BR34 Statistical Final Analysis Plan

A RANDOMIZED TRIAL OF DURVALUMAB AND TREMELIMUMAB ± PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH METASTATIC (STAGE IV) SQUAMOUS OR NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC)

CCTG Protocol Number: BR.34

REGULATORY SPONSOR: CANADA: CCTG
Australia: NHMRC-CTC
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SUPPORTED BY: AstraZeneca

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1. Introduction

The document describes the final data analysis plan for Canadian Cancer Trials Group (CCTG) study BR34, which is supported by AstraZeneca.

The study was activated on Feb. 15th of 2017, and has 28 Canadian centres plus 15 Australian centres. Accrual was completed in November 2018, with 301 patients (300 planned) enrolled, 53 from Australia and the remainder from Canadian sites. The data has been collected and cleaned by CCTG according to the data management plan for this study.

All analyses will be performed by the trial bIOtatistician at CCTG and a final statistical analysis report will be prepared. A copy of this report will be sent to the study chair for the writing of the manuscript and to AstraZeneca. If needed, AstraZeneca may conduct additional analyses as required to support regulatory submissions.

1.1 Study Design

BR34 is a prospective, randomized, multi-center study in patients with metastatic squamous and non-squamous non-small cell lung cancer. The primary objective is to compare the effect between the treatments of durvalumab/Tremelimumab and the durvalumab/Tremelimumab + standard 1st line platinum-based Chemotherapy on overall survival (OS) in the study population. Patients will be randomized with a 1:1 ratio to two study treatment arms, stratified by smoking status (< 100 cigarettes (Never smoked) vs previous vs current), disease stage (IVA vs. IVB), and histology type (squamous vs. non-squamous).

Secondary objectives include comparisons of progression free survival (PFS), objective response rate (ORR), quality of life (QoL), health economics between treatment arms, assessment of the toxicity and safety of the study treatments, and to determine the prognostic and predictive effect of tumour PD-L1 expression assessed by IHC on efficacy.

Sample size: The sample size for this study is determined to compare the OS in all randomized patients between 2 study treatment arms. Assuming a 2-year survival rate of 40% for the durvalumab and Tremelimumab arm, to detect a hazard ratio (HR) of 0.67 (in comparison of Chemotherapy + durvalumab and Tremelimumab to durvalumab and Tremelimumab) with 80% power using a 1-sided 5% level test, we need to accrue 300 patients (150 in each arm) in 18 months, the required number of events (a minimum of 155) would be observed with another 15 months follow up. Log-rank test stratified by stratification factors at randomization will be used to test the difference in OS between two treatment arms.

Treatment Group Assignment: Treatment assignment was performed centrally using Mango software located in central office of CCTG. The randomization algorithm minimizes the chance of an imbalance between the two treatment arms within study center with respect to the following stratification factors: 1) smoking status (< 100 cigarettes (Never smoked) vs previous vs current), 2) disease stage (IVA vs. IVB), and 3) histology type (squamous vs. non-squamous).

1.2 Time of the analysis

There is a planned interim analysis (IA) in addition to the final analysis for this study. The IA was planned to perform on PFS when 154 PFS events (PDs or deaths without documented PD) had been observed in the trial. The analysis is mainly to check if the study regimen has the potential targeted treatment effect or not, if not, resource on the trial could be allocated to other important studies. The futility guideline was based on the estimate of the hazard ratio of IO + Chemotherapy in comparison to IO treatment alone in comparison of PFS. If the estimated HR is 0.86 or greater, the study treatment may not have the targeted treatment effect. Otherwise, we will continue the trial to obtain the required number of events for final analysis on OS. In middle of Feb. 2019, the required number of events for IA on PFS was observed. The trial study team used the Feb. 28 of 2019 as the

data cutoff date for the analysis. The IA was performed at the end of June of 2019 with 199 PFS events. The analysis report was sent to CCTG DSMC to review, and the DSMC recommendation was to continue the trial for final analysis of OS.

This document is to describe the statistical analysis plan for the final analysis according to the study protocol with a minimum of 155 deaths observed. The SAP is prepared to support publication of the study results, AstraZeneca will prepare a supplementary SAP for analyses supporting submissions to regulatory authorities. The document will be finalized before any of the analysis for the final trial database. A data cutoff point will be pre-specified for data included in the analysis.

It should be pointed out that the detailed SAPs for correlative study and the health economic analysis will be prepared separately after the final analysis.

2. Methods and Analyses

2.1 Analyses Populations

Analysis populations for this analysis include the intention to treat (ITT) population (i.e. all as randomized patients) and the as-treated population (i.e. all patients who received at least one dose of the study treatments).

Analysis of pretreatment characteristics and all efficacy endpoints, such as PFS and OS, will be based on the ITT population. Safety and drug exposure analyses will be performed on the as-treated population.

2.2 Conventions for Calculating Key Data

Baseline evaluations are those collected closest, but prior to or on the day of randomization.

When either day or month of a date is missing, the missing day and/or month will be imputed by the midpoints within the smallest known interval. For example, if the day of the month is missing for any date used in a calculation, the 15th 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 July of the year will be used to replace the missing day. However, logic checks will be performed to ensure that no imputed data date is after the patient's death.

2.3 Analysis Conventions

All comparisons will be by treatment arm unless otherwise specified.

The following baseline factors that will be used to adjust the analyses where appropriate are listed below:

- Smoking status (never (< 100) vs previous vs current)
- Disease stage (IVA vs. IVB)
- Histology type (squamous vs. non-squamous)

(Note: for each factor, missing/unknown will be added category whenever appropriate.)

2.4. Randomization and Pre-treatment Characteristics

2.4.1 Definitions and Variables

2.4.1.1 Accrual

X Number (%) of randomized patients per study center (Table 1).

2.4.1.2 Randomization/Stratification

- Smoking status (never vs previous vs current)
- Disease stage (IVA vs. IVB)
- Histology type (squamous vs. non-squamous) (table 2).

(Note: An unknown/missing category will be added to each factor whenever appropriate.)

X Treatment randomized to receive will be compared with the actual treatment received during the first cycle to identify any discrepancies (Table 3)

X Baseline patient characteristics will be compared with the patient's corresponding stratification assignment to identify any discrepancies (Table 4)

2.4.1.3 Ineligibility and significant entry violations/deviations (Table 5)

X Eligible patients: % yes, no

X Reasons for ineligibility: % for each reason and combination of reasons for ineligibility.

X Significant entry violations/deviations: number and % for each deviation.

2.4.1.4 Summary of Follow-up

A table showing the median, min and max follow-up will be presented by treatment group and for all patients included in the analysis (Table 6, Median follow up uses the K-M estimate from the OS while reverse the event status. The min and max are based on patients who are still alive.).

2.4.1.5 Patient Characteristics (Table 7)

X Sex: % male, female

X Race: % Caucasian, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Not reported (or refused), Other.

