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
FSH	Follicle-stimulating hormone
HR	Hazard ratio
IgG4	Immunoglobulin G4
IN	Inevaluable
IV	Intravenous
INR	International Normalized Ratio (for Prothrombin Time)
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
irAE	Immune Related Adverse Event
KRAS	Kirsten rat sarcoma gene
LDH	Serum Lactate Dehydrogenase
LKA	Last day the patient is Known Alive
LLN	Lower Limit of Normal
LVEF	Left ventricular ejection fraction
MAX	Maximum
MIN	Minimum
MPM	Malignant pleural mesothelioma
MPV	Major Protocol Violation
mRECIST	RECIST1.1 modified for use in mesothelioma
NA	Not Assessed
NC	Not Computed
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression Disease
PD1	Programmed cell death protein 1

PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
RBC	Red Blood Cell Count
RECIST	Response Evaluation Criteria in Solid Tumors
SAS	Statistical Analysis System
SD	Stable Disease
STD	Standard Deviation
TSH	Thyroid-stimulating hormone
WBC	White Blood Cell Count

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1. Background and Rationale

The objective of this statistical analysis plan is to describe the interim and final analyses performed by the Canadian Cancer Trials Group (CCTG) for the phase III component of IND.227 trial. It will be used for the writing of CCTG study reports on both interim and final analyses of this study.

The data will be collected and cleaned by CCTG. All analyses will be performed by a senior biostatistician in CCTG and statistical analysis reports (SAR) will be prepared. The report of interim analyses will be presented only to the CCTG Data and Safety Monitoring Committee (DSMC). If the DSMC recommend termination based on the interim analysis, a copy of the SAR will be provided to Merck and the Phase 3 database transferred to Merck per contract. The phase 2 data will also be provided.

The final analysis will be performed as described in the protocol when 334 OS events have occurred. The complete IND.227 database will also be transferred to Merck by the CCTG biostatistician after the completion of the study and the statistical analysis for the trial has been completed and the SAR finalized.

A copy of the report from the final analysis (+/- interim analysis if the study is terminated) will be sent to the study chairs for the writing of the manuscript.

Rationale of the Study:

Programmed cell death ligand 1 (PD-L1), the ligand for programmed cell death protein 1 (PD-L1), is part of a complex system of receptors and ligands that are involved in controlling T-cell activation, which acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumours to help evade detection and elimination by the host immune system. Overexpression of PD-L1 has been found to be associated with poor prognosis in a number of solid tumours including malignant pleural mesothelioma (MPM). Clinically, blockade of the PD-1 inhibitory checkpoint pathway by inhibiting PD-L1/ PD-1 engagement has been shown to induce tumour regression across many cancer types, including melanoma and renal cell, colon and lung cancers. Pembrolizumab is an IgG4 kappa isotype antibody with stabilizing sequence alteration at the Fc domain to eliminate antibody directed cytotoxicity, targeting PD1. This phase III component of this study was designed to evaluate whether pembrolizumab improves overall survival when added to standard chemotherapy in malignant pleural mesothelioma (MPM).

Research Hypothesis:

The primary hypothesis in the phase III component of this study is that pembrolizumab when added to standard chemotherapy will have a greater clinical efficacy compared to standard chemotherapy alone in patients in malignant pleural mesothelioma as measured by overall survival.

2. Study Description

2.1 Study Design

Study CCTG IND.227 is a multi-centre, open-label, randomized phase II/III trial in patients with malignant pleural mesothelioma. In the phase II component of this study, patients were randomized in 1:1:1 ratio by a minimization algorithm into the following three arms: standard chemotherapy alone (Arm A), pembrolizumab with standard chemotherapy (Arm B), pembrolizumab alone (Arm C) after stratification by histological subtype (epithelioid vs. other). A total of 126 patients (42 per arm) were planned to recruit in 24 months and be followed for a minimum of 8 months to

observe 63 events to detect an increase in progression free survival (PFS), the primary endpoint of the phase II component, from a median of 7.5 months for Arm A to 11.5 months (HR=0.65) by one of the experimental treatment arms with 80% power at a 1-sided 0.2 level. A full safety review by the trial committee would be performed when 12 patients have been randomized to each arm and followed for at least 6 weeks to ensure the tolerability and safety of combining pembrolizumab with chemotherapy. An interim analysis was scheduled when 22 patients on each treatment arm had been evaluated for 16 week disease control (DC) status. If the DC rate (percentage of patients with CR, PR and SD at 16 weeks) in Arm B or C was no worse than the control arm (Arm A), we would continue to full accrual. Otherwise, the accrual to the arm with DC rate worse than Arm A will be stopped. If the DC rates in both Arms B and C were worse than the control arm, the trial would be stopped.

IND.227 was activated on October 7, 2016. The interim analysis for phase II component was performed in November 2017, which included a total of 61 randomized patients (21 on Arm A, 19 on Arm B, and 21 on Arm C). It was decided to discontinue Arm C based on the recommendation of CCTG DSMC after their review of interim analyses results. The trial was continued as a two-arm phase III trial comparing Arm A to Arm B with overall survival as the primary endpoint and the target sample size of 440 patients, which includes patients randomized to Arm A and Arm B during the phase II component but not included in the phase II interim analysis.

Two analyses will be performed for the phase III component: an interim analysis 11 months after last patient is randomized and a final analysis when 334 events have been observed. This analysis plan describes the interim and final analyses .

The CCTG DSMC reviews safety data every six months (usually at the time of the bi-annual CCTG Spring and Fall meetings) and as otherwise required. These analyses are prepared by a CCTG/Queen's Senior Biostatistician.

2.2 Treatment Allocation

The study is planned to randomize 440 subjects using a 1:1 allocation to pembrolizumab with standard chemotherapy (Arm B) and standard chemotherapy alone (Arm A). The randomization is dynamically balanced by histological subtype (epithelioid vs. other histology) and study center using the method of minimization. A centralized system is used to randomize all patients in this study.

3. Objectives

3.1 Primary

The primary objective of this study is to evaluate whether pembrolizumab improves overall survival when added to standard chemotherapy in malignant pleural mesothelioma (MPM).

3.2 Secondary

Secondary objectives are:

- To evaluate whether pembrolizumab improves progression-free survival (mRECIST) when added to standard chemotherapy in malignant pleural mesothelioma (MPM).

- To assess antitumour activity of pembrolizumab, alone or given to patients receiving standard chemotherapy including objective response rate (complete and partial response), using mRECIST.
- To evaluate the quality of life impact of pembrolizumab, alone or given to patients receiving standard chemotherapy as measured by time from randomization to first deterioration in the three common MPM Quality of Life scales.
- To evaluate the incremental cost effectiveness and cost utility ratios between arms.

[Note: The last two objectives will be addressed separately from this analysis plan].

3.3 Exploratory

Exploratory objectives are:

- To explore the predictive and prognostic value of PD-L1 expression and presence of inflammatory cell subsets within the tumour microenvironment.
- To explore the predictive and prognostic value of exploratory blood-based biomarkers and genomic biomarkers.
- To evaluate the quality of life impact of pembrolizumab, alone or given to patients receiving standard chemotherapy as measured by standard QoL analyses.
- To assess antitumour activity of pembrolizumab, alone or given to patients receiving standard chemotherapy including immune (i) response rate (i-complete and i-partial response) using iRECIST modified for mesothelioma.

[Note: The first two objectives will be addressed separately from this analysis plan].

4. Endpoints

4.1 Primary Efficacy

The primary efficacy endpoint is overall survival.

4.2 Secondary Efficacy

The secondary efficacy endpoints are progression-free survival, objective response rate, and time to first deterioration in the three common MPM Quality of Life scales between the two treatment arms.

4.3 Safety

The safety endpoints are serious and non-serious adverse events (clinical and laboratory), laboratory parameters, dosing data (including dose interruptions, total delivered dose and dose modifications) and reasons off treatment.

5. Sample Size and Power

The primary objective of this study is to assess the additional effect of pembrolizumab to standard chemotherapy by comparing overall survival (OS) between Arm B and Arm A among all randomized patients. The median OS for Arm A is estimated as 16 months. To detect an increase of median OS to 22.9 months (HR=0.7) by Arm B with 90% power at a 2-sided 0.05 level, a

minimum of 334 events would be required to observe from two treatment arms. The required number of events would be observed by accruing a total of up to 430 patients during 34 months of accrual with 31 months follow-up. If the median OS for Arm A is 13.5 months as originally estimated, the total duration of the trial may be shortened from 65 months to 59 months. Assuming 10 patients would drop out earlier, the final sample size of randomized patients would be 440 (220 per arm).

If the success criterion for OS is met, 70% of its alpha (two-sided 0.035) will be passed to progression free survival (PFS) and 30% of its alpha (two-sided 0.015) will be passed to objective response rate (ORR). The median PFS for Arm A is estimated as 7 months. To detect an increase of median PFS to 10 months (HR=0.70) by Arm B with 90.6% power at a 2-sided 0.035 level, a minimum of 376 events would be required to observe from two treatment arms with a total of 440 patients randomized, assuming an annual dropout rate of 13%. With 440 patients randomized, the power for ORR testing at a 2-sided 0.015 level is approximately 87.5% to detect a 17% difference between an underlying ORR of 43% in arm A and 60% in arm B.

6. Data Set Descriptions

A total of 520 patients were enrolled in IND.227: 440 to phase III, 40 were enrolled to Arm A and B and included in the interim DCR analysis of the phase II component and 40 patients were enrolled to Arm C before that arm was closed to accrual.

The primary analysis population for the analysis in this statistical analysis plan will exclude the 40 participants from the phase II Arms A and B that were included as part of the phase II interim analysis. Arm C patients are also excluded.

Three types of analysis samples will be used within the phase III population of IND.227:

All Randomized Patients:

All patients who have been randomized with the treatment arm being as randomized.

Response-Evaluable Patients:

All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable).

A blinded independent review (BICR) will be conducted and response assessed by blinded independent central review (BICR) will be used as the primary analysis; CCTG will also conduct analyses using 'investigator response-reviewed by CCTG'.

All Treated Patients:

All patients who received at least one dose of any protocol treatment (pembrolizumab, cisplatin, carboplatin, pemetrexed) will be included. In the event of protocol violations where patients on Arm A receive pembrolizumab in error, patients randomized to Arm A who have received at least one dose of pembrolizumab on study (from Cancer Treatment Section of Treatment Report) will

be grouped with patients randomized to Pembrolizumab with standard chemotherapy (Arm B) in the analyses of safety.

7. Statistical Analysis

7.1 General Methods

All comparisons between treatment arms will be carried out using a two-sided test at an alpha level of 5% unless otherwise specified.

When appropriate, discrete variables are summarized with the number and proportion of subjects falling into each category, and compared using Fisher's exact test. Continuous and ordinal categorical variables are summarized using the mean, median, standard error, minimum and maximum values and when appropriate, compared using the Wilcoxon test. All confidence intervals are computed based on normal approximations except those for rates, which will be computed based on the exact method.

Time to event variables are summarized using Kaplan-Meier plots. Primary comparisons of the treatment groups are made using the stratified log-rank test. Primary estimates of the treatment differences are obtained with the hazard ratios and 95% confidence intervals from stratified Cox regression models using treatment arm as the single factor.

Percentages given in the summary tables will be rounded and may therefore not always add up to exactly 100%. Listings, tabulations, and statistical analyses will be carried out using the SAS (Statistical Analysis System, SAS Institute, North Carolina, USA) software.

Unless otherwise specified, date of randomization and stratification factors will be taken from the Centralized Randomization File.

Baseline evaluations will be those collected on Eligibility Checklist and Baseline Report and closest to, but no later than, the first day of study medication for treated subjects and closest to, but no later than, the date of randomization, for subjects who were randomized but who never received treatment.

Laboratory results, adverse events, and other symptoms are coded and graded using the Common Terminology Criteria for Adverse Events (CTCAE v4.0).

Response will be assessed using mRECIST. iRECIST and RECIST 1.1 will also be used for exploratory and sensitivity analyses on all randomized patients.

7.2 Data Conventions

When converting a number of days to other units, the following conversion factors will be used:

1 year = 365.24 days

1 month = 30.4367 days

[Note: CCTG's usual standard uses 356.25 days for a year and 30.4375 days for a month. The conversion factors used here only apply to this trial to align with Merck's standard.]

When either day or month of a date is missing, the missing day and/or month will be imputed by the earliest possible date. For example, if the day of the month is missing for any date used in a

calculation, the 1st of the month will be used to replace the missing day. If the month and day of the year are missing for any date used in a calculation, the first of January of the year will be used to replace the missing date. For concomitant medication (CM) start and end dates, the following imputation rule will be used: for CM end date, impute with Dec 31 if both month and day are missing; impute with last day of the month if only day is missing; for CM start date, impute using general rule stated above first. If the collected portion of CM start date is before treatment start date, use general rule stated above first. If CM end date is on/after treatment start date or if CM end date is missing, the CM start date is imputed to be on/after the treatment start date, i.e., the imputed CM start date using general rule, or treatment start date, whichever is later.

