STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE III , OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB COMPARED WITH CHEMOTHERAPY IN PATIENTS WITH TREATMENT-NAÏVE ADVANCED OR RECURRENT (STAGE IIIB NOT AMENABLE FOR MULTIMODALITY TREATMENT) OR METASTATIC (STAGE IV) NON-SMALL CELL LUNG CANCER WHO ARE DEEMED UNSUITABLE FOR PLATINUM-CONTAINING THERAPY (IPSOS)**

PROTOCOL NUMBER: MO29872

STUDY DRUG: Atezolizumab (RO5541267)

VERSION NUMBER: 3.0

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SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted] (Trial Statistician, Cytel, Inc), [redacted] (Study Lead Statistician, Roche)

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STATISTICAL ANALYSIS PLAN V3.0 AMENDMENT RATIONALE

The Statistical Analysis Plan (SAP) for Study MO29872 (IPSOS) has been amended to reflect the following changes:

- Analysis that handles the potential over-stratification is changed to be reported as sensitivity analysis (See Section 4.4.5.2)
- Safety Population has been renamed to Safety-Evaluable Population
- OS and Investigator assessed PFS according to RECIST v1.1 in patients with PD L1 expression defined by the SP142 mmunohistochemistry (IHC) assay added as secondary endpoints (See section 4.4.2.5)
- Addition of Unconfirmed ORR as sensitivity analysis (Section 4.4.5.8)
- Clarification on analysis of Duration of Response (Section 4.4.2.4)
- Clarification on the summary of ECG Abnormalities (Section 4.6.5)
- Clarification on sensitivity analysis of primary endpoint in case of misstratification (Section 4.4.5.3)

STATISTICAL ANALYSIS PLAN V2.0 AMENDMENT RATIONALE

The Statistical Analysis Plan (SAP) for Study MO29872 (IPSOS) has been amended to reflect the following changes made in the Study:

- The emerging data from other atezolizumab monotherapy studies in first-line NSCLC (IMpower110), as well as other studies in similar