X Age: < 65 vs. ≥ 65, median, min and max;

X ECOG Performance status: % 0, 1;

X METASTATIC DISEASE AT DIAGNOSIS (No vs. Yes);

X Prior Radiation Therapy (Yes vs. No)

X Smoking status (never vs previous vs current)

X Disease stage (IVA vs. IVB)

X Histology type (squamous vs. non-squamous).

X PD-L1 Expression (≥50% VS. 25 – 49% VS 1-24% VS. <1%)

X **Blood TMB (< 20 vs. ≥ 20 mut/Mb)**

(Note: Form 1 data/later imported correlative data. Missing or unknown will be added as a category whenever appropriate).

2.4.1.6 Extent of disease at baseline (Table 8)

X Number (%) of patients with target lesions only, and both target and non-target lesions

X involved disease sites (target or non-target lesions):
- X #(%) Abdomen
- X # (%) Adrenals
- X # (%) Bone
- X # (%) Brain
- X # (%) Chest wall
- X # (%) Kidney
- X # (%) liver
- X # (%) lung
- X # (%) Nodes
- X # (%) Pleura
- X # (%) Pleural effusion
- X # (%) Subcutaneous tissue
- X # (%) others

2.4.1.7 Baseline symptoms (Table 9)

The NCI CTCAE V4.0 will be used for the categorization of all baseline symptoms.

- X Any event per patient: % yes, no
- X Event by body system
- X Grade of type of event (1, 2, 3, 4)

2.4.1.8 Baseline Hematology/Biochemistry (Table 10)

CTC grades will be used to summarize the baseline hematology/biochemistry data.

% by CTC grades

- X WBC
- X hemoglobin
- X Platelets
- X differential (neutrophils and lymphocytes)
- X serum creatinine
- X total bilirubin
- X alkaline phosphatase
- X ALT (SGPT)
- X AST (SGOT)
- X LDH
- X Hypoalbuminemia
- X Amylase
- X Lipase
- X PTT

2.4.1.9 Concomitant Medications on study entry (Table 11)

A concomitant medication is defined as a medication, which was taken within one week prior to date of randomization

- X Any concomitant medication: % yes, no
- X Number of patients for each type of medication.

2.4.1.10 Major Medical Problems (Table 12)

A major medical problem is defined as a problem ongoing, and any previous significant or relevant medical problems at baseline.

X Any major problem: % yes, no

X Type of the major problem: % diabetes, cardiac, etc.

2.4.2 Analysis of pre-treatment characteristics

No formal statistical tests will be performed to assess homogeneity of baseline characteristics between the arms. Categorical variables will be tabulated with number and row percentages by treatment arm and for all patients. Continuous variables (e.g., age) will be presented using summary statistics (n, median, min and max) by treatment arm based on all randomized patients by arm according to the ITT population.

2.5 Efficacy

2.5.1 Definitions of Efficacy Variables

2.5.1.1 Overall Survival

Overall survival (OS) is defined as the time from the randomization to the date of death of any cause, or censored at the last known alive date before or on data cutoff date.

Overall Survival Time (months) =

((date of death or the last known alive date - date of randomization) + 1) / 30.4375

2.5.1.2 Progression free survival

PFS is defined as the time from the date of randomization to the date of first documented disease progression or death without documented PD (from any cause). Patients who are alive and disease progression free at the time of the analysis will be censored at their last disease assessment date.

PFS Time (months) =

[(date of disease progression or death from any cause - date of randomization) + 1] / 30.4375.

2.5.1.3 Tumor Response

Tumor response and progression will be evaluated in this study using the revised international criteria proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee, and the modified iRECIST guidelines.

Best overall best response status to protocol treatment will be classified and used for the analysis as follows**.**

Complete Response (CR): disappearance of target and non-target lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases before CR can be accepted. Confirmation of response is only required in non-randomised studies.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is only required in non-randomised studies.

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

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table S1: Integration of target, non-target and new lesions into response assessment

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

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

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

iRECIST Response Assessment

Overall response will also be assessed using iRECIST *[Seymour 2016]*. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumour burden, or the appearance of new lesions, does not reflect true tumour progression (called pseudo-progression or PSPD).

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

Table S2: Time-point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: • further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD SOM ≥5 mm and / or • NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD ≥5 mm and / or • previously identified NT lesion iUPD (need not be unequivocal) and /or • size or number of new lesions previously identified

Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on • increase in size or number of new lesions previously identified
* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.				

Table S3: iRECIST Best Overall Response (iBOR)

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

- Table assumes a randomised study where confirmation of CR or PR is not required.
- NE = not evaluable that cycle.
- Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

All patients will have their iBOR from the start of study treatment until the end of treatment.

2.5.1.4 Response rate

The overall best response rate is calculated as responders (CR+PR) / (all randomized patients) and the evaluable response rate is calculated as responders (CR+PR) / (all patients evaluable for RECIST response). (*Evaluable for Response*. 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).

Similarly, the iResponse rate according to i**RECIST** is calculated as responders (iCR+iPR) / (all randomized patients) and the evaluable response rate is calculated as responders (iCR+iPR) / (all patients evaluable for iRECIST response). (*Evaluable for iResponse*. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for iresponse (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable).

2.5.2 Analysis of Efficacy Outcomes

All efficacy analyses will be presented by treatment arm based on the ITT population.

2.5.2.1 Overall Survival

Kaplan-Meier curves for the distribution of OS by treatment arm will be displayed in Figure 1. The primary test of the difference between the two treatment arms will be the log-rank test stratified by stratification factors used at randomization (values collected at randomization)

- Smoking status (never (< 100 cigarettes) vs previous vs current)
- Disease stage (IVA vs. IVB)
- Histology type (squamous vs. non-squamous).

As a sensitivity analysis, log rank test stratified by stratification factors with data collected/corrected at baseline (data reported in baseline report or corrected in WEC) to test the difference between treatment arms.

The 1–sided p-value for above tests will be presented.

The estimated hazard ratio (HR) (IO + Chemotherapy vs. IO alone (Referent group)) from the Cox regression model stratified by stratification factors for the study will be reported (table 13).

An unstratified analysis will also be performed.

For patients who died, their causes of death will be summarized (Table 14).

Subgroup Analysis: The analysis of OS will be presented for each level of stratification factors, PD-L1 expression levels and **TMB levels** to check the homogeneity of treatment effect across the levels of those factors.

Median survivals for each level of stratification factors, the PD-L1 IHC expression levels and the TMB levels, HR and its 90% C.I. in comparison between treatment arms will be presented. To test the homogeneity of treatment effect across the level of stratification factors, Cox regression model will be used with interaction terms included (Exclude those with missing for test the interaction) (Table 15).