7.3 Study Conduct

All randomized patients are included in the analyses of study conduct. Information will be tabulated by randomized treatment (unless otherwise indicated) and pooled treatments.

7.3.1 Patient Disposition

- Number of patients randomized, treated, never treated **(Table 1)**
- Number of alive patients **(Table 2)**
- Median (estimated by Kaplan-Meier method) and range (minimum and maximum) **(Table 2)** of the follow-up time (months) defined as time from the day of randomization (as recorded in centralized randomization file) to the last day the patient is known alive (LKA) as the last recorded date known alive or censored at the time of death and calculated as

  [(date of death or LKA – date of randomization) + 1)]/30.4367.

7.3.2 Accrual Patterns

- Number of patients randomized by country and center **(Table 3)**
- Number of patients by stratification factor at randomization and accrual **(Table 4)**
- Accrual of patients by calendar time pooled across two treatment arms **(Figure** 1**)**

7.3.3 Eligibility Violations/Protocol Deviations

Eligibility violations of inclusion or exclusion criteria are centrally reviewed by CCTG; a field (y/n) for eligibility status and reason for ineligibility is entered in the database. A major protocol violation (MPV) is a serious instance of non-compliance with the protocol which has the potential to pose a significant risk of substantive harm to the study subject or to affect the scientific integrity of the study. MPVs are coded by CCTG based on its standard codes.

- Number of patients eligible, not eligible **(Table 5)**
- Major protocol violations: % for each type of violations **(Table 5)**.

Deviations from randomization will be summarized as follows:

- Treatment as randomized versus as treated **(Table 6)**

7.4 Study Population

All randomized patients are included in the study population analyses. Information will be tabulated by randomized treatment (unless otherwise indicated) and pooled treatments.

7.4.1 Patient Pretreatment Characteristics

- Gender: Female, Male **(Table 7)**
- Race: White, Black/African American, … **(Table 7)**
- Age: median, minimum, maximum values**;** number <65, ≥65 **(Table 7)**
- ECOG Performance Status: 0, 1 **(Table 7)**
- BSA: median, minimum, maximum values **(Table 7)**
- Any occupational or known asbestos exposure: Yes, No, Unknown (**Table 7**)
- Months from first histological diagnosis of pleural mesothelioma to randomization: median, minimum, maximum **(Table 7)**
- Histology sub-type: epitheliod, sarcomatoid, mixed/biphasic, other **(Table 7)**
- EORTC prognostic score defined as EPS=0.55 (if WBC>8.3 x 10^9/L) + 0.6 (if PS=1 or 2) + 0.52 (if histological diagnosis probable or possible) + 0.67 (if histology=sarcomatoid) + 0.6 (if male): ≤1.27, >1.27
- PD-L1 CPS: positive, negative, unknown, not done **(Table 7)**
  [Note: cutoff used to determine positive is 1%]

7.4.2 Prior Surgery

- Number of patients with prior surgery for the study disease **(Table 8)**
- Procedure/site of prior surgery **(Table 8)**

7.4.3 Prior Radiotherapy

- Number of patients with prior radiotherapy **(Table 9)**
- Prior radiotherapy by site and total dose of radiotherapy (cGy) **(Table 9)**

7.4.4 Prior Systemic Therapy

- Number of subjects with prior systemic therapy and type of prior systemic therapy (adjuvant, neo-adjuvant, else) **(Table 10)**
- Number of subjects with specific drug/agent **(Table 10)**

7.4.5 Extent of Disease

- Number of patients with target lesions (including pleural rind)**,** number of target lesions, largest measure, site of target lesions **(Table 11)**
- Number of patients with non-target lesions, number of non-target lesions, site of non-target lesions **(Table 12)**
  [Note: numbers in **Table 12** might be skewed due to the fact that for initial patients pleural thickening was not reported as non-target disease, only for later patients with pleural rind.]

7.4.6 Baseline Exams

- Baseline signs and symptoms **(Table 13)**
- Baseline hematology: WBC, neutrophils, platelets, hemoglobin, lymphocytes **(Table 14)**
- Baseline serum chemistry: total bilirubin, AST, ALT, serum creatinine, potassium, alkaline phosphatase, LDH, calcium, creatinine clearance, magnesium, albumin, glucose random, amylase, lipase, C-reactive protein (**Table 15**);
- Baseline thyroid function tests: TSH, T3 free, T3 total, T4 free, T4 total **(Table 16)**

- Baseline Coagulation Tests (**Table 17**)
- Baseline Urinalysis Tests **(Table 18)**
- Baseline ECG **(Table 19)**
- Baseline LVEF **(Table 19)**

7.4.7 Concomitant Medications and Major Medical Problems at Baseline

- Number of patients with concomitant medication **(Table 20)**
- Number of patients with any steroid within 7 days prior to starting protocol treatment **(Table 20)**
- Number of patients with past or current other major medical problems **(Table 21)**
- Number of patients with hypothyroidism (**Table 21)**

7.4.8 Tobacco Smoking History at Baseline

- Ever smoked any tobacco product: Yes, No, Unknown (**Table 22**)
- Currently smoking: Yes, No (**Table 22**)
- Current average number of cigarettes per day: median, minimum, maximum (**Table 22**)
- Years from quitting smoking to randomization: median, minimum, maximum (**Table 22**)
- Years from beginning smoking cigarettes to randomization: median, minimum, maximum (**Table 22**)
- Total number of years of smoking cigarettes: median, minimum, maximum (**Table 22**)
- Average number of cigarettes smoked per day: median, minimum, maximum (**Table 22**)
- Average pack years of cigarettes smoked: median, minimum, maximum **(Table 22)**

7.5 Extent of Exposure

Patients included are those who received at least one dose of protocol treatment as defined in Section 6.

7.5.1 Study Therapy

During protocol treatment, patients on Arm B are planned to receive pembrolizumab 200mg by infusion over 30 minutes on day 1 of a 3-week cycle for a total of 2 years, while patients on both Arms A and B are planned to receive pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 by infusion on day 1 of a 3-week cycle for a maximum of 6 cycles. Some patients on both Arms A and B may substitute carboplatin (AUC 5-6) for cisplatin if cisplatin is contraindicated on a case-by-case basis after review and approval by CCTG.

Duration of a treatment (in weeks) during the study is defined as follows:

[last date of the treatment– first date of the treatment+ 1]/7,

where the first and last date of the treatment is taken from respective treatment administration section of CRF TREATMENT REPORT.

The following variable will be summarized using the data set of all patients treated:

- Number of patients by cycle of therapy **(Table 23)**
- Total number of cycles of treatment per patient **(Table 24)**
- Total treatment duration of pembrolizumab, pemetrexed, and cisplatin or carboplatin per patient (Table 25**)**

- Number of patients who substitute carboplatin for cisplatin for each reason **(**Table 26**)**

7.5.2 Dose Reduction, Omission, Delay, Increase or Infusion Interruption

The administration of pembrolizumab, pemetrexed, and cisplatin or carboplatin in a cycle may be modified (dose delayed, omitted, reduced, interrupted, or increased) because of toxicity or other reasons. For each drug, the following variables will be summarized using the data set of all treated patients:

- Number of patients with at least one cycle delayed, omitted, reduced, interrupted (infusion complete), interrupted (infusion incomplete), or increased (Table 27**)**
- Reason for these dose modifications (Table 27**)**

7.5.3 Cumulative Dose, Dose Intensity and Relative Dose Intensity

The cumulative dose (mg, mg/m^2, AUC) per patient for each drug is the total dose (mg, mg/m^2, AUC) the patient received, which is defined as the sum of the actual dose level (mg, mg/m^2 or AUC) over the study **(**Table 28**).**

The actual dose intensity of a drug (mg, mg/m^2, or AUC per week) per patient is defined as:

$$\text{Actual Dose Intensity} = \frac{\text{Cumulative dose (mg, } \frac{\text{mg}}{\text{m}^2}\text{, or AUC)}}{[\text{last dosing date} - \text{first dosing date} + 21]/7}.$$

where first and last dosing date is taken from Drug Administration Section of Treatment Report **(Table 29).**

The relative dose intensity per patient is defined as the actual dose intensity (mg, mg/m^2, or AUC per week) divided by the planned weekly dose as assigned in the protocol, which is 200/3 mg/week for pembrolizumab, 500/3 mg/m^2/week for pemetrexed, 25 mg/m^2/week for cisplatin, 5/3 or 6/3 AUC/week for carboplatin based on the number on day 1 of cycle 1.

The patient relative dose intensities will be grouped according to the following categories: < 60%,≥ 60% - < 80%, ≥ 80% - < 95%, ≥ 95% (**Table 30**).

7.5.4 Off Study Therapy

The reason for off of each study therapy will be taken from End of Treatment Section of End Of Treatment Report.

The following information will be summarized for off study therapy **(**Table 31**):**

- Number of patients off study therapy
- Reason off study therapy

7.6 Efficacy

7.6.1 Overall survival

For all randomized patients, survival is calculated from the day of randomization (as recorded in Centralized Randomization File) to death (Date/Cause of Death Section of Death Report). For alive patients, survival is censored at the last day the patient is known alive (LKA) as the last recorded date known alive. The derivation of date of LKA uses the latest date of

assessment/visit/measurement that shows robust evidence of alive status. The date of LKA will be the last of dates listed in **Table 80**.

Survival time (in months) is defined as

[(date of death or LKA − date of randomization) + 1]/30.4367.

A frequency table for the number of patients who died and cause of death in each treatment arm will be provided (**Table 32**). Kaplan-Meier curve for proportions of survival in each treatment arm will be displayed (**Figure 2**).

The comparison of overall survival between the two treatment arms is the primary objective of this study. The primary analysis will be the log-rank test **(Table 33)** stratified by the factor coded as:

Stratification Factor (at randomization)

Histological subtype	1 = Epithelioid	0=other histology

The hazard ratio of pembrolizumab combined with standard chemotherapy (ARM B) over standard chemotherapy alone (ARM A) and two-sided 95% CI will be calculated **(Table 33)** based on the Cox regression model stratified by above stratification factor, and with treatment arm coded as ARM B=1 and ARM A=0. The 95% confidence intervals for the median survival will be computed using the method of Brookmeyer and Crowley.

In order to assess the influence of the potential prognostic factors shown and coded below on the comparison of survival between treatment arms, a stratified Cox regression model will be used with all variables (treatment arm and prognostic factors) included to estimate hazard ratios and 95% confidence intervals **(Table 33).**

Prognostic factors (at baseline)

Gender	0 = Female	1 = Male
Age	0 = ≥65	1 = < 65
ECOG performance status	0 = 1	1= 0

No interactions will be considered in the model**.**

7.6.2 Overall Survival by Subsets

For each level of the following baseline variables, medians with 95% C.I. and the hazard ratio (unstratified) with 95% CI of pembrolizumab combined with standard chemotherapy (ARM B) over standard chemotherapy alone (ARM A) will be produced **(Table 34):**

- Gender: male, female
- Age: <65, ≥65
- Race: white, black, other
- Performance status at baseline: ECOG 0, 1
- Histological type: epithelioid, sarcomatoid, mixed/biphasic, others
  [Note: actual histological type from central pathology review will be used if available.]
- Baseline c-reactive protein level: ≥1 mg/dL, <1 mg/dL
- Baseline platelet count: $\leq 400 \times 10^9$/L, $>400 \times 10^9$/L
- Baseline WBC: ≤8.3x109/L, $>8.3 \times 10^9$/L
- Baseline hemoglobin: <146 g/l, ≥ 146 g/L
- EORTC prognostic score: ≤1.27, >1.27

- PD-L1 CPS: positive, negative
  [Note: cut off used to determine positive is 1%]

7.6.3 Progression-free Survival

Progression-free survival (PFS) will be calculated for all patients from the day of randomization until the first observation of disease progression (date of objective relapse or progression of Relapse/Progression Report) or death due to any cause (recorded in Date/Cause of Death Section of Death Report) as the (difference+1) unless definitive therapy (list agreed between Merck/CCTG) initiated or greater than or equal to two consecutive scheduled imaging are missing right before this first observation of disease progression or death. Response and progression on all arms of this study will be evaluated in this study using a modified RECIST (mRECIST). PFS assessed by BICR will be used; PFS based on investigator assessment will be used as sensitivity analyses and will also be published by CCTG. Sensitivity analysis will be performed by CCTG on not censoring patients with greater than or equal to two consecutive scheduled imaging are missing right before the disease progression or death. Another sensitivity analysis will be performed by CCTG on not censoring patients with definitive therapy.

A frequency table will be provided describing progression and censoring as follows **(Table 35):**

- Number of patients who progress (documented progression, death without documented progression) during treatment or follow-up
- Number of patients censored (alive and not progressed or missing greater than or equal to two consecutive scheduled imaging before observation of an event)

Analyses for PFS will be similar to that for overall survival as previously described. A Kaplan-Meier curve for PFS in each treatment arm will be displayed (**Figure 3**). In the primary analysis, PFS for the two treatments will be compared using the stratified log-rank test **(Table 38).** A stratified Cox regression model will estimate the pembrolizumab combined with standard chemotherapy (ARM B) over standard chemotherapy alone (ARM A) PFS hazard ratio and 95% CI **(Table 38).** In addition, a stratified Cox regression model adjusted for covariates will be applied to verify the impact of the prognostic factors on the treatment effect **(Table 38).**

Coding for treatment arm, stratification variables and prognostic factors is identical to that presented in **Section 7.6.1**.

Progression summary tables similar to **Table 35** are also produced with progression defined by iRECIST (Table 36) and RECIST 1.1 (Table 37). Another analysis for PFS will be performed with progression defined by iRECIST, the Kaplan-Meier curve will be presented in **Figure 4** and the analysis table is presented in **Table 39**.

7.6.4 Progression-free survival by Subsets

Subset analyses performed for overall survival will also be performed for PFS (**Table 40).** PFS by subset will also be analyzed with progression defined by iRECIST (Table 41).

7.6.5 Objective Response (mRECIST)

All patients will have their response classified every 6 weeks for first 3 assessments then every 12 weeks using a modified RECIST criteria for assessment of response in malignant pleural mesothelioma. The best objective response (mRECIST) to protocol treatment is determined by investigators for patients who permanently discontinued protocol treatment and collected in "Best Objective Response-RECIST" section of END OF TREATMENT REPORT. For patients who are still on protocol treatment and followed for response at final clinical cut-off, their best response is defined as the "best verified" response they have achieved up to the time of clinical cut-off determined by CCTG Senior Investigator based on data on "Response Assessment" section of TREATMENT REPORT.

Best response to protocol treatment will be summarized for all randomized patients **(**

Table 42**).**

The primary analysis of response will be the comparison of the objective response rate (CR+PR) between treatment arms among all the randomized patients using the Cochran-Mantel-Haenszel (CMH) statistic adjusted for stratification factor for all randomized patients **(Table 43)** as defined in Section 6.

In addition, a stratified logistic regression model adjusted for covariates will be applied to verify the impact of the prognostic factors on the treatment effect **(Table 43**). For all stratified logistic regression models, estimates of the odds ratio(s) and 95% confidence interval(s) will be given.

Stratified logistic regression odds ratios will be estimated using PROC PHREG in SAS. A dummy time variable will be created, where all responders will be classified as events with an arbitrary time = t_0, and non-responders as censored with time t_1, where $t_1 > t_0$. The DISCRETE option will be used for tied observations.

Coding for treatment, stratification variable and prognostic factors is identical to that presented in Section 7.4.1.

7.6.6 Treatment Response by Subsets

For all randomized patients, the objective response rate will be presented for each treatment arm in the subgroups defined by the categorical variables listed below **(Table 44)**. No formal comparisons are planned:

- Gender (male, female)
- Age (<65 years, ≥65 years)
- Race (white, black, other)
- Performance status at baseline (ECOG 0, ECOG 1)
- Histological type: epithelioid, sarcomatoid, mixed/biphasic, others
  [Note: actual histological type from central pathology review will be used if available.]
- Baseline c-reactive protein level (≥1 mg/dL, >1 ma/dL)
- Baseline platelet count: ≤400x10^9/L, >400x10^9/L
- Baseline WBC: ≤8.3x109/L, >8.3x10^9/L
- Baseline hemoglobin: <146 g/l, ≥ 146 g/L
- EORTC prognostic score: ≤1.27, >1.27
- PDL1 result (positive, negative)
  [Note: There would be various versions of the PDL1 results: results from sites at the time of patient enrollment and from central assessments by a Merck approved vendor. Some assays were repeated for earlier patients using the 22C3 IHC test. The PDL1 done by the vendor using 22C3 will be used for the analysis. In the case of missing data, sensitivity analysis using the hierarchy (22C3 > other vendor assay > site assay) will be conducted by CCTG.]

7.6.7 Duration of Objective Response

For patients whose best objective responses are classified as CR or PR at any reporting period during the study, the duration of objective response is calculated as the time from CR or PR is documented (whichever is the first) until first observation of objective disease relapse or progression or death due to any cause unless greater than or equal to two consecutive scheduled imaging are missing right before this first observation of disease progression or death. If a patient has not relapsed/progressed or died

or there are greater than or equal to two consecutive scheduled imaging are missing right before the disease progression or death, duration of objective response will be censored on the date of last disease assessment. Sensitivity analysis may be performed to not censor patients with great than or equal to two consecutive scheduled imaging are missing right before the disease progression or death.

All randomized patients with CR or PR are included in this analysis. The median duration of objective response and associated 95% confidence intervals will be computed and compared by the stratified log-rank test adjusting for stratification factors at randomization **(Table 45).**

7.6.8 Treatment Immune Response (iRECIST)

All patients will also have their response classified every 6 weeks for first 3 assessments then every 12 weeks using the modified iRECIST guidelines. The best immune response (iRECIST) to protocol treatment is determined by investigators for patients who permanently discontinued protocol treatment and collected in "Best Immune Response-i-RECIST" section of END OF TREATMENT REPORT. For patients who are still on protocol treatment and followed for response at final clinical cut-off, their best immune response is defined as the "best verified" response they have achieved up to the time of clinical cut-off determined by CCTG Senior Investigator based on data on "Response Assessment" section of TREATMENT REPORT.

All analyses performed for objective response as listed above will be performed similarly for iRECIST response (**Table 46** to **Table 49**).

7.6.9 Response (RECIST1.1 response)

All patients will also have their response classified every 6 weeks for first 3 assessments then every 12 weeks using RECIST 1.1. For patients who are still on protocol treatment and followed for response at final clinical cut-off, their best response is defined as the "best verified" response they have achieved up to the time of clinical cut-off determined by CCTG Senior Investigator based on data on "Response Assessment" section of TREATMENT REPORT.

All analyses performed for objective response as listed above will be performed similarly for RECIST 1.1 response (**Table 50** to **Table 53)**

7.7 Safety

The safety analyses will based on the All Treated population defined in Section 6. Adverse events and laboratories are graded and categorized using the CTCAE v4.0 criteria except where CTCAE grades are not available.

7.7.1 Adverse Events

Adverse events will be recorded on the serious adverse event and adverse events sections of case report forms.

Drug related adverse events are those events with a relation to protocol therapy of 3=possible, 4=probable or 5=definite.

Serious adverse events are those events reported with a CTCAE Grade of 3 or higher.

Comparisons between treatment arms on adverse events (any vs. other, severe vs. other) will be carried out using a two sided Fisher's exact test at an alpha level of two-sided 5%.

The following variables are summarized. Tabulations of overall adverse events will be presented by treatment group.

- Adverse events: worst CTCAE grade per patient **(Table 54)**
- Serious adverse events: worst CTCAE grade per patient **(Table 55)**
- Drug related adverse events: worst CTCAE grade per patient **(Table 56)**
- Drug related serious adverse events: worse CTCAE grade per patient **(Table 57)**
- Drug related adverse events leading to treatment discontinuation **(Table 58)**

- Immune-related adverse events: worst CTCAE grade per patient **(Table 59)**
  [Note: A list of Immune-related adverse events will be provided before the final analysis]

7.7.2 Laboratory Evaluations

Laboratory evaluations reported on CRF TREATMENT REPORT and 4-WEEK POST TREATMENT REPORT and on CRF FOLLOW UP REPORT will be included in the calculation for laboratory adverse events. Laboratory results will be classified according to CTCAE version 4.0. Laboratory tests that are not covered by the CTCAE grading system will be summarized according to the following categories: normal and above the upper normal limits.

7.6.2.1 Hematology

- Hemoglobin, platelets, WBC, neutrophils, lymphocytes: worst CTCAE grade per patient **(Table 60)**

7.7.2.2 Biochemistry

- Total bilirubin, AST, ALT, serum creatinine, potassium, alkaline phosphatase, LDH, calcium, creatinine clearance, magnesium, albumin, glucose random, amylase, lipase, C-reactive protein: worst CTCAE grade per patient **(Table 61)**

7.6.2.2 Thyroid function tests

- TSH, T3 free, T3 total, T4 free, T4 total: worst CTCAE grade per patient **(Table 62)**

7.6.2.3 Coagulation

- PT, INR, PTT **(Table 63)**

7.6.2.4 Endocrine biochemistry

- ACTH, cortisol serum, prolactin, FSH, PTH, luteinizing hormone **(Table 64)**

7.7.3 Other Safety

7.6.3.1 Cardiac Function

Cardiac function of patients is evaluated as clinically indicated by ECG or LVEF during protocol treatment for patients with results reported on Treatment Report.

- Number of patients by normal or abnormal ECG, by treatment group **(Table 65)**
- Number of patients by normal (≤LLN) or abnormal LVEF, by treatment group **(Table 65)**

7.6.3.2 Urinalysis

Dipstick urinalysis is performed as clinically indicated during protocol treatment.

- Results of urinalysis, by treatment group **(Table 66)**

7.6.3.3 Hospitalizations

- Number of patients and cycles for which patients were hospitalized during protocol treatment or within 4 weeks after the completion of protocol treatment will be summarized by treatment

group (**Table 67**)

7.6.3.4 Transfusions

Patients who received transfusions or blood products during or 4 weeks after protocol therapy will be summarized as follows:

- Number of patients who received any blood transfusions (red cell concentrates, platelets, and/or other) **(Table 68)**

7.7.4 Deaths on Study/Adverse Events Leading to Discontinuations of Protocol Treatment

- Deaths during protocol treatment or within 30 days of last protocol treatment: number of patients who died and cause of death from Date/Cause of Death Section of Death Report **(Table 69)**
- Number of patients with adverse events leading to discontinuations of each protocol therapy as identified from Off Protocol Treatment - Adverse Events of End of Treatment Report **(Table 70)**

7.8 Tobacco Smoking, Concomitant Medications, Other Anti-Cancer Treatments, and Major Medical Problems

Smoking history was assessed during protocol treatment. Concomitant medication is defined as medication, other than protocol therapy, which is taken by patients any time on treatment or 4 weeks after end of treatment. Major medical problems are those reported during protocol treatment but thought unrelated to protocol treatment. Patients may also receive any other anti-cancer treatment during and after being taken off protocol treatment.

- Tobacco smoking during protocol treatment by treatment group **(Table 71)**
- Concomitant medications for patients during or 4 weeks after protocol treatment by treatment group **(Table 72)**
- Major medical problem during protocol treatment (reported on Treatment Report), by treatment group **(Table 73)**
- Anti-cancer treatments for patients during protocol treatment or 4 weeks after completion of protocol treatment, by treatment group **(Table 74)**
- Anti-cancer treatments for patients during follow-up, by treatment group **(Table 74)**

7.9 Quality of Life

The quality of life of patients in this study is assessed at baseline, day 1 of each cycle, 4 weeks after completion of all protocol therapy, then at each follow-up visit using EORTC QLQ-C30 (version 3.0) and QLQ-LC13. The following are the scoring algorithms for these instruments.

7.9.1 EORTC QLQ-C30

The EORTC core questionnaire, QLQ-C30 (version 3.0), consists of five Functional Scales, Global Health Status, and nine Symptoms Scales. Each scale in the questionnaire will be scored (0 to 100) according to the EORTC recommendations in the EORTC QLQ-C30 Scoring Manual. The scoring method is summarized below. In this summary Qi refers to the ith question on the QLQ-C30.

Functional scale's scores:

- Physical functioning: (1 - ((Q1+Q2+Q3+Q4+Q5)/5 -1)/3) * 100

- Role functioning: (1 - ((Q6+Q7)/2-1)/3) * 100
- Emotional functioning: (1 - ((Q21+Q22+Q23+Q24)/4-1)/3) * 100
- Cognitive functioning: (1 - ((Q20+Q25)/2-1)/3) * 100
- Social functioning: (1 - ((Q26+Q27)/2-1)/3) * 100

Global health status score:

- Global health status/QoL: ((Q29+Q30)/2-1)/6 * 100

Symptom scale's scores:

- Fatigue: ((Q10+Q12+Q18)/3-1)/3 * 100
- Nausea and vomiting: ((Q14+Q15)/2-1)/3 * 100
- Pain: ((Q9+Q19)/2-1)/3 * 100
- Dyspnea: ((Q8-1)/3 * 100
- Insomnia: (Q11-1)/3 * 100
- Appetite loss: (Q13-1)/3 * 100
- Constipation: (Q16-1)/3 * 100
- Diarrhea: (Q17-1)/3 * 100
- Financial difficulties: (Q28-1)/3 * 100

Missing items in a scale will be handled by the methods outlined in the scoring manual. In particular, values will be imputed for missing items by "assuming that the missing items have values equal to the average of those items which are present" for any scale in which at least half the items are completed. A scale in which less than half of the items are completed will be treated as missing.

7.9.1.2 EORTC QLQ-LC13

There are one symptom domain and 10 single items that can be derived from EORTC QLQ-LC13. The method handling missing answers to the questions and scoring algorithm are the same as that for QLQ-C30 symptom domain and single item. As before, higher scores for the symptom domain and single items indicate the symptom is more severe. The following is the list of questions defining these domains and single items.