Subgroup Analysis by PD-L1 expression levels: Kaplan-Meier curves for the distribution of overall survival by treatment arm will be displayed for PD-L1 expression levels of ≥25% (Figure 2) and those with < 25% patients (Figure 3) respectively. The primary test of the difference between the two treatment arms will be the log-rank test stratified by stratification factors used at randomization (values collected at baseline). Median survivals, HR and its 90% C.I. in comparison between treatment arms will be presented. Cox regression model stratified by stratification factors will be used with interaction terms included to test the differential treatment effects between PD-L1 expression levels ≥ 25% and those with PD-L1 expression levels < 25% patients.

Subgroup Analysis by TMB levels: Kaplan-Meier curves for the distribution of overall survival by treatment arm will be displayed for TMB levels of ≥20% (Figure 4) and those with < 20% patients (Figure 5) respectively. The primary test of the difference between the two treatment arms will be the log-rank test stratified by stratification factors used at randomization (values collected at baseline). Median survivals, HR and its 90% C.I. in comparison between treatment arms will be presented. Cox regression model stratified by stratification factors will be used with interaction terms included to test the differential treatment effects between TMB levels ≥ 20% and those with TMB levels < 20% patients.

2.5.2.2 Progression Free Survival

The same analysis for OS will be carried out for PFS (Table 16, 18). The summary of patients disease status in PFS evaluation, and reason for censoring, which includes receiving anti-cancer therapy for NSCLC, prior to documentation of disease progression will be tabulated (Table 17). The anti-cancer therapy received after the

progression will also be tabulated (Table 19).

2.5.2.3 Response Rate

Responses (CR+PR vs. other) will be summarized in a frequency table for all randomized patients by treatment arm and for patients with target lesions or patients with non-target lesions (see Table 20). The comparison of both overall and evaluable response rate will be done using a Cochran-Mantel-Haenszel (CMH) test stratified for stratification factors at randomization, at a 1-sided 5% level of significance (table 21). Unstratified Chi-square test will also be presented for test response rates between treatment arms.

Frequency tables of the overall and evaluable response rate will be given by some categorical variables which are baseline value of the stratification variables and selected factors for each treatment arm (see Table 22).

The same analysis will be performed for iResponse rate.

2.6 Drug Exposure

2.6.1 Definitions and Variables

2.6.1.1 Duration of Study Therapies in Weeks

Duration of study therapy (cycles) is defined as the number of cycles from the first cycle of Durvalumab + Tremelimumab / Chemotherapy vs. Durvalumab + Tremelimumab to the last cycle that the patient took.

- X Duration of study therapy (cycles) for all patients by treatment arms (Table 23): median, min and max

2.6.1.2 Cumulative dose and dose intensity of IO+Chemotherapy /IO

The total of Chemotherapy, Durvalumab, Tremelimumab doses taken by the patients is defined as the sum of each IO, CHEMOTHERAPY taken by patients during the duration of the study.

Dose intensity is defined as the cumulative dose received divided by the duration of the study therapy in weeks.

Relative dose intensity is defined as dose intensity divided by the dose prescribed for the duration of the study therapy (prescribed dose times the duration of a patient was on treatment).

- X Total of IO+Chemotherapy /IO doses (Table 23): median, min and max.
- X Dose intensity per patient during the study (Table 23): median, min and max.
- X Relative dose intensity during the study (Table 23): median, min and max.

2.6.1.3 Dose adjustment, interruption or discontinuation (Table 24)

IO+Chemotherapy/IO dose may be adjusted (slowing/interruption of infusion rate, omission of a dose, or permanent discontinuation) because of toxicities or other reasons.

- X The number of patients with at least one dose adjustment/interruption or discontinuation during the study
- X specify the primary reason for the dose omission/interruption: % of patients with each reason (e.g., hematologic toxicity, other AEs, etc.)
- X number of patients discontinued protocol treatment
- X specify reasons for protocol treatment discontinuation: % of patients with each reason (e.g., AEs, progressive disease, intercurrent illness, etc.)

2.6.2 Analysis

All variables will be summarized for all treated patients by treatment arm.

2.7 Concomitant medications, transfusion and hospitalization

2.7.1 Definition and Variables

Concomitant medications are all other medications (other than study drugs) taken at any time on-study. Hospitalizations are those which occur at any time on-study.

- **X** any concomitant medications or treatments per patient (Table 25): % yes, no**.**
- X any prophylactic or supportive care medications per patient (Table 25): % yes, no
- X any concomitant medication for acute immune related adverse events per patient (Table 25): % yes, no
- X any hospitalization per patient (Table 25): % yes, no, Duration: Median and range.

2.7.2 Analysis

Supportive and concomitant medications and therapies will be displayed for all treated patients. The data will be presented as shown in the table samples in Table 25.

2.8 Safety

2.8.1 Definitions and variables

2.8.1.1 Laboratory tests

Analyses of laboratory data will include analyses of hematology and biochemistry tests. The hematology data include WBC, platelets, neutrophils, hemoglobin and the biochemistry data include ALT(SGPT), total bilirubin, serum creatinine, albumin, LDH, (Tables 26-27). Laboratory results will be graded according to the CTC criteria version 4.0.

All laboratory data collected at any time during the study for these tests will be included in the analyses of worst value on study and those collected during a specific cycle for these tests will be included in the analyses of worst value during that cycle.

All tests specified above:

- X CTC grade for worst value on-study (for hematology and biochemistry tests): %0, 1, 2, 3, 4
- X CTC grade for worst value by cycle (for hematology and biochemistry tests): %0, 1, 2, 3, 4

2.8.1.2 Toxicity/adverse event/intercurrent illness

The CTC version 4.0 will be used to summarize toxicities/adverse events/intercurrent illnesses. Events will be displayed by primary term. All toxicities/adverse events/intercurrent illnesses data collected at any time will be included in the analyses of worst value on study will be included in the analyses of worst value during that cycle. All the analyses will be repeated to include only the toxicities/adverse events/intercurrent illnesses which are drug related (The relation to protocol therapy higher than or equal to 3).

- X Any event during the study (Table 28): % yes
- X Worst severity per patient per primary term on study (Table 26): % CTC grade 1, 2, 3, 4, unknown

X Toxicity/adverse event/intercurrent illness which are serious (reasons for seriousness in the toxicity table higher than or equal to 1), fatal only (reason for seriousness in the toxicity table equal to 1), leading to hospitalization (reason for seriousness in the toxicity table equal to 3) (Table 29)

X Toxicity/adverse event/intercurrent illness that led to study drug discontinuation (Table 30)

X Toxicity/adverse event/intercurrent illness that led to dose interruptions (Table 31)

X Deaths within 90 days from last treatment administration (Table 32)

X Cause of death within 90 days from last treatment administration (Table 32):

2.8.2 Analysis

All patients who received at least one dose of study medication will be included in the safety analyses. Overall AE rate and grade 3+ AE rate by treatment arm will be compared using the chi-square tests. Top 10 toxicities**,** and drug related grade 3 or higher will be compared using the Fisher's exact test for comparison of the toxicity rates between 2 treatment arms.

2.9 Off-study

2.9.1 Definitions and Variables

X For each study drug， the number of patients off the drug and the reasons for off the drug will be presented. (Table 33): Number and % of all randomized patients

2.9.2 Analysis

Tables will be presented by treatment arm and for all patients.
For Patients who were off treatment due to protocol treatment toxicities, a table will be prepared to tabulate the number of patients for each toxicity.

2.10 Quality of Life (QoL)

2.10.1 Definitions and Variables

2.10.1.1 EORTC QLQ-C30

There are five functional domains and three symptom domains that can be derived from EORTC QLQ-C30 (see below for definitions). If the number of unanswered questions in each domain is within a limit specified with the definition for each domain, the score is calculated as for function domains:
Score=100-(((Total score for the answered questions/(no. of questions answered))-1)*100/3)
In addition, for symptom domains:
Score = (((Total score for the answered questions/(no. of questions answered))-1)*100/3)
Otherwise, the score will be recorded as "missing". For each single item, the score will be recorded as "missing" if the answer to this item is missing.

Functional Domains:

X Physical: Questions: 1, 2, 3, 4, 5
Score=missing if number of above questions not answered is greater than 2;

X Role: Questions: 6, 7
Score=missing if number of above questions not answered is greater than 0;

X Emotional: Questions: 21, 22, 23, 24
Score=missing if number of above questions not answered is greater than 2;

X Cognitive: Questions: 20, 25
Score=missing if number of above questions not answered is greater than 0;

X Social: Questions: 26, 27

Score=missing if number of above questions not answered is greater than 0;

Symptom Domains:

X Fatigue: Questions: 10, 12, 18
Score=missing if number of above questions not answered is greater than 1;

X Nausea and vomiting: Questions: 14, 15
Score=missing if number of above questions not answered is greater than 0;

X Pain: Questions: 9, 19
Score=missing if number of above questions not answered is greater than 0.

There are also six single items in EORTC QLC-C30 pertaining to common symptoms and one global assessment that can be derived from EORTC QLQ-C30. The single items are:

Single Items:

X Dyspnea: Question 8;
X Sleep: Question 11;
X Appetite: Question 13;
X Constipation: Question 16;
X Diarrhea: Question 17;
X Financial: Question 28.

They are all scored using the following formula:
Score = (Answered score to the question-1)*100/3.

The **Global Assessment** includes Questions 29 and 30. If number of these two questions not answered is greater than 0, its score will be "missing"; Otherwise,
Score = ((Total scores for the answered questions/(no. of questions answered))-1)*100/6.

2.10.1.2 EORTC QLQ-LC13

There are one symptom domain and 10 single items that can be derived from EORTC QLQ-LC13 (see below for definitions). The following are the scoring algorithms for these domains/items.

Symptom Domains/Items:

X Cough: Question: 31
Score=missing if the answer to this item is missing;
Otherwise, Score = (Answered score to the question-1)*100/3;

X Hemoptysis: Question: 32
Score=missing if the answer to this item is missing;
Otherwise, Score = (Answered score to the question-1)*100/3;

X Dyspnea domain: Questions: 33, 34, 35
Score=missing if number of above questions not answered is greater than 1;
Otherwise,
Score = ((Total scores for the answered questions/(no. of questions answered))-1)*100/3.

X Sore mouth: Questions: 36
Score=missing if the answer to this item is missing;
Otherwise, Score= (Answer to the question-1)*100/3;

X Trouble swallowing: Questions: 37
Score=missing if the answer to this item is missing;
Otherwise, Score= (Answer to the question-1)*100/3;

X Peripheral neuropathy: Questions: 38
Score=missing if the answer to this item is missing;

Otherwise, Score= (Answer to the question-1)*100/3;

X Hair loss: Questions: 39
Score=missing if the answer to this item is missing;
Otherwise, Score= (Answer to the question-1)*100/3;

X Pain in chest: Questions: 40
Score=missing if the answer to this item is missing;
Otherwise, Score= (Answer to the question-1)*100/3;

X Pain in shoulder: Questions: 41
Score=missing if the answer to this item is missing;
Otherwise, Score=(Answer to the question-1)*100/3;

X Pain elsewhere: Questions: 42
Score=missing if the answer to this item is missing;
Otherwise, Score=(Answer to the question-1)*100/3;

X Pain medication: Questions: 43
Score=missing if the answer to this item is missing;
Otherwise, Score=(Answer to the question-1)*100/3;

2.10.2 Analysis

All analyses on quality of life scores will be exploratory and will include all randomized patients with available data.

2.10.2.1 Determination of Assessment Times

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) At each cycle during the IO+ CHEMOTHERAPY/IO alone: If the QoL is assessed within 2 week 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) At progression: If the QoL is assessed within 1 week when the progression is documented;
3) At four weeks following the completion of the last cycle: 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 off treatment periods: patients are supposed to be seen in clinic and complete QOL questionnaire every 12 weeks after their week 4 visit following the completion of the last cycle. If the QoL is assessed within 5 weeks before or after the expected date for a given follow-up period, this assessment is considered as an assessment for that period.

2.10.2.2 Calculation of Compliance Rates

The method used to calculate the compliance rates of QoL assessment (See Tables 34) 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:

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 the cycle is the total number of patients who received this cycle of treatment;
3) At progression: the number expected is the total number of patients who has progressed;

4) 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 did not have PD before the time point;
5) Other off treatment period: patients are supposed to complete QoL questionnaire every 12 weeks. The expected number of forms is determined by the total number of patients at one month following the completion of last cycle minus the number of patients who have died or progressed during that and previous follow up period.

2.10.2.3 Cross-sectional analysis

The mean and standard deviation of QL scores at baseline and mean and standard deviation of QoL change scores from baseline at each assessment time will be calculated (see Table 35). Then Wilcoxon Rank-Sum test is used to compare two treatment arms in terms of change in QOL score at each assessment time from baseline (see Table 36).

2.10.2.4 QoL response analysis

QOL response analysis is the NCIC QoL committee recommended analysis, and is calculated as follows: for a functional domain, a change score of 10 points from baseline was defined as clinically relevant. Patients were considered improved if reported a score 10-points or better than baseline at any time of QOL assessment. Conversely, patients were considered worsened if reported a score minus 10-points or worse than baseline at any time of QOL assessment without above defined 10-point improvement. Patients whose scores were between 10-point changes from baseline at every QOL assessment were considered as stable. In contrast to functional domains, for the determination of patient's QOL response, classification of patients into improved and worsened categories is revered for symptom domains and single items. Chi-square test is then performed to compare the distributions of these three categories between two arms, and Mantel-Haenszel chi-square test for trend is used to test if there is a trend that patients in one treatment arm have higher proportions in the better QoL categories than those on the other arm. (Table 37).