X	Cough:	Question: 31
X	Hemoptysis:	Question: 32
X	Dyspnea domain:	Questions: 33, 34, 35
X	Sore mouth:	Questions: 36
X	Trouble swallowing:	Questions: 37
X	Peripheral neuropathy:	Questions: 38
X	Hair loss:	Questions: 39
X	Pain in chest:	Questions: 40
X	Pain in shoulder:	Questions: 41
X	Pain elsewhere:	Questions: 42
X	Pain medication:	Questions: 43

Missing items in a scale will be handled by the methods outlined in the scoring manual. In particular, values will be imputed for missing items by "assuming that the missing items have values equal to the average of those items which are present" for any scale in which at least half

the items are completed. A scale in which less than half of the items are completed will be treated as missing.

7.9.2 Data Sets

The analyses of quality of life data will be restricted to randomized patients who have a measurement at baseline and at least one measurement after baseline.

Since the quality of life may not be assessed at the exact times as specified in the protocol, the following will be the scheme to determining the time frame of a QoL assessment:

1) Baseline: Baseline evaluation is the QoL questionnaire collected closest, but prior to, the date of randomization;
2) Each cycle during treatment: If the QoL is assessed within 1.5 weeks before or after the first day of treatment was given for a specific cycle, say cycle m, this assessment is considered as cycle m assessment;
3) Four weeks following the completion of protocol therapies: if the QoL is assessed within 2 week before or after the date when patients are seen in the clinic for their week 4 visit following the last cycle, this assessment is considered as week 4 follow up assessment;
4) Other follow-up visit: patients are supposed to be seen in clinic and complete QoL questionnaire every 12 weeks before progression after their week 4 visit following the completion of the last cycle. If the QoL is assessed within 6 weeks before or after the expected date for a given follow-up period, this assessment is considered as an assessment for that period.

If more than one questionnaire is available for the baseline window, then the latest non-missing measurement, per question, will be considered. If more than one questionnaire is available at a time point other than baseline, then the average (per question) of the non-missing measurements will be used.

7.9.3 Compliance

The compliance rates of QoL assessment is calculated as the number of forms received out of the number of forms expected at each assessment point defined based on the following principles (**Table 75**):

1) At baseline: the number of forms expected is the total number of patients who are eligible for the study and required to fill out QoL questionnaires.
2) During the treatment period: the number expected at each cycle is the total number of patients who received this cycle of treatment;
3) Four weeks following the completion of last cycle: because patients are required to fill out one follow-up form at this time point, the number of forms expected is determined by the total number of patients who completed this form;
4) Other follow-up visits: The expected number of forms at each follow-up visit is determined by the total number of patients who completed corresponding follow-up form and have not had a confirmed PD.

7.9.4 Primary Analyses of QoL

The primary endpoints in the quality of life analysis are defined as the time from randomisation to deterioration in the following three QoL symptoms: cough (Question 1 in QLQ LC13), dyspnea

(Question 8 in QLQ C30), chest pain (Questions 10 in QLQ LC13) (Table 45). These symptoms were selected because they are clinically relevant and frequently present in patients with advanced non-small cell lung cancer. Patients will be considered as deteriorated for a given symptom if their change score from the baseline on the domain/single item defining this symptom is 10 points or higher at any time-point after the baseline assessment with a confirmation by a subsequent visit of a 10 point or worse deterioration. The value of 10 points on a 100 scale was chosen because previous studies have indicated that a 10% change of highest possible score are perceived as clinically significant.

For each symptom, all patients who had a baseline and at least one of the follow-up QoL assessments for this symptom will be included in the time to deterioration analysis. Patients will be censored at the time of the last QoL questionnaire completion if they had not deteriorated before that. The unstratified log-rank test is the primary method to compare the time to deterioration in each symptom between the two treatment arms. The Hochberg procedure (reference 4) will be used to adjust the p-values of the log-rank tests for these three comparisons (**Table 76**).

7.9.5 Baseline and Change Score Analysis

Descriptive statistics for EORTC QoL score (mean, standard deviation) will be presented for each scale at baseline. The same statistics will be generated at each time of post-baseline evaluations. The comparability of mean baseline scores and change scores at each time of post-baseline evaluation between treatment groups will be assessed using a Wilcoxon rank sum test (**Table 77** and **Table 78**).

7.9.6 QoL Response Analysis

QoL response for functional scales and global health status is calculated as follows: A change score of 10 points from baseline is defined as clinically relevant. Patients are considered to have clinical improvement if reporting a score 10-points or better than baseline at any time of QoL assessment. Conversely, patients are considered worsened if reporting a score minus 10-points or worse than baseline at any time of QoL assessment without any improvement. Patients whose scores are between 10-point changes from baseline at every QoL assessment will be considered as stable. In contrast to functional scales, for the determination of patient's QoL response, classification of patients into improved and worsened categories is reversed for symptom scales. A Chi-square test will then be performed to compare the distributions of these three categories between two arms (**Table 79**).

8. Planned Interim Analysis

The interim efficacy analysis will be conducted on OS, PFS and ORR 11 months after last patient is randomized. Early termination will be considered when the two-sided p-value of the stratified log-rank test for the comparison of OS between two treatment arms is significant as indicated by the methodology of Lan-DeMets with O'Brien-Fleming type boundaries. The nominal significant value for the final analysis of OS will be adjusted based on actual number of events observed to ensure the overall type I error of OS hypothesis testing is controlled at a two-sided 0.05 level.

The interim analysis will conduct all of the planned analysis and tables for the final analysis. An interim report including key efficacy results will be presented only to CCTG DSMC and the

recommendation of the DSMC regarding continuation of the trial will be communicated to relevant parties per the DSMC charter, including to Merck. The key efficacy tables and figures included in the DSMC interim report are:

- Patient Disposition (Section **7.3.1: Table 1** and **Table 2**)
- Accrual Patterns (Section **7.3.2: Table 3** and **Table 4**)
- Patient Characteristics (Section **7.4.1: Table 7**)
- Study therapy summary (Section **7.5.1**: **Table 23, Table 24,** Table 25 **and** Table 26**)**
- Off study therapy summary (Sections **7.5.4**: **Table 31**)
- Overall Survival: Number of deaths and Kaplan-Meier plots with log-rank test stratified by the stratification factor and hazard ratio and its two-sided 95% confidence interval (Section **7.6.1**: **Table 32**, **Figure 2** and part of **Table 33**)
- Overall Survival by Subsets: (Section **7.6.2**: **Table 34**)
- Progression Free Survival (mRECIST): Number of PFS events and Kaplan-Meier plots with log-rank test stratified by the stratification factor and hazard ratio and its two-sided 95% confidence interval (Section **7.6.3**: **Table 35**, **Figure 3** and part of **Table 38**)
- Objective response (mRECIST): Summary of objective treatment response and duration of objective response (Sections **7.6.5** and **7.6.7**:

- **Table** 42 and **Table 45**)
- Adverse events (Section **7.7.1**: **Table 54**, **Table 55**, and **Table 56, Table 57, Table 58** and **Table 59**)
- Deaths on study and Adverse events leading to discontinuations of protocol therapy (Section **7.7.4**: **Table 69** and **Table 70**)

9. Appendices

Appendix 1: Tables and Figure

Table 1: Patient Disposition

Data set: All Randomized Patients			
	Number of patients (%)		
	Pembrolizumab with standard chemotherapy	Standard chemotherapy alone	Total
Randomized	N=***	N=***	N=***
Treated	*** (**)	*** (**)	*** (**)
On study	*** (**)	*** (**)	*** (**)
Off study(1)	*** (**)	*** (**)	*** (**)
Never Treated	*** (**)	*** (**)	*** (**)

(1) Off all study therapies.

Table 2: Follow-up of Patients

Data set: All Randomized Patients			
	Number of patients (%)		
	Pembrolizumab with Standard Chemotherapy	Standard chemotherapy alone	Total
Number of patients alive	*** (%)	*** (%)	*** (%)
Follow-up (months)			
median	**	**	**
Minimum-maximum	**-**	**-**	**-**

Table 3: Accrual by Country and Center

Data set: All Randomized Patients			
	Number of patients (%)		
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N = ***	Total N = ***
Canada	*** (**)	*** (**)	*** (**)
Center #1	*** (**)	*** (**)	*** (**)
Center #2	*** (**)	*** (**)	*** (**)
…	*** (**)	*** (**)	*** (**)
Italy	*** (**)	*** (**)	*** (**)
Center #1	*** (**)	*** (**)	*** (**)
Center #2	*** (**)	*** (**)	*** (**)
…	*** (**)	*** (**)	*** (**)
…			

Table 4: Actual Stratification Factor vs. Stratification Factor at Randomization

Data set: All Randomized Patients				
	Number of patients (%)			
	Pembrolizumab with standard chemotherapy N = ***		Standard chemotherapy alone N=***	
	Actual histological subtype			
Histological subtype at randomization*	Epithelioid	Other histology	Epithelioid	Other histology
Epithelioid	** (**)	** (**)	** (**)	** (**)
Other histology	** (**)	** (**)	** (**)	** (**)

*Source: Centralized Randomization File

Figure 1: **Accrual by Calendar Time**

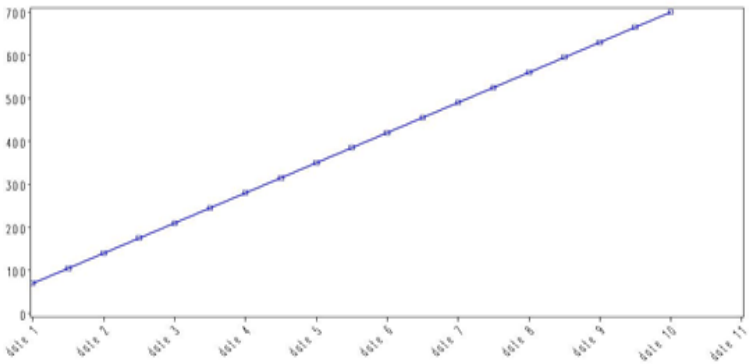

Table 5: Eligibility and Reasons for Ineligibility and Major Protocol Violations

Data set: All Randomized Patients			
	Number of Patients (%)		
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***	Total N=***
Eligible	*** (**)	*** (**)	*** (**)
Not Eligible	*** (**)	*** (**)	*** (**)
Major protocol violation			
<violation type 1>	**	**	**
<violation type 2>	**	**	**
...			

Table 6: Treatment as Randomized Versus as Treated

Data set: All Randomized Patients			
	Number of Patients (%) Randomized Arm		
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***	Total N=***
Treatment received			
Both pembrolizumab and standard chemotherapy	*** (**)	*** (**)	*** (**)
Pembrolizumab only	*** (**)	*** (**)	*** (**)
Standard chemotherapy only	*** (**)	*** (**)	*** (**)
Not treated	*** (**)	*** (**)	*** (**)

Table 7: Pretreatment Characteristics at Baseline

	Number of patients (%)		
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***	Total N=***
Gender			
Female	** (**)	** (**)	** (**)
Male	** (**)	** (**)	** (**)
Race			
White	** (**)	** (**)	** (**)
Black or African American	** (**)	** (**)	** (**)
....	** (**)	** (**)	** (**)
Age (years)			
N	**	**	**
Median	**	**	**
Min - Max	** - **	** - **	** - **
< 65	** (**)	** (**)	** (**)
≥ 65	** (**)	** (**)	** (**)
ECOG Performance Status			
0	** (**)	** (**)	** (**)
1	** (**)	** (**)	** (**)
BSA (m^2)			
N	**	**	**
Median	**	**	**
Min - Max	** - **	** - **	** - **
Any occupational or known asbestos exposure			
No	** (**)	** (**)	** (**)
Yes, asbestos only	** (**)	** (**)	** (**)
Yes, occupational only	** (**)	** (**)	** (**)
Yes, both asbestos and occupational	** (**)	** (**)	** (**)
Unknown	** (**)	** (**)	** (**)
Months from First Histological Diagnosis to Randomization			
N	**	**	**
Median	**	**	**
Min - Max	** - **	** - **	** - **
Histological subtype			
Epitheliod	**(**)	**(**)	** (**)
Sarcomatoid	**(**)	**(**)	**(**)
Mixed/biphasic	**(**)	**(**)	**(**)
Other	**(**)	**(**)	**(**)
EORTC Prognostic Score			
≤1.27	** (**)	** (**)	** (**)
>1.27	** (**)	** (**)	** (**)

PDL1 Result			
Positive	** (**)	** (**)	** (**)
Negative	** (**)	** (**)	** (**)
Unknown	** (**)	** (**)	** (**)
Not Done	** (**)	** (**)	** (**)

Table 8: Prior Surgery for Study Disease

Data set: All Randomized Patients			
	Number of Patients (%)		
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***	Total N=***
Prior surgery			
No	*** (**)	*** (**)	*** (**)
Yes	*** (**)	*** (**)	*** (**)
Surgical procedure			
Biopsy	*** (**)	*** (**)	*** (**)
Pleurectomy	*** (**)	*** (**)	*** (**)
Pleuradhesis	*** (**)	*** (**)	*** (**)
Others	***(**)	*** (**)	*** (**)
Site of surgery			
Site 1	*** (**)	*** (**)	*** (**)
…	*** (**)	*** (**)	*** (**)