3. Tables

Table 1: Accrual by Center

Data set: All Randomized Patients			
	Number of patients (%)		
	IO+Chemotherapy N = ***	IO N = ***	Total N = ***
Center #1	*** (**)	*** (**)	*** (**)
Center #2	*** (**)	*** (**)	*** (**)
Center #3	*** (**)	*** (**)	*** (**)
...	*** (**)	*** (**)	*** (**)

Table 2: Accrual by Stratification Factor at Randomization

Data set: All Randomized Patients

	Number of patients (%)		
	IO+Chemotherapy N = ***	IO N=***	Total N = ***
Stage			
IVA	** (**)	** (**)	** (**)
IVB	** (**)	** (**)	** (**)
Smoking Status			
< 100	** (**)	** (**)	** (**)
Former	** (**)	** (**)	** (**)
Current	** (**)	** (**)	** (**)
Disease Histology			
squamous	** (**)	** (**)	** (**)
non-squamous	** (**)	** (**)	** (**)

Source: Centralized Randomization File

Table 3: Treatment as Randomized Versus as Treated at Cycle 1

Data set: All Randomized Patients			
	Number of Patients (%) Randomized Arm		
	IO+Chemotherapy N=***	IO N=***	Total N=***
Treatment Received			
IO+Chemotherapy	*** (**)	*** (**)	*** (**)
IO	*** (**)	*** (**)	*** (**)
Not treated	*** (**)	*** (**)	*** (**)

Table 4: Discrepancies between Stratification Level as Randomized and at Baseline

Data set: All Randomized Patients						
	Number of patients (%)					
	IO+Chemotherapy N=***		IO N=***		Total N=***	
Any difference	*** (**)		*** (**)		*** (**)	
At baseline	As Randomized		As Randomized		As Randomized	
Stage	IVA	IVB	IVA	IVB	IVA	IVB
IVA	**	**	**	**	**	**
IVB	**	**	**	**	**	**
Smoking status	< 100	Prev| Curr	< 100	Prev| Curr	< 100	prev| Curr
< 100	**	** | **	**	** | **	**	** | **
Prev	**	** | **	**	** | **	**	** | **
Curr	**	** | **	**	** | **	**	** | **
Histology Type	Squa	Non-Squa	Squa	Non-Squa	Squa	Non-Squa
squamous	**	**	**	**	**	**
non-squamous	**	**	**	**	**	**

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

Data set: All Randomized Patients			
	Number of Patients (%)		
	IO+CHEMOTHERAPY N=***	IO N=***	Total N=***
Eligible	*** (**)	*** (**)	*** (**)
Not Eligible	*** (**)	*** (**)	*** (**)
Reason for ineligibility			
<Reason 1>	**	**	**
<Reason 2>	**	**	**
...	**	**	**
Major protocol violation			
<violation 1>	**	**	**
<violation 2>	**	**	**
...	**	**	**

Table 6: Follow-up for Patients included in analysis

Data set: All Randomized Patients with PD-L1+			
	IO+CHEMOTHERAPY arm	IO arm	All patients
Median (Min, Max)	*** (**, **)	*** (**, **)	*** (**, **)

The same table will be presented for all randomized patients and by arm.

Table 7: Patients Characteristics at Baseline

Data set: All Randomized Patients			
	Number of patients (%)		
	IO+CHEMOTHERAPY N=***	IO N=***	Total N=***
Sex			
Female	** (**)	** (**)	** (**)
Male	** (**)	** (**)	** (**)
Race			
White	** (**)	** (**)	** (**)
Black	** (**)	** (**)	** (**)
....	** (**)	** (**)	** (**)
Age (years)			
N	**	**	**
Median	**	**	**
Min - Max	** - **	** - **	** - **
≤ 65	** (**)	** (**)	** (**)
> 65	** (**)	** (**)	** (**)
Histology type			
Non-Squa	** (**)	** (**)	** (**)
squamous	** (**)	** (**)	** (**)
…	** (**)	** (**)	** (**)
Smoking history			
Never smoked	** (**)	** (**)	** (**)
Former Smoker	** (**)	** (**)	** (**)
Current smoker	** (**)	** (**)	** (**)
ECOG PS			
0	** (**)	** (**)	** (**)
1	** (**)	** (**)	** (**)
Meta Disease at Diag			
Yes			
No			
Prior RT			
Yes			
No			

PD-L1			
≥25%	** (**)	** (**)	** (**)
< 25%	** (**)	** (**)	** (**)
TMB			
≥ 20%	** (**)	** (**)	** (**)
< 20%		** (**)	** (**)
Unknown	** (**)		
	** (**)	** (**)	** (**)

Add an unknown category where it is appropriate.

The same table will be presented for all randomized patients by arm.

Table 8: Extent of Disease (All Target and Non-Target Lesions)

Data set: All Randomized Patients			
	Number of Patients (%)		
	IO+Chemotherapy N=***	IO alone N=***	Total N=***
Presence of Target Lesions			
Patients with target lesions only	*** (**)	*** (**)	*** (**)
Patients with non-target lesions only	*** (**)	*** (**)	*** (**)
Patients with both target and non-target lesions	*** (**)	*** (**)	*** (**)
Disease Site[(1)]			
Abdomen	*** (**)	*** (**)	*** (**)
Adrenals	*** (**)	*** (**)	*** (**)
Bone	*** (**)	*** (**)	*** (**)
Brain	*** (**)	*** (**)	*** (**)
Chest Wall	*** (**)	*** (**)	*** (**)
Kidney	*** (**)	*** (**)	*** (**)
Liver	*** (**)	*** (**)	*** (**)
Lung	*** (**)	*** (**)	*** (**)
Nodes	*** (**)	*** (**)	*** (**)
Pleura	*** (**)	*** (**)	*** (**)
pleural effusion	*** (**)	*** (**)	*** (**)
Subcutaneous Tissue	*** (**)	*** (**)	*** (**)
CNS meta			
Other	*** (**)	*** (**)	*** (**)
Number of disease sites			
1	*** (**)	*** (**)	*** (**)
2	*** (**)	*** (**)	*** (**)
3	*** (**)	*** (**)	*** (**)
4	*** (**)	*** (**)	*** (**)
≥5	*** (**)	*** (**)	*** (**)

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

Table 9: Baseline Signs and Symptoms

Data set: All Randomized Patients (IO+Chemotherapy Arm)

	Number of patients (%) N=***					
	Worst grade					Any grade
	NR	1	2	3	4	
Patients with any sign/symptom at baseline	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with particular sign or symptom, within body system:						
Body System 1(1)	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 2	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 3	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Body System 2(1)						
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)

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

NOTE: Same table to be made for IO Arm

Table 10: Baseline Hematology/Biochemistry

Data set: All Randomized Patients (IO+CHEMOTHERAPY Arm)			
	Number of Patients (%)		
	IO+CHEMOTHERAPY N = ***	IO N = ***	Total N=***
Hematology:			
WBC			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported (1)	** (**)	** (**)	** (**)
Differential			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported (1)	** (**)	** (**)	** (**)
Platelet			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported (1)	** (**)	** (**)	** (**)
Hemoglobin			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported (1)	** (**)	** (**)	** (**)
Biochemistry:			
serum creatinine			
Grade 0	** (**)	** (**)	** (**)
Grade 1	** (**)	** (**)	** (**)
Grade 2	** (**)	** (**)	** (**)
Grade 3	** (**)	** (**)	** (**)
Grade 4	** (**)	** (**)	** (**)
Not reported (1)	** (**)	** (**)	** (**)
…….			