Table 9: Prior Radiation Therapy

Data set: All Randomized Patients			
	Number of patients (%)		
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***	Total N=***
Any Prior Radiotherapy			
No	*** (**)	*** (**)	*** (**)
Yes	*** (**)	*** (**)	*** (**)
Site of any prior radiotherapy[(1)]			
Site #1	*** (**)	*** (**)	*** (**)
Site #2	*** (**)	*** (**)	*** (**)
Site #3	*** (**)	***(**)	***(**)
...			
Total Dose of radiotherapy (cGy)	*** (**)	***(**)	***(**)

[(1)] Patient may have more than one site of radiotherapy

Table 10: Prior Systemic Therapy

Data set: All Randomized Patients			
	Number of patients (%)		
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***	Total N=***
With at least one prior systemic therapy	*** (**)	*** (**)	*** (**)
Type of prior systemic therapy			
At least one adjuvant	*** (**)	*** (**)	*** (**)
At least one neo-adjuvant	*** (**)	*** (**)	*** (**)
At least one advanced/recurrent/metastatic	*** (**)	*** (**)	*** (**)
Drug/agent			
Drug/agent 1	*** (**)	*** (**)	*** (**)
…	*** (**)	*** (**)	*** (**)

Table 11: Extent of Disease (Target Lesions)

Data set: All Randomized Patients			
	Number of Patients with Target Lesions (%)		
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***	Total N=***
Presence of Target Lesions			
Patients with at least one target lesion	*** (**)	*** (**)	*** (**)
Number of Target Lesions			
1	*** (**)	*** (**)	*** (**)
2	*** (**)	*** (**)	*** (**)
3	*** (**)	*** (**)	*** (**)
4	*** (**)	*** (**)	*** (**)
5	*** (**)	*** (**)	*** (**)
Largest Target Lesion in cm			
< 2	*** (**)	*** (**)	*** (**)
2-5	*** (**)	*** (**)	*** (**)
> 5-10	*** (**)	*** (**)	*** (**)
> 10	*** (**)	*** (**)	*** (**)
Site of Target Lesion[(1)]			
Abdomen	*** (**)	*** (**)	*** (**)
Adrenals	*** (**)	*** (**)	*** (**)
Bone	*** (**)	*** (**)	*** (**)
Brain	*** (**)	*** (**)	*** (**)
Liver	*** (**)	*** (**)	*** (**)
Lung	*** (**)	*** (**)	*** (**)
Nodes	*** (**)	*** (**)	*** (**)
Pleura	*** (**)	*** (**)	*** (**)
Skin	*** (**)	*** (**)	*** (**)
Subcutaneous Tissue	*** (**)	*** (**)	*** (**)
....	*** (**)	*** (**)	*** (**)

[(1)] Patients may have target lesions at more than one site

Table 12: Extent of Disease (Non-Target Lesions)

Data set: All Randomized Patients			
	Number of Patients (%)		
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***	Total N=***
Patients with non-target lesion	*** (**)	*** (**)	*** (**)
Site of non-target lesion[(1)]			
Abdomen	*** (**)	*** (**)	*** (**)
Adrenals	*** (**)	*** (**)	*** (**)
Bone	*** (**)	*** (**)	*** (**)
Brain	*** (**)	*** (**)	*** (**)
Liver	*** (**)	*** (**)	*** (**)
Lung	*** (**)	*** (**)	*** (**)
Nodes	*** (**)	*** (**)	*** (**)
Pleura	*** (**)	*** (**)	*** (**)
Skin	*** (**)	*** (**)	*** (**)
Subcutaneous Tissue	*** (**)	*** (**)	*** (**)
…	*** (**)	*** (**)	*** (**)
Number of non-target lesions			
1	*** (**)	*** (**)	*** (**)
2	*** (**)	*** (**)	*** (**)
3	*** (**)	*** (**)	*** (**)
4	*** (**)	*** (**)	*** (**)
≥5	*** (**)	*** (**)	*** (**)

[(1)] Patients may have non-target lesions at more than one site

Table 13: Baseline Symptoms and Adverse Event

Data set: All Randomized Patients (Pembrolizumab with standard chemotherapy Arm)					
	Number of patients (%) N=***				
	Worst grade				Any grade
	1	2	3	4	
Patients with any symptom/ adverse event at baseline	** (**)	** (**)	** (**)	** (**)	** (**)
Category 1[(1)]					
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]					
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)

(1) Patients may have more than one event within a category

NOTE: Same table to be made for Standard chemotherapy alone Arm

Table 14: Baseline Hematology

Data set: All Randomized Patients			
	Number of Patients (%)		
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N = ***	Total N=***
Hemoglobin			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
Platelets			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
WBC			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
Neutrophils			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
Lymphocytes			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)

[(1)] Not done or outside the 7-day window prior to randomization

Table 15: Baseline Chemistry

Data set: All Randomized Patients			
	Number of Patients (%)		
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N = ***	Total N=***
Total bilirubin			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
Alkaline phosphatase			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
ALT			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
AST			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
LDH			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
Serum Creatinine			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
Hyperkalemia			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
Hypokalemia			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)
Hypercalcemia			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [(1)]	** (**)	** (**)	** (**)

Hypocalcemia			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [1]	** (**)	** (**)	** (**)
Hypermagnesemia			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [1]	** (**)	** (**)	** (**)
Hypomagnesemia			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [1]	** (**)	** (**)	** (**)
Hyperglycemia			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [1]	** (**)	** (**)	** (**)
Hypoglycemia			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [1]	** (**)	** (**)	** (**)
Hyperalbuminemia			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [1]	** (**)	** (**)	** (**)
Hypoalbuminemia			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [1]	** (**)	** (**)	** (**)
Creatinine clearance			
Normal	** (**)	** (**)	** (**)
High [2]	** (**)	** (**)	** (**)
Not reported [1]	** (**)	** (**)	** (**)
Amylase			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)

Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [1]	** (**)	** (**)	** (**)
C-Reactive Protein			
Normal (<1 mg/dL)	** (**)	** (**)	** (**)
High (⩾1 mg/dL)	** (**)	** (**)	** (**)
Not reported [1]	** (**)	** (**)	** (**)
Lipase			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported [1]	** (**)	** (**)	** (**)

[1] Not done or outside the 7-day window prior to randomization
[2] Higher than upper lower limit

Table 16: Baseline Thyroid Function Tests

Data set: All Treated Patients		
	Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N = ***
TSH		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T3 Free		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T3 Total		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T4 Free		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T4 Total		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
TSH		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)

>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)
T3 Free		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)
>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)
T3 Total		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)
>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)
T4 Free		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)
>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)
T4 Total		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)
>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)

Data set: All Treated Patients		
	Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N = ***
TSH		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T3 Free		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T3 Total		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T4 Free		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T4 Total		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
TSH		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)
>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)
T3 Free		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)
>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)
T3 Total		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)
>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)
T4 Free		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)
>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)

T4 Total		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)
>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)

Table 17: Baseline Coagulation Tests

Data set: All Randomized Patients			
	Number of Patients (%)		
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N = ***	Total N = ***
PT			
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
INR			
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
PTT			
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)

Table 18 : Baseline Urinalysis

Data set: All Randomized Patients			
	Number of patients (%)		
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***	Total N=***
Urinalysis – WBC			
Negative/trace	**(**)	**(**)	**(**)
1+(>20 mg/dL–30 mg/dL)	**(**)	**(**)	**(**)
2+(>30 mg/dL–100 mg/dL)	**(**)	**(**)	**(**)
3+(>100 mg/dL– 300 mg/dL)	**(**)	**(**)	**(**)
4+(>300 mg/dL)	**(**)	**(**)	**(**)
Urinalysis – RBC			
Negative/trace	**(**)	**(**)	**(**)

1+(>20 mg/dL–30 mg/dL)	**(**)	**(**)	**(**)
2+(>30 mg/dL–100 mg/dL)	**(**)	**(**)	**(**)
3+(>100 mg/dL– 300 mg/dL)	**(**)	**(**)	**(**)
4+(>300 mg/dL)	**(**)	**(**)	**(**)
Urinalysis – Protein			
Negative/trace	**(**)	**(**)	**(**)
1+(>20 mg/dL–30 mg/dL)	**(**)	**(**)	**(**)
2+(>30 mg/dL–100 mg/dL)	**(**)	**(**)	**(**)
3+(>100 mg/dL– 300 mg/dL)	**(**)	**(**)	**(**)
4+(>300 mg/dL)	**(**)	**(**)	**(**)

Table 19: Baseline Cardiac Function

Data set: All Randomized Patients			
	Number of patients (%)		
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***	Total N=***
Baseline ECG: Results			
Normal	*** (**)	*** (**)	*** (**)
Abnormal not clinically significant	*** (**)	*** (**)	*** (**)
Abnormal clinically significant	*** (**)	*** (**)	*** (**)
ECG not performed	*** (**)	*** (**)	*** (**)
Baseline LVEF: Results			
Normal (>LLN)	*** (**)	*** (**)	*** (**)
Abnormal (<LLN)	*** (**)	*** (**)	*** (**)
LVEF not performed	*** (**)	*** (**)	*** (**)

Table 20: Concomitant Medications prior to starting protocol treatment

Data set: All Randomized Patients			
	Number of patients (%)		
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***	Total N=***
Any concomitant medication [(1)]			
No	** (**)	** (**)	** (**)
Yes	** (**)	** (**)	** (**)
Any steroid medication [(1)]			
No	** (**)	** (**)	** (**)
Yes	** (**)	** (**)	** (**)

[(1)]Taken within 7 days prior to starting protocol treatment .

Table 21: Major Medical Problems at Baseline

Data set: All Randomized Patients			
	Number of patients (%)		
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N = ***	Total N=***
Patients with at least one past or current major medical problem	** (**)	** (**)	** (**)
Medical Problem[(1)]			
(from highest to lowest in frequency)			
Hypothyroidism	** (**)	** (**)	** (**)
Diabetes	** (**)	** (**)	** (**)
...			

(1) patients may report more than one medical problem reported

Table 22: Tobacco Smoking History at Baseline

Data set: All Randomized Patients

	Number of patients (%)		
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N = ***	Total
Ever smoked any tobacco product			
Yes	** (**)	** (**)	** (**)
No	** (**)	** (**)	** (**)
Unknown	** (**)	** (**)	** (**)
Currently smoking			
Yes	** (**)	** (**)	** (**)
No	** (**)	** (**)	** (**)
Current Average number of cigarettes per day			
N	**	**	**
Median	**	**	**
Min - Max	** - **	** - **	** - **
Years from quitting smoking to randomization			
N	**	**	**
Median	**	**	**
Min - Max	** - **	** - **	** - **
Years from beginning smoking cigarettes to randomization			
N	**	**	**
Median	**	**	**
Min - Max	** - **	** - **	** - **
Total number of years of smoking cigarettes			
N	**	**	**
Median	**	**	**
Min - Max	** - **	** - **	** - **
Average number of cigarettes smoked per day			
N	**	**	**
Median	**	**	**
Min - Max	** - **	** - **	** - **
Average pack years of cigarettes smoked			
N	**	**	**
Median	**	**	**
Min - Max	** - **	** - **	** - **

Table 23: Number of Patients by Cycle

Data Set: All Treated Patients		
	Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N = ***
Cycle 1	** (**)	** (**)
2	** (**)	** (**)
3	** (**)	** (**)
...		

Table 24: Number of Cycles of Protocol Therapy per Patient

Data Set: All Treated Patients		
	Pembrolizumab with standard chemotherapy	Standard chemotherapy alone
Number of cycles:		
N	**	**
Median	*	*
Min – Max	* - *	* - *

Table 25: Total treatment Duration of Protocol Therapy

Data Set: All Treated Patients							
	Pembrolizumab with standard chemotherapy				Standard chemotherapy alone		
	Pembrolizumab	Pemetrexed	Cisplatin	Carboplatin	Pemetrexed	Cisplatin	Carboplatin
Duration in weeks:							
N	**	**	**		**	**	**
Median	*	*	*		*	*	*
Min – Max	* - *	* - *	* - *		* - *	* - *	* - *

Table 26: Number of Patients who Substitute Carboplatin for Cisplatin for Different Reasons

Data Set: All Treated Patients		
	Pembrolizumab with standard chemotherapy	Standard chemotherapy alone
Reason for substituting Carboplatin for Cisplatin:		
Reason 1	**	**
Reason 2	**	**
…	**	**

Table 27: Number of Patients with Modifications of Protocol Therapy

Data Set: All Treated Patients		
	Pembrolizumab with standard chemotherapy	Standard chemotherapy alone

	Pembrolizumab	Pemetrexed	Cisplatin	Carboplatin	Pemetrexed	Cisplatin	Carboplatin
Patients with at least one cycle with (type of modification*) over all cycles	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Reason for (type of modification)							
Reason 1	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
…	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)

* Delayed, omitted, reduced, interrupted (infusion completed), interrupted (infusion incomplete), or increased

Table 28: Cumulative Dose

Data Set: All Treated Patients							
	Pembrolizumab with standard chemotherapy				Standard chemotherapy alone		
	Pembrolizumab	Pemetrexed	Cisplatin	Carboplatin	Pemetrexed	Cisplatin	Carboplatin
Cumulative dose per patient (<unit>)							
N	**	**	**	**	**	**	**
Mean (SD)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Median	**	**	**	**	**	**	**
Min-Max	** - **	** - **	** - **	** - **	** - **	** - **	** - **

Table 29: Actual Dose Intensity

Data Set: All Treated Patients							
	Pembrolizumab with standard chemotherapy				Standard chemotherapy alone		
	Pembrolizumab	Pemetrexed	Cisplatin	Carboplatin	Pemetrexed	Cisplatin	Carboplatin
Dose intensity							
N	**	**	**	**	**	**	**
Mean (SD)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Median	**	**	**	**	**	**	**
Min-Max	** - **	** - **	** - **	** - **	** - **	** - **	** - **

Table 30: Relative Dose Intensity

Data Set: All Treated Patients							
	Pembrolizumab with standard chemotherapy				Standard chemotherapy alone		
	Pembrolizumab N=***	Pemetrexed N=***	Cisplatin N=***	Carboplatin N=***	Pemetrexed N=***	Cisplatin N=***	Carboplatin N=***
Relative Dose intensity							
≥ 95% planned intensity	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
≥ 80% - < 95% planned intensity	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
≥ 60% - < 80% planned intensity	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
< 60% planned intensity	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)

Table 31: Off Protocol Therapy Summary

Off Each Protocol Treatment

Data Set: All Treated Patients							
	Pembrolizumab with standard chemotherapy				Standard chemotherapy alone		
	Pembrolizumab N=***	Pemetrexed N=***	Cisplatin N=***	Carboplatin N=***	Pemetrexed N=***	Cisplatin N=***	Carboplatin N=***
Off treatment	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Reason off treatment							
Treatment Completed	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Progressive disease (objective)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Symptomatic progression	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Intercurrent Illness – adverse events unrelated to protocol treatment	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Adverse events related to protocol therapy	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Adverse events related another protocol agent	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patient Refusal (not related to adverse event)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Death	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Other reason	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)

Table 32: All Deaths

Data set: All Randomized Patients		
	Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
Number of Patients who died	** (**)	** (**)
Cause of Death		
Study-specific malignant disease only	**	**
Adverse event possibly, probably or definitely related to protocol treatment	**	**
Complication from a non-protocol treatment for this malignancy (malignant disease may or may not be contributory)	**	**
Death from disease with Medical Assistance in Dying	**	**
Other Primary Malignancy	**	**
Other Condition or Circumstance	**	**

Figure 2: Kaplan-Meier Curves for Overall Survival

Table 33: Log Rank and Cox Regression Model for Overall Survival

Data set: All Randomized Patients						
		Univariate Analysis[1]			Multivariate Analysis[2]	
Treatment Arm/ Prognostic Factors at Baseline	N	Median Survival (Months) (95% CI)	Hazard Ratio[4] (95% CI)	Log-rank p-value	Hazard Ratio[4] (95% C.I.)	P-value from Cox regression
Treatment arm				0.***		0.***
Pembrolizumab with standard chemotherapy	***	**.** (**.**,**.**)	**.** (**.**,**.**)		**.** (**.**,**.**)	
Standard chemotherapy alone	***					
Gender				0.***		0.***
Male	***	**.** (**.**,**.**)	NC [3]		**.** (**.**,**.**)	
Female	***					
Age				0.***		0.***
<65	***	**.** (**.**,**.**)	NC		**.** (**.**,**.**)	
≥65	***					
ECOG performance status				0.***		0.***
0	***	**.** (**.**,**.**)	NC		**.** (**.**,**.**)	
1	***					

(1) Stratified; (2) Stratified Cox regression with all factors included; (3) NC = not computed
(4) Hazard ratio of first category over second category

Table 34: Survival by Subsets

Data set: All Randomized Patients						
		Pembrolizumab with standard chemotherapy		Standard chemotherapy alone		
Factors	Value	N	Median Survival 95% C.I.	N	Median Survival 95% C.I.	Hazard Ratio[(1)] 95% C.I.
Histological subtype	Epithelioid	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Mixed/biphasic	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Sarcomatoid	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Others	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Performance Status at baseline	ECOG 0	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	ECOG 1	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Age	<65	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	≥65	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Gender	Female	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Male	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Race	White	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Black	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Other	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Baseline C-reactive protein level	≥1 mg/dL	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	<1 mg/dL	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Baseline platelet count	≤400x10^9/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	>400x10^9/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Baseline WBC	≤8.3x109/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	>8.3x10^9/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Baseline hemoglobin	<146 g/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	≥ 146 g/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
EORTC prognostic score	≤1.27	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	>1.27	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
PDL1	Positive	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)

Negative	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)

(1) Pembrolizumab with standard chemotherapy over standard chemotherapy alone hazard ratio (Unstratified)

Table 35: Progression Summary using mRECIST

Data set: All Randomized Patients

	Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
Patients who progressed	*** (**)	*** (**)
Progression on protocol treatment	**	**
Progression off protocol treatment	**	**
Death (without documented progression)	**	**
Patients who were censored	*** (**)	*** (**)
Reason Censored		
Lost to follow-up	**	**
Not progressed	**	**
missing greater than or equal to two consecutive scheduled imagings before observation of an event	**	**

Table 36: Progression Summary using iRECIST

Data set: All Randomized Patients

	Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
Patients who progressed	*** (**)	*** (**)
Progression on protocol treatment	**	**
Progression off protocol treatment	**	**
Death (without documented progression)	**	**
Patients who were censored	*** (**)	*** (**)
Reason Censored		
Lost to follow-up	**	**
Not progressed	**	**
missing greater than or equal to two consecutive scheduled imagings before observation of an event	**	**

Table 37: Progression Summary using RECIST 1.1

Data set: All Randomized Patients

	Number of Patients (%)

	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
Patients who progressed	*** (**)	*** (**)
Progression on protocol treatment	**	**
Progression off protocol treatment	**	**
Death (without documented progression)	**	**
Patients who were censored	*** (**)	*** (**)
Reason Censored		
Lost to follow-up	**	**
Not progressed	**	**
missing greater than or equal to two consecutive scheduled imagings before observation of an event	**	**

Figure 3: Kaplan-Meier Curves for Progression Free Survival (mRECIST)

Figure 4: Kaplan-Meier Curves for Progression Free Survival (iRECIST)

Table 38: Log Rank and Cox Regression Model for Progression Free Survival (PFS, progression defined using mRECIST)

Data set: All Randomized Patients						
			Univariate Analysis[1]		Multivariate Analysis[2]	
Treatment Arm/ Prognostic Factors at Baseline	N	Median PFS (Months)	Hazard Ratio[4] (95% CI)	Log-rank p-value	Hazard Ratio[4] (95% C.I.)	P-value from Cox regression
Treatment arm				0.***		0.***
Pembrolizumab with standard chemotherapy	***	**.**	**.**		**.**	
Standard chemotherapy alone	***	**.**	(**.**,**.**)		(**.**,**.**)	
Gender				0.***		0.***
Male	***	**.**	NC [3]		**.**	
Female	***	**.**			(**.**,**.**)	
Age				0.***		0.***
<65	***	**.**	NC		**.**	
∃65	***	**.**			(**.**,**.**)	
ECOG performance status				0.***		0.***
0	***	**.**	NC		**.**	
1	***	**.**			(**.**,**.**)	

(1) Stratified; (2) Stratified Cox regression with all factors included; (3) NC = not computed
(4) Hazard ratio of first category over second category

Table 39: Log Rank and Cox Regression Model for Progression Free Survival (PFS, progression defined using iRECIST)

Data set: All Randomized Patients						
			Univariate Analysis[1]		Multivariate Analysis[2]	
Treatment Arm/ Prognostic Factors at Baseline	N	Median PFS (Months)	Hazard Ratio[4] (95% CI)	Log-rank p-value	Hazard Ratio[4] (95% C.I.)	P-value from Cox regression
Treatment arm				0.***		0.***
Pembrolizumab with standard chemotherapy	***	**.**	**.**		**.**	
Standard chemotherapy alone	***	**.**	(**.**,**.**)		(**.**,**.**)	
Gender				0.***		0.***
Male	***	**.**	NC [3]		**.**	
Female	***	**.**			(**.**,**.**)	
Age				0.***		0.***
<65	***	**.**	NC		**.**	
∃65	***	**.**			(**.**,**.**)	

ECOG performance status				0.***	0.***
0	***	**.**	NC	**.**	
1	***	**.**		(**.**,**.**)	

(1) Stratified; (2) Stratified Cox regression with all factors included; (3) NC = not computed
(4) Hazard ratio of first category over second category

Table 40: Progression Free Survival (PFS) by Subsets (progression defined using mRECIST)

Data set: All Randomized Patients						
Factors	Value	Pembrolizumab with standard chemotherapy		Standard chemotherapy alone		
		N	Median PFS 95% C.I.	N	Median PFS 95% C.I.	Hazard Ratio[(1)] 95% C.I.
Histological subtype	Epithelioid	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Mixed/biphasic	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Sarcomatoid	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Others	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Performance Status at baseline	ECOG 0	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	ECOG 1	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Age	<65	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	≥65	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Gender	Female	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Male	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Race	White	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Black	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Other	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Baseline C-reactive protein level	≥1 mg/dL	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	<1 mg/dL	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Baseline platelet count	≤400x10^9/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	>400x10^9/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Baseline WBC	≤8.3x109/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	>8.3x10^9/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Baseline hemoglobin	<146 g/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	≥ 146 g/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
EORTC prognostic score	≤1.27	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	>1.27	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)

PDL1	Positive	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Negative	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)

(1) Pembrolizumab with standard chemotherapy over standard chemotherapy alone hazard ratio (Unstratified)

Table 41: Progression Free Survival (PFS) by Subsets (progression defined by iRECIST)

Data set: All Randomized Patients						
		Pembrolizumab with standard chemotherapy		Standard chemotherapy alone		
Factors	Value	N	Median PFS 95% C.I.	N	Median PFS 95% C.I.	Hazard Ratio(1) 95% C.I.
Histological subtype	Epithelioid	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Mixed/biphasic	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Sarcomatoid	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Others	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Performance Status at baseline	ECOG 0	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	ECOG 1	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Age	<65	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	≥65	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Gender	Female	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Male	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Race	White	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Black	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Other	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Baseline C-reactive protein level	≥1 mg/dL	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	<1 mg/dL	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Baseline platelet count	≤400x10^9/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	>400x10^9/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
Baseline WBC	≤8.3x109/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	>8.3x10^9/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)

Baseline hemoglobin	<146 g/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	≥ 146 g/L	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
EORTC prognostic score	≤1.27	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	>1.27	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
PDL1	Positive	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)
	Negative	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)

(1) Pembrolizumab with standard chemotherapy over standard chemotherapy alone hazard ratio (Unstratified)

Table 42: Objective Treatment Response (progression defined by mRECIST)

Data set: All Randomized Patients

	Number of Patients (%)[a] N=***	
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
Patients with at least one target lesion	N=***	N=***
Response-evaluable	N=***	N=***
Complete response (CR)	** (**)	** (**)
Partial response (PR)	** (**)	** (**)
Stable disease (SD)	** (**)	** (**)
Progressive disease (PD)	** (**)	** (**)
Inevaluable for response (IN)	** (**)	** (**)
<Reason 1>	**	**
<Reason 2>	**	**
....	...	....
Not response evaluable	N=***	N=***
Never treated	**	**
Not assessed (NA)	**	**
Patients with no target lesions	N=***	N=***
Response-evaluable	N=***	N=***
Complete response (CR)	**	**
Progressive disease (PD)	**	**
Non-CR/non-PD	**	**
Inevaluable for response (IN)	**	**
<Reason 1>	**	**
<Reason 2>	**	**
....	...	....
Not response evaluable	N=***	N=***
Not assessed (NA)	**	**
Never treated	**	**

[a] percentages are calculated out of the number of randomized patients

Table 43: Cochran-Mantel-Haenszel and Logistic Regression Model for Objective Response (progression defined by mRECIST)

Data set: All Randomized Patients				
	Univariate Analysis [1]		Multivariate Analysis [2]	
Treatment/ Prognostic Factors	Odds Ratio [4] (95%CI)	CMH p-value	Odds Ratio [4] (95% C.I.)	p-value from logistic regression
Treatment arm		0.***		0.***
Pembrolizumab with standard chemotherapy: standard chemotherapy alone	**.** (**.**,**.**)		**.** (**.**,**.**)	
Gender		0.***		0.***
Male: Female	NC [3]		**.** (**.**,**.**)	
Age		0.***		0.***
<65: ≥65	NC		**.** (**.**,**.**)	
ECOG performance status		0.***		0.***
0:1	NC		**.** (**.**,**.**)	

(1) Stratified
(2) Stratified Logistic regression, all factors included
(3) NC = not computed
(4) Odds ratio of first category over second category

Table 44: Objective Response According to Pretreatment Characteristics (progression defined by mRECIST)