(1) Not done or outside the 14-day window prior to start of therapy

NOTE: Same table to be made for IO Arm

Table 11: Concomitant Medications at Baseline

Data set: All Randomized Patients			
	Number of patients (%)		
	IO+CHEMOTHERAPY N=***	IO N=***	Total N=***
Any concomitant medication at baseline [(1)]			
No	** (**)	** (**)	** (**)
Yes	** (**)	** (**)	** (**)

[(1)]Any medication taken within one week prior to start of therapy treatment

Table 12: Major Medical Problems at Baseline

Data set: All Randomized Patients			
	Number of patients (%)		
	IO+CHEMOTHERAPY N = ***	IO N = ***	Total N=***
Patients Reporting at least one medical problem	** (**)	** (**)	** (**)
Type Medical Problem[(1)] (from highest to lowest in frequency)			
Diabetes	** (**)	** (**)	** (**)
Bronchopulmonary	** (**)	** (**)	** (**)
Gastrointestinal	** (**)	** (**)	** (**)
Cardiovascular	** (**)	** (**)	** (**)
Hypertension	** (**)	** (**)	** (**)
Endocrine/metabolic	** (**)	** (**)	** (**)
Genitourinary	** (**)	** (**)	** (**)
Musculoskeletal	** (**)	** (**)	** (**)
HENT	** (**)	** (**)	** (**)
...			

(1) patients may report more than one medical problem

Table 13: Log Rank and Cox Regression Model for OS

Data set: All Randomized Patients included in the interim analysis

		Univariate Analysis[1]		Univariate Analysis[2]	
Treatment Arm/ Prognostic Factors at Baseline	Median Survival (Months)	Hazard Ratio (95% CI)	Log-rank p-value	Hazard Ratio (95% C.I.)	Log-rank p-value
Treatment arm			0.***		0.***
IO+CHEMOTHERAPY	**.**	**.**		**.**	
IO	**.**	(**.**,**.**)		(**.**,**.**)	

(1) Stratified (value at randomization)
(2) Stratified (values reported in Form 1)

Table 14: Death Summary

Data set: All Randomized Patients

	Number of Patients (%)	
	IO+Chemotherapy N=***	IO alone N=***
Patients who died	*** (**)	*** (**)
Cause of Death		
Non-small cell lung cancer	** (**)	**(**)
Toxicity from protocol treatment	** (**)	** (**)
Combination of NSCLC and protocol treatment complication	** (**)	** (**)
Non-protocol treatment complication	** (**)	** (**)
Combination of NSCLC and non-protocol treatment complication	** (**)	** (**)
Other primary malignancy	** (**)	** (**)
Other condition and circumstances	** (**)	** (**)
Patients who were censored	*** (**)	*** (**)
Reason Censored		
Still alive	** (**)	** (**)
Lost to follow-up	** (**)	** (**)

Table 15: Survival by Subsets

Data set: All Randomized Patients

Factors	Value	IO+Chemotherapy N	IO+Chemotherapy Median Survival 90% C.I.	IO alone N	IO alone Median Survival 90% C.I.	Hazard Ratio[(1)] 90% C.I.	P-value-test interaction
Histology Type At baseline	Non-Squa	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	0.****
	Squamous	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
Tobacco Use At baseline	Never	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	0.****
	Ever used	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
Disease Stage At baseline	IVA	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	0.****
	IVB	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
PD-L1 At baseline	≥50%	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	0.****
	25- 49%	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
	1-24%%	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
	< 1%	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
TMB	≥20%	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	0.****
	< 20%	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	

(1) IO+Chemotherapy over IO alone hazard ratio (Unstratified)

Table 16: Log Rank and Cox Regression Model for Progression Free Survival

Data set: All Randomized Patients					
	Univariate Analysis[1]			Univariate Analysis[2]	
Treatment Arm/ Prognostic Factors at Baseline	Median Survival (Months)	Hazard Ratio (90% CI)	Log-rank p-value	Hazard Ratio (90% C.I.)	Log-rank p-value
Treatment arm			0.***		0.***
IO+Chemotherapy	**.**	**.**		**.**	
IO alone	**.**	(**.**,**.**)		(**.**,**.**)	

(1) Stratified (value at randomization)
(2) Stratified (values reported in Form 1)

Table 17: Progression Summary

Data set: All Randomized Patients

	Number of Patients (%)	
	IO + Chemotherapy N=***	IO alone N=***
Patients who progressed	*** (**)	*** (**)
Progression on study	**	**
Progression during follow-up	**	**
Death (without documented progression)	**	**
Patients who were censored	*** (**)	*** (**)
Reason Censored		
Received anti-cancer therapy before documented progression:		
Chemotherapy	**	**
Radiotherapy	**	**
Hormonal therapy	**	**
Immunotherarpy	**	**
EGFR inhibitors	**	**
....	**	**
Lost to follow-up	**	**
Not progressed	**	**

Table 18: Progression Free Survival by Subsets

Data set: All Randomized Patients

Factors	Value	IO+Chemotherapy N	IO+Chemotherapy Median Survival 90% C.I.	IO alone N	IO alone Median Survival 90% C.I.	Hazard Ratio[(1)] 90% C.I.	P-value-test interaction
Histology Type At baseline	Non-Squa	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	0.****
	Squamous	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
Tobacco Use At baseline	Never	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	0.****
	Ever used	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
Disease Stage At baseline	IVA	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	0.****
	IVB	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
PD-L1 IHC Level	≥50%	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	0.****
	25- 49%	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
	1-24%	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
	< 1%	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
TMB	TMB						0.****
TMB	≥20%	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	
	< 20%	**	**.** (**.**,**.**)	**	**.** (**.**,**.**)	**.** (**.**,**.**)	

(1) IO+Chemotherapy over IO alone hazard ratio (Unstratified)

Table 19: Anti-Cancer Therapy Received After Relapse

Data set: All Randomized patients		
	Number of patients (%)	
	IO+Chemotherapy N=***	IO N =***
Number of patients with any follow-up therapy	*** (**)	*** (**)
Chemotherapy (1)	*** (**)	*** (**)
Agent (Pemetrexed; taxotere; etc….	*** (**)	*** (**)
EGFR inhibitor (1)	*** (**)	*** (**)
Agent (erlotinib, gefitinib; etc)	*** (**)	*** (**)
Radiotherapy (1)	*** (**)	*** (**)
Hormonal therapy (1)	*** (**)	*** (**)
Immunotherapy (1)	*** (**)	*** (**)
Other (1)	*** (**)	*** (**)

(1) Patients could have more than one type of therapy.

Table 20: Treatment Response

Data set: All Randomized Patients

	Number of Patients (%)* N=***	
	IO+Chemotherapy N=***	IO alone N=***
Patients with at least one target lesion**	N=***	N=***
Complete response (CR)	** (**)	** (**)
Partial response (PR)	** (**)	** (**)
Stable disease (SD)	** (**)	** (**)
Progressive disease (PD)	** (**)	** (**)
Inevaluable for response (IN)	** (**)	** (**)
<Reason 1>	**	**
<Reason 2>	**	**
....	...	....
Patients with no target lesions***	N=***	N=***
Complete response (CR)	**	**
Stable Disease (SD)	**	**
Progressive disease (PD)	**	**
Inevaluable for response (IN)	**	**
<Reason 1>	**	**
<Reason 2>	**	**
....	...	....

* percentages are calculated out of the number of patients in each category
** only patients with at least one target lesion are evaluable as defined by RECIST
*** patients with non-measurable disease only were followed for complete response, and disease progression. Patients who were assessed but did not meet the definition of CR or PD were recorded as SD.

Table 21: Cochran Mantel Haenszel for Best Response

Data set: All Randomized Patients

	Univariate Analysis (1)		Univariate Analysis(2)	
Treatment/ Prognostic Factors	Odds Ratio (90%CI)	CMH p-vlaue	Odds Ratio (90% C.I.)	CMH p-vlaue
Treatment arm		0.***		0.***
IO+Chemotherapy: IO alone	**.** (**.**,**.**)		**.** (**.**,**.**)	

(1) Stratified (value at randomization)
(2) Stratified (values reported in Form 1)

Table 22: Best Response According to Baseline Stratification Factors

Data set: All Randomized Patients		
	Number of Responses/Number of Patients (%)	
	IO+Chemotherapy N=***	IO alone N=***
Histology Type		
Non-Squa	**/** (**)	**/** (**)
Squamous	**/** (**)	**/** (**)
Tobacco Use		
Never	**/** (**)	**/** (**)
Ever used	**/** (**)	**/** (**)
Disease Stage		
IVA	**/** (**)	**/** (**)
IVB	**/** (**)	**/** (**)
PD-L1		
≥50%	**/** (**)	**/** (**)
25-49%	**/** (**)	**/** (**)
1-24%	**/** (**)	**/** (**)
< 1%	**/** (**)	**/** (**)
TMB		
≥20%	**/** (**)	**/** (**)
< 20%	**/** (**)	**/** (**)

NOTE: Same table to be made based on all response evaluable patients

Table 23: Total Treatment Duration and Dose of IO+CHEMOTHERAPY /IO

Data Set: All Treated Patients		
	IO+CHEMOTHERAPY	IO
Duration in cycles:		
N	***	***
Median	*	*
Min – Max	* - *	* - *
Total dose:		
Durv		
N	***	***
Median	*	*
Min – Max	* - *	* - *

Dose Intensity:		
Durv		
N	***	***
Median	*	*
Min – Max	* - *	* - *
Relative Dose Intensity:		
Durv		
N	***	***
Median	*	*
Min – Max	* - *	* - *
Total dose:		
Tremelimumab		
N	***	***
Median	*	*
Min – Max	* - *	* - *
Dose Intensity:		
Tremelimumab		
N	***	***
Median	*	*
Min – Max	* - *	* - *
Relative Dose Intensity:		
Tremelimumab		
N	***	***
Median	*	*
Min – Max	* - *	* - *
Total dose:		
Chemotherapy*		
N	***	
Median	*	
Min – Max	* - *	
Dose Intensity:		
Chemotherapy*		
N	***	
Median	*	
Min – Max	* - *	
Relative Dose Intensity:		
Chemotherapy*		
N	***	
Median	*	
Min – Max	* - *	

*Chemotherapy for each of drug for the study, i.e., cisplatin, *carboplatin,* gemcitabine,

Table 24: Dose adjustment, Interruption or Discontinuation

Data Set: All Treated Patients

	Number of patients (%)	
	IO+Chemotherapy (N=***)	IO (N=***)
At least one doseadjustment, interruption or discontinuation	** (**)	** (**)
Primary reason for dose interruption		
<reason 1>	** (**)	** (**)
<reason 2>	** (**)	** (**)
...	** (**)	** (**)
Protocol treatment discontinuation	** (**)	** (**)
Primary reasons for discontinuation	** (**)	** (**)
<reason 1>	** (**)	** (**)
<reason 2>	** (**)	** (**)
……		
Secondary reasons for discontinuation		
<reason 1>	** (**)	** (**)
<reason 2>	** (**)	** (**)
……	** (**)	** (**)

Table 25: Summary of Supportive and Concomitant Medications and Therapy, Transfusion and hospitalization

Data Set: All Treated Patients						
	Number of patients (%)					
	IO+Chemotherapy (n = ***)		IO (n = ***)		TOTAL (n = ***)	
Any radiation therapy	***	(**)	***	(**)	***	(**)
Any blood transfusion	***	(**)	***	(**)	***	(**)
Any concomitant medication	***	(**)	***	(**)	***	(**)
Any hospitalization	***	(**)	***	(**)	***	(**)
Days of hospitalization	**		**		**	
Median	**-**		**-**		**-**	
Range						

* Patients may have received more than one type of concomitant medication

Table 26: Hematology: Worst Ever Grade per Patient on Study

Data set: All Treated Patients		
	Number of patients (%)	
	IO+CHEMOTHERAPY	IO
WBC		
Number of patients	**	**
Grade 0	** (**)	** (**)
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Platelets		
Number of patients	**	**
Grade 0	** (**)	** (**)
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Neutrophils		
Number of patients	**	**
Grade 0	** (**)	** (**)
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Hemoglobin		
Number of patients	**	**
Grade 0	** (**)	** (**)
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)

……

Table 27: Biochemistry: Worst Ever Grade per Patient on Study

Data set: All Treated Patients		
	Number of patients (%)	
	IO+CHEMOTHERAPY	IO
ALT (SGPT)		
Number of patients	**	**
Grade 0	** (**)	** (**)
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Total bilirubin		
Number of patients	**	**
Grade 0	** (**)	** (**)
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Creatinine		
Number of patients	**	**
Grade 0	** (**)	** (**)
Grade 1	** (**)	** (**)
Grade 2	** (**)	** (**)
Grade 3	** (**)	** (**)
Grade 4	** (**)	** (**)
Albumin		
Number of patients	**	**
Normal	** (**)	** (**)
Low[(1)]	** (**)	** (**)
High[(2)]	** (**)	** (**)
LDH		
Number of patients	**	**
Normal	** (**)	** (**)
Low[(1)]	** (**)	** (**)
High[(2)]	** (**)	** (**)

[(1)] Less than lower normal limit
[(2)] Greater than upper normal limit
NOTE: Patients can have more than one category (low and/or high)

Table 28: Toxicity/Adverse Events/Intercurrent Illness (Worst Ever Grade on Study)

Data set: All Treated Patients (IO+CHEMOTHERAPY Arm)

	Number of patients (%) N=***					
	Worst grade					Any grade
	NR	1	2	3	4	
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: In IO Arm, the same type of table will be made. Same type of tables which include only the toxicities/adverse events/intercurrent illnesses which are drug related will be made for both IO+Chemotherapy and IO arms.