Data set: All Randomized Patients		
	Number of Responses/Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
Histological type		
Epithelioid	**/** (**)	**/** (**)
Mixed/biphasic	**/** (**)	**/** (**)
Sarcomatoid	**/** (**)	**/** (**)
Others	**/** (**)	**/** (**)
Gender		
Male	**/** (**)	**/** (**)
Female	**/** (**)	**/** (**)
Age		
< 65 years	**/** (**)	**/** (**)
≥ 65 years	**/** (**)	**/** (**)
Race		
White	**/** (**)	**/** (**)
Black	**/** (**)	**/** (**)
Other	**/** (**)	**/** (**)
Baseline performance status		
ECOG 0-1	**/** (**)	**/** (**)
ECOG 2	**/** (**)	**/** (**)
Baseline C-reactive protein level		
⩾1 mg/dL	**/** (**)	**/** (**)
<1 mg/dL	**/** (**)	**/** (**)
Baseline platelet		
≤400x10^9/L	**/** (**)	**/** (**)
>400x10^9/L	**/** (**)	**/** (**)
Baseline WBC		
≤8.3x10^9/L	**/** (**)	**/** (**)
>8.3x10^9/L	**/** (**)	**/** (**)
Baseline hemoglobin		
< 146 g/L	**/** (**)	**/** (**)
≥ 146 g/L	**/** (**)	**/** (**)
EORTC prognostic score		
≤1.27	**/** (**)	**/** (**)
>1.27	**/** (**)	**/** (**)
PDL1		
Positive	**/** (**)	**/** (**)
Negative	**/** (**)	**/** (**)

Table 45: Duration of Objective Response (progression defined by mRECIST)

Data set: All Randomized Patients with CR or PR			
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***	P-value(1)
Median Duration of Response (months) (95% CI)	*** (**-**)	*** (**-**)	.**

(1) Stratified

Table 46: Immune Response (iRECIST)

Data set: All Randomized Patients

	Number of Patients (%)[a] N=***	
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
Patients with at least one target lesion	N=***	N=***
Response-evaluable	N=***	N=***
Immune Complete response (iCR)	** (**)	** (**)
Immune Partial response (iPR)	** (**)	** (**)
Immune Stable disease (iSD)	** (**)	** (**)
Immune confirmed progression (iCPD)	** (**)	** (**)
Immune unconfirmed progression (iUPD)	** (**)	** (**)
Inevaluable for response (IN)	** (**)	** (**)
<Reason 1>	**	**
<Reason 2>	**	**
....	...	....
Not response-evaluable	N=***	N=***
Never treated	**	**
Not assessed (NA)	**	**
Patients without any target lesion	N=***	N=***
Response-evaluable	N=***	N=***
Immune confirmed progression (iCPD)	**	**
Immune Stable disease (iSD)	**	**
Immune unconfirmed progression (iUPD)	** (**)	** (**)
Inevaluable for response (IN)	**	**
<Reason 1>	**	**
<Reason 2>	**	**
....	...	....
Not response-evaluable	N=***	N=***
Not assessed (NA)	**	**
Never treated	**	**

[a] percentages are calculated out of the number of randomized patients

Table 47: Cochran-Mantel-Haenszel and Logistic Regression Model for Immune Response (iRECIST)

Data set: All Randomized Patients				
	Univariate Analysis [1]		Multivariate Analysis [2]	
Treatment/ Prognostic Factors	Odds Ratio [4] (95%CI)	CMH p-value	Odds Ratio [4] (95% C.I.)	p-value from logistic regression
Treatment arm		0.***		0.***
Pembrolizumab with standard chemotherapy: standard chemotherapy alone	**.** (**.**,**.**)		**.** (**.**,**.**)	
Gender		0.***		0.***
Male: Female	NC [3]		**.** (**.**,**.**)	
Age		0.***		0.***
<65: ≥65	NC		**.** (**.**,**.**)	
ECOG performance status		0.***		0.***
0:1	NC		**.** (**.**,**.**)	

(1) Stratified
(2) Stratified Logistic regression, all factors included
(3) NC = not computed
(4) Odds ratio of first category over second category

Table 48: Immune Response According to Pretreatment Characteristics (iRECIST)

Data set: All Randomized Patients		
	Number of Responses/Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
Histological type		
Epithelioid	**/** (**)	**/** (**)
Mixed/biphasic	**/** (**)	**/** (**)
Sarcomatoid	**/** (**)	**/** (**)
Others	**/** (**)	**/** (**)
Gender		
Male	**/** (**)	**/** (**)
Female	**/** (**)	**/** (**)
Age		
< 65 years	**/** (**)	**/** (**)
≥ 65 years	**/** (**)	**/** (**)
Race		
White	**/** (**)	**/** (**)
Black	**/** (**)	**/** (**)
Other	**/** (**)	**/** (**)
Baseline performance status		
ECOG 0-1	**/** (**)	**/** (**)
ECOG 2	**/** (**)	**/** (**)
Baseline C-reactive protein level		
⩾1 mg/dL	**/** (**)	**/** (**)
<1 mg/dL	**/** (**)	**/** (**)
Baseline platelet		
≤400x10^9/L	**/** (**)	**/** (**)
>400x10^9/L	**/** (**)	**/** (**)
Baseline WBC		
≤8.3x10^9/L	**/** (**)	**/** (**)
>8.3x10^9/L	**/** (**)	**/** (**)
Baseline hemoglobin		
< 146 g/L	**/** (**)	**/** (**)
≥ 146 g/L	**/** (**)	**/** (**)
EORTC prognostic score		
≤1.27	**/** (**)	**/** (**)
>1.27	**/** (**)	**/** (**)
PDL1		
Positive	**/** (**)	**/** (**)
Negative	**/** (**)	**/** (**)

Table 49: Duration of Immune Response (iRECIST)

Data set: All Randomized Patients with iCR or iPR			
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***	P-value(1)
Median Duration of Response (months) (95% CI)	*** (**-**)	*** (**-**)	.**

(1) Stratified

Table 50: Objective Response (progression defined by RECIST 1.1)

Data set: All Randomized Patients

	Number of Patients (%)[a] N=***	
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
Patients with at least one target lesion	N=***	N=***
Response-evaluable	N=***	N=***
Complete response (CR)	** (**)	** (**)
Partial response (PR)	** (**)	** (**)
Stable disease (SD)	** (**)	** (**)
Progressive disease (PD)	** (**)	** (**)
Inevaluable for response (IN)	** (**)	** (**)
<Reason 1>	**	**
<Reason 2>	**	**
....	...	....
Not response evaluable	N=***	N=***
Never treated	**	**
Not assessed (NA)	**	**
Patients with no target lesions	N=***	N=***
Response-evaluable	N=***	N=***
Complete response (CR)	**	**
Progressive disease (PD)	**	**
Non-CR/non-PD	**	**
Inevaluable for response (IN)	**	**
<Reason 1>	**	**
<Reason 2>	**	**
....	...	....
Not response evaluable	N=***	N=***
Not assessed (NA)	**	**
Never treated	**	**

[a] percentages are calculated out of the number of randomized patients

Table 51: Cochran-Mantel-Haenszel and Logistic Regression Model for Objective Response (progression defined by RECIST 1.1)

Data set: All Randomized Patients				
	Univariate Analysis [1]		Multivariate Analysis [2]	
Treatment/ Prognostic Factors	Odds Ratio [4] (95%CI)	CMH p-value	Odds Ratio [4] (95% C.I.)	p-value from logistic regression
Treatment arm		0.***		0.***
Pembrolizumab with standard chemotherapy: standard chemotherapy alone	**.** (**.**,**.**)		**.** (**.**,**.**)	
Gender		0.***		0.***
Male: Female	NC [3]		**.** (**.**,**.**)	
Age		0.***		0.***
<65: ≥65	NC		**.** (**.**,**.**)	
ECOG performance status		0.***		0.***
0:1	NC		**.** (**.**,**.**)	

(1) Stratified
(2) Stratified Logistic regression, all factors included
(3) NC = not computed
(4) Odds ratio of first category over second category

Table 52: Objective Response According to Pretreatment Characteristics (progression defined by RECIST 1.1)

Data set: All Randomized Patients		
	Number of Responses/Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
Histological type		
Epithelioid	**/** (**)	**/** (**)
Mixed/biphasic	**/** (**)	**/** (**)
Sarcomatoid	**/** (**)	**/** (**)
Others	**/** (**)	**/** (**)
Gender		
Male	**/** (**)	**/** (**)
Female	**/** (**)	**/** (**)
Age		
< 65 years	**/** (**)	**/** (**)
≥ 65 years	**/** (**)	**/** (**)
Race		
White	**/** (**)	**/** (**)
Black	**/** (**)	**/** (**)
Other	**/** (**)	**/** (**)
Baseline performance status		
ECOG 0-1	**/** (**)	**/** (**)
ECOG 2	**/** (**)	**/** (**)
Baseline C-reactive protein level		
⩾1 mg/dL	**/** (**)	**/** (**)
<1 mg/dL	**/** (**)	**/** (**)
Baseline platelet		
≤400x10^9/L	**/** (**)	**/** (**)
>400x10^9/L	**/** (**)	**/** (**)
Baseline WBC		
≤8.3x10^9/L	**/** (**)	**/** (**)
>8.3x10^9/L	**/** (**)	**/** (**)
Baseline hemoglobin		
< 146 g/L	**/** (**)	**/** (**)
≥ 146 g/L	**/** (**)	**/** (**)
EORTC prognostic score		
≤1.27	**/** (**)	**/** (**)
>1.27	**/** (**)	**/** (**)
PDL1		
Positive	**/** (**)	**/** (**)
Negative	**/** (**)	**/** (**)

Table 53: **Duration of Objective Response (progression defined by RECIST 1.1)**

Data set: All Randomized Patients with CR or PR			
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***	P-value(1)
Median Duration of Response (months) (95% CI)	*** (**-**)	*** (**-**)	.**

(1) Stratified

Table 54: Adverse Events

Data set: All randomized patients						
	Number of patients (%) N=***					
	Worst grade					Any grade
	1	2	3	4	5	
Patients with any AE	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with AE within category						
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...						
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...						

(1) Patients may have more than one event within a category.

Table 55: Serious adverse events

Data set: All randomized patients				
	Number of patients (%) N=***			
	Worst grade			Any grade 3 or higher AE
	3	4	5	
Patients with any AE	** (**)	** (**)	** (**)	** (**)
Patients with AE within category				
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)

(1) Patients may have more than one event within a category.

Table 56: Drug Related Adverse Events

(1) Related to Pembrolizumab

Data set: All Treated Patients on Pembrolizumab with Standard Chemotherapy Arm						
	Number of patients (%) N=***					
	Worst grade					Any grade
	1	2	3	4	5	
	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with AE related to Pembrolizumab within category						
Category 1[(a)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(a)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)

(a) Patients may have more than one event within a category.

NOTE: Same type of tables to be made for both treatment arms for adverse events related to pemetrexed, cisplatin, or carboplatin.

Table 57: Drug Related Serious adverse events

Data set: All Treated Patients on Pembrolizumab with Standard Chemotherapy Arm				
	Number of patients (%) N=***			
	Worst grade			Any grade 3 or higher AE
	3	4	5	
Patients with any AE	** (**)	** (**)	** (**)	** (**)
Patients with AE within category				
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)

(1) Patients may have more than one event within a category.

NOTE: Same type of tables to be made for both treatment arms for serious adverse events related to pemetrexed, cisplatin, or carboplatin.

Table 58: Drug Related Adverse Events leading to treatment discontinuation

(1) Related to Pembrolizumab

Data set: All Treated Patients on Pembrolizumab with Standard Chemotherapy Arm

	Number of patients (%) N=***					
	Worst grade					Any grade
	1	2	3	4	5	
	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with AE related to Pembrolizumab within category						
Category 1[(a)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(a)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)

(b) Patients may have more than one event within a category.

NOTE: Same type of tables to be made for both treatment arms for adverse events related to pemetrexed, cisplatin, or carboplatin leading to treatment discontinuation.

Table 59: Immune-Related Adverse Events

Data set: All Treated Patients on Pembrolizumab with Standard Chemotherapy Arm

	Number of patients (%) N=***					
	Worst grade					Any grade
	1	2	3	4	5	
	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with Immune-related AE within category						
Category 1[(a)]						
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(a)]						
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)

(c) Patients may have more than one event within a category.

Table 60: Hematology: Worst Grade per Patient

Data set: All Treated Patients		
	Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N = ***
Hemoglobin		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Platelet		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
WBC		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Neutrophils		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Lymphocytes		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)

Table 61: Serum Chemistry: Worst Grade per Patient

Data set: All Treated Patients		
	Number of Patients (%)	
	PEMBROLIZUMAB WITH STANDARD CHEMOTHERAPY N = ***	STANDARD CHEMOTHERAPY ALONE N = ***
Total bilirubin		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Alkaline phosphatase		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
ALT		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
AST		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
LDH		
Normal	** (**)	** (**)
High [(1)]	** (**)	** (**)
Serum Creatinine		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Hyperkalemia		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Hypokalemia		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Hypercalcemia		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Hypocalcemia		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)

Grade 4	** (**)	** (**)
Hypermagnesemia		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Hypomagnesemia		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Hyperalbuminemia		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Hypoalbuminemia		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Creatinine clearance		
Normal	** (**)	** (**)
High [(1)]	** (**)	** (**)
Amylase		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Lipase		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
C-reactive protein		
Normal (< mg/dL)	** (**)	** (**)
High (≥1 mg/dL)	** (**)	** (**)

[(1)] Greater than upper normal limit

Table 62: Thyroid Function Tests: Worst during protocol treatment

Data set: All Treated Patients		
	Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N = ***
TSH		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T3 Free		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T3 Total		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T4 Free		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T4 Total		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
TSH		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)
>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)
T3 Free		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)
>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)
T3 Total		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)
>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)
T4 Free		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)

>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)
T4 Total		
Normal	** (**)	** (**)
>1-1.5xULN	** (**)	** (**)
>1.5-2.0xULN	** (**)	** (**)
>2.0-5.0xULN	** (**)	** (**)
>5.0xULN	** (**)	** (**)

Data set: All Treated Patients		
	Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N = ***
TSH		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T3 Free		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T3 Total		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T4 Free		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)
T4 Total		
Normal	** (**)	** (**)
<1-0.5xLLN	** (**)	** (**)
<0.5-0.1xLLN	** (**)	** (**)
<0.1xLLN	** (**)	** (**)

Table 63: Coagulation Tests: Worst during Protocol Treatment

Data set: All Treated Patients		
	Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N = ***
PT		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
INR		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
PTT		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)

Table 64: Endocrine Biochemistry: Worst during Protocol Treatment

Data set: All Treated Patients		
	Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N = ***
ACTH		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Cortisol serum		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Prolactin		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
FSH		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Leutinizing Hormone		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
PTH		
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)

Table **65: Cardiac Function**

Data set: All Treated Patients		
	Number of patients (%)	
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
ECG reported	*** (**)	*** (**)
All Normal	**	**
At least one abnormal but none clinically important	**	**
At least one abnormal and clinically important	**	**
ECG not reported/not performed	*** (**)	*** (**)
LVEF reported	*** (**)	*** (**)
All Normal	**	**
At least one abnormal	**	**
LVEF not reported/not performed	*** (**)	*** (**)

Table 66 : Urinalysis

Data set: All Treated Patients		
	Number of patients (%)	
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
Urinalysis – WBC		
Negative/trace	**(**)	**(**)
1+(>20 mg/dL–30 mg/dL)	**(**)	**(**)
2+(>30 mg/dL–100 mg/dL)	**(**)	**(**)
3+(>100 mg/dL– 300 mg/dL)	**(**)	**(**)
4+(>300 mg/dL)	**(**)	**(**)
Urinalysis – RBC		
Negative/trace	**(**)	**(**)
1+(>20 mg/dL–30 mg/dL)	**(**)	**(**)
2+(>30 mg/dL–100 mg/dL)	**(**)	**(**)
3+(>100 mg/dL– 300 mg/dL)	**(**)	**(**)
4+(>300 mg/dL)	**(**)	**(**)
Urinalysis – Protein		
Negative/trace	**(**)	**(**)
1+(>20 mg/dL–30 mg/dL)	**(**)	**(**)
2+(>30 mg/dL–100 mg/dL)	**(**)	**(**)
3+(>100 mg/dL– 300 mg/dL)	**(**)	**(**)
4+(>300 mg/dL)	**(**)	**(**)

Table 67: Hospitalization

Data set: All Treated Patients		
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
Number (%) cycles with hospitalization	**/** (**)	**/** (**)
Number (%) of patients hospitalized	** (**)	** (**)

Table 68: Transfusion

Data set: All Treated Patients		
	Number of patients (%)	
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
Number (%) of patients transfused	** (**)	** (**)
Type of transfusion [(1)]		
Number of patients received red cell concentrates	**	**
Number of patients received platelets	**	**
Number of patients received other transfusions	**	**

[(1)] All cycles

Table 69: Deaths During or within 30 days of Last Protocol Treatment

Data set: All Treated Patients		
	Number of Patients (%)	
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N=***
Number of Patients who died during or within 30 days of last protocol treatment	** (**)	** (**)
Cause of Death		
Study-specific malignant disease only	**	**
Adverse event possibly, probably or definitely related to protocol treatment	**	**
Complication from a non-protocol treatment for this malignancy (malignant disease may or may not be contributory)	**	**
Death from disease with Medical Assistance in Dying	**	**
Other Primary Malignancy	**	**
Other Condition or Circumstance	**	**

Table 70: Adverse Event leading to Discontinuation of Protocol Treatment

Data Set: All Treated Patients							
	Pembrolizumab with standard chemotherapy				Standard chemotherapy alone		
	Pembrolizumab N=***	Pemetrexed N=***	Cisplatin N=***	Carboplatin N=***	Pemetrexed N=***	Cisplatin N=***	Carboplatin N=***
Number discontinued for adverse events	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
<Adverse event 1>	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
<Adverse event 2>	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
....	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)

Table 71: Tobacco Smoking History

Data set: All Treated Patients		
	Pembrolizumab with standard chemotherapy	Standard chemotherapy alone
Smoked tobacco during protocol treatment	** (**)	** (**)

Table 72: Concomitant Medications

Data set: All Treated Patients		
	Number of patients (%)	
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N=***
Any concomitant medication during or 4 weeks after protocol treatment		
No	** (**)	** (**)
Yes	** (**)	** (**)
Type of concomitant medications(1)		
Medication A	** (**)	** (**)
…		
Any steroid or anti-emetic medication during or 4 weeks after protocol treatment		
No	** (**)	** (**)
Yes	** (**)	** (**)

(1) Patients may have received more than one concomitant medication.

Table 73: Major Medical Problems

Data set: All Treated Patients		
	Number of patients (%)	
	Pembrolizumab with standard chemotherapy N = ***	Standard chemotherapy alone N=***
Any major medical problem during protocol treatment for patients		
No	** (**)	** (**)
Yes	** (**)	** (**)
Type of major medical problems(1)		
Medical problem A	** (**)	** (**)
…		

(1) Patients may have more than one major medical problem.

Table 74: Anti-Cancer Treatment

	Number of patients (%)	
	Pembrolizumab with standard chemotherapy N=***	Standard chemotherapy alone N =***
Number of patients with any other anti-cancer treatment during or 4 weeks after protocol treatment	*** (**)	*** (**)
Chemotherapy [(1)]	*** (**)	*** (**)
Drug 1 …	***	***
Radiotherapy [(1)]	*** (**)	*** (**)
Surgery[(1)]	*** (**)	*** (**)
Procedure 1…	***	***
Hormonal therapy [(1)]	*** (**)	*** (**)
Drug 1 …	***	***
Immunotherapy [(1)]	*** (**)	*** (**)
Drug 1 …	***	***
Other [(1)]	*** (**)	*** (**)
Drug 1 …	***	***
Number of patients with any new anti-cancer treatment during follow-up	*** (**)	*** (**)
Chemotherapy [(1)]	*** (**)	*** (**)
Drug 1 …	***	***
Radiotherapy [(1)]	*** (**)	*** (**)
Surgery[(1)]	*** (**)	*** (**)
Procedure 1…	***	***
Hormonal therapy [(1)]	*** (**)	*** (**)
Drug 1 …	***	***
Immunotherapy [(1)]	*** (**)	*** (**)
Drug 1 …	***	***
Other [(1)]	*** (**)	*** (**)
Drug 1 …	***	***

(1) Patients could have more than one type of anti-cancer treatment.

Table 75: Compliance Rate with QoL Assessment by Treatment Arm

	Pembrolizumab with standard chemotherapy		Standard chemotherapy alone	
	Expected	Received (%)	Expected	Received (%)
Baseline	***	** (**)	***	** (**)
Cycle 2	***	** (**)	***	** (**)
…	***	** (**)	***	** (**)
4 weeks after treatment	***	** (**)	***	** (**)
Follow-up visit 1	***	** (**)	***	** (**)
…	***	** (**)	***	** (**)

Table 76: Time to Deterioration in QoL Primary Endpoints

Data set: All patients who had baseline and at least one follow-up QoL assessment						
	Pembrolizumab with standard chemotherapy		Standard chemotherapy alone		p-value	
	N	Median (months) (95% CI)	N	Median (months) (95% CI)	Unadjusted(1)	Adjusted(2)
Cough	***	**.** (**.**, **.**)	***	**.** (**.**, **.**)	.**	.**
Dyspnea	***	**.** (**.**, **.**)	***	**.** (**.**, **.**)	.**	.**
Pain	***	**.** (**.**, **.**)	***	**.** (**.**, **.**)	.**	.**

(1) From log-rank test;
(2) By Hochberg procedure.

Table 77: QoL: Summary Baseline Scores

	Pembrolizumab with standard chemotherapy	Standard chemotherapy alone	P value*
Functional scales			
Physical			0.***
N	***	***	
Mean	***	***	
STD	***	***	
...	...	...	
Global health status			0.***
N	***	***	
Mean	***	***	
STD	***	***	
Symptom scales			
Fatigue			0.***
N	***	***	
Mean	***	***	
STD	***	***	
…	…	…	

* Wilcoxon rank sum test

Table 78: Summary QOL Change Scores from Baseline for Scale/Domain/Item at Each Time Period*

	Pembrolizumab with standard chemotherapy	Standard chemotherapy alone	P Value**
Scale/Domain/Item			
Cycle 2			.**
N	***	***	
Mean	***	***	
STD	***	***	
…			.**
N			
Mean	***	***	
STD	***	***	
4 weeks after treatment			.**
N			
Mean	***	***	
STD	***	***	
Follow-up 1			.**
N			
Mean	***	***	
STD	***	***	
…			.**
N			
Mean	***	***	
STD	***	***	

* Table will be provided for each scale/domain/item.
** Wilcoxon rank sum test

Table 79: Results for QOL Response Analyses

Domain	Pembrolizumab with standard chemotherapy N (%)			Standard chemotherapy alone N (%)			P-value*
	Improved	Stable	Worsened	Improved	Stable	Worsened	
EORTC QLQ-C30							
Physical	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Role	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Emotional	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Cognitive	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Social	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Global	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Pain	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Fatigue	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Nausea	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Dyspnea	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Sleep	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Appetite	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Constipation	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Diarrhea	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Financial	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
EORTC QLQ-LC13							
Cough	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Hemoptysis	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Dyspnea	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Sore month	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Trouble swallowing	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Peripheral neuropathy	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Hair loss	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Pain in chest	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Pain in shoulder	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Pain elsewhere	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Pain medication	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**

* Chi-square test

Table 80: Dates used to derive LKAD

Data	**CRF Section Name**	**Date Variable as the source of LKAD**	**Description**	**Note**
form date (follow up form)				
I227PHY	Physical Exam	PE_DT	Date of Exam	
I227VIT	Vital Signs	VS_DT	Date of test	

I227DA	Drug Administration	SDA_DT	Dose administrate date where the SDA_GIVDOS not equal to 0.	Only for ivi/imi protocol therapy
Protocol therapy (treatment form)				Only for ivi/imi protocol therapy
I227DM	Dose Modification and Reason	DOSMOD_DT	Dose modification date where DOSMOD_TYP_IV in ('RED','INC')	For all protocol drug therapy
I227XT	Lesion evaluation	LES_TAR_TEST_DT, LES_NTAR_TEST_DT, LES_NEW_TEST_DT	Date of Test for Target, non-target and new lesion	
I227ORI	Other Radiology Investigations	RAD_INV_DT	Date of Test	
I227LAB	Hematology and Biochemistry	SAE_LT_RECOV_DT	Date of blood collection	
I227EBIO	Endocrine Biochemistry	EBIO_DT	Date of blood collection	
I227COAG	Coagulation	COAG_DT	Date of blood collection	
I227UR	Urinalysis	URIN_DT	Date of urinalysis	
I227CD	Cardiac Function (including ECG, LVEF)	LVEF_DT, ECG_DT	Date of ECG/LVEF	
I227TRN	Transfusions	TRAN_DT	Date of Transfusions	
I227HOSP	Hospitalization	HOSP_ADM_DT, HOSP_DIS_DT	Admission Date and Discharge Date	
I227SAE	Adverse Event (SAE)	SAE_AE_ONSET_PA, SAE_AE_RES_PA	Date of onset and Date of Resolution (SAE)	
I227SAELAB	Tests (Numeric)	SAE_LT_WORST_DT	Date of Worst Value	
I227SAETEST	Tests (Non-numeric)	SAE_OI_DT	Date (of Test)	
I227CT	Cancer Treatment	TRT_STP_PA, TRT_STRT_PA (use the original date which may contains partial date)	Treatment Start Date/Treatment Stop Date	
Radiation (**treatment form**)	Cancer Treatment	TRT_STRT_PA, TRT_STP_DT (F5 only)	start and completion dates	Must be complete dates
Surgery (**treatment form**)	Cancer Treatment	TRT_STRT_PA (F5 only)	date of surgery	
Anti-cancer Rx (**treatment form**)	Cancer Treatment	TRT_STRT_PA (F5 only)	start date	Must be complete dates