Table 29: Worst Ever Grade Toxicities/Adverse Event/Intercurrent Illness which are Serious, Fatal Only, Leading to Hospitalization

Data set: All Treated Patients (IO+CHEMOTHERAPY Arm)

	Number of patients (%) N=***					
	Worst grade					Any grade
	NR	1	2	3	4	
Patients with serious AE within category						
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Patients with fatal AE within category						
Category 1[(1)]						
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]						
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Patients with AE leading to hospitalization within category						
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 1[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...						
	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Category 2[(1)]	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
Event 1	**(**)	**(**)	**(**)	**(**)	**(**)	**(**)
...						

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

NOTE: In IO Arm, the same type of table will be made. Same type of tables which include only the toxicities/adverse events/intercurrent illnesses which are drug related will be made for both IO+CHEMOTHERAPY and IO arms.

Table 30: Worst Ever Grade Toxicity/Adverse Event/Intercurrent Illness Led to Dose Discontinuation

Data set: All Treated Patients (IO+CHEMOTHERAPY Arm)

	Number of patients (%) N=***					
	Worst grade					Any grade
	NR	1	2	3	4	
Patients with any AE led to study drug discontinuation	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with AE led to study drug discontinuation 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: In IO Arm, the same type of table will be made. Same type of tables which include only the toxicities/adverse events/intercurrent illnesses which are drug related will be made for both IO+CHEMOTHERAPY and IO arms.

Table 31: Worst Ever Grade Toxicity/Adverse Event/Intercurrent Illness Led to Dose Interruption

Data set: All Treated Patients (**IO+CHEMOTHERAPY** Arm)

	Number of patients (%) N=***					
	Worst grade					Any grade
	NR	1	2	3	4	
Patients with any AE led to dose interruption	** (**)	** (**)	** (**)	** (**)	** (**)	** (**)
Patients with AE led to dose interruption 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: In IO Arm, the same type of table will be made. Same type of tables which include only the toxicities/adverse events/intercurrent illnesses which are drug related will be made for both IO+CHEMOTHERAPY and IO arms.

Table 32: Deaths on Study within 90 Days of the Last Treatment

Data set: All Treated Patients		
	Number of Patients (%)	
	IO+CHEMO THERAPY N=***	IO alone N=***
Number of Patients who died within 30 days of last treatment	** (**)	** (**)
Cause of Death		
NSCLC	** (**)	** (**)
Toxicity from protocol treatment	** (**)	** (**)
NSCLC + Toxicity from Protocol Treatment complication	** (**)	** (**)
Non-protocol Treatment Complication	** (**)	** (**)
NSCLC + Non-protocol Treatment Complication	** (**)	** (**)
Other Primary Malignancy	** (**)	** (**)
Other Condition or Circumstance	** (**)	** (**)

Table 33: Reason Off-Protocol Therapy

	Number of patients (%) **IO+CHEMO THERAPY** (n = ***)		IO alone (n = ***)		TOTAL (n = ***)	
Number (%) patients off the drug*	**	(**)	**	(**)	**	(**)
Reasons off study						
Progressive disease	**	(**)	**	(**)	**	(**)
Clinical progression	**	(**)	**	(**)	**	(**)
Intercurrent disease	**	(**)	**	(**)	**	(**)
Toxicity to protocol treatment	**	(**)	**	(**)	**	(**)
Death	**	(**)	**	(**)	**	(**)
Other	**	(**)	**	(**)	**	(**)
Unknown	**	(**)	**	(**)	**	(**)
Never treated	**	(**)	**	(**)	**	(**)

*The same table will be made for each drug on the study by treatment arm.

Table 34: Compliance (Received/Expected) with QoL Assessment by Treatment Arm

	IO+ Chemotherapy		IO alone	
Period	Expected	Received (%)	Expected	Received (%)
Baseline	***	*** (**.*)	***	*** (**.*)
Day 1 Cycle2	***	*** (**.*)	***	*** (**.*)
Cycle3	***	*** (**.*)	***	*** (**.*)
…	***	*** (**.*)	***	*** (**.*)
At progression	***	*** (**.*)	***	*** (**.*)
4 weeks	***	*** (**.*)	***	*** (**.*)
Every 12 Wks	***	*** (**.*)	***	*** (**.*)
…	***	*** (**.*)	***	*** (**.*)

Table 35: Baseline Score for Each Domain/item

Domain/item		IO + Chemotherapy	IO alone	P-value
Physical	N	***	***	0.**
	MEAN	**.**	**.**	
	STD DEV	**.**	**.**	
Emotional	N	***	***	0.**
	MEAN	**.**	**.**	
	STD DEV	**.**	**.**	
…	N	***	***	0.**
	MEAN	**.**	**.**	
	STD DEV	**.**	*.**	
……..				

Table 36: Mean QOL Change Scores from Baseline for Global Domain at Each Assessment Time

	IO+ Chemotherapy		IO alone		
Assessment	N	Mean (SD)	N	Mean (SD)	P value*
Day 1 Cycle2	***	**.** (**.**)	***	**.** (**.**)	0.**
Cycle3	***	**.** (**.**)	***	**.** (**.**)	0.**
…	***	**.** (**.**)	***	**.** (**.**)	0.**
Progression	***	**.** (**.**)	***	**.** (**.**)	0.**
Week 4 after Last cycle	***	**.** (**.**)	***	**.** (**.**)	0.**
Month4	▬▬▬▬	**.** (**.**)	***	**.** (**.**)	0.**
…	……	……..			

*Wilcoxon test.

(There will be one table for each domain/item).

Table 37: Results for QOL Response Analyses

Domain	IO+Chemotherapy Improved N (%)	Stable N (%)	Worsen N (%)	IO alone Improved N (%)	Stable N (%)	Worsen N (%)	P-value
EORTC QLQ-C30							
Physical	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Role	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Emotional	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Cognitive	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Social	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Global	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Pain	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Fatigue	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Nausea	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Dyspnea	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Sleep	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Appetite	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Constipation	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Diarrhea	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Financial	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
EORTC QOL-LC13							
Cough	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Hemoptysis	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Dyspnea	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Sore Month	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Trouble Swallowing	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Peripheral neuropathy	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Hair loss	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Pain in chest	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Pain in shoulder	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Pain elsewhere	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**
Pain medication	***(**)	***(**)	***(**)	***(**)	***(**)	***(**)	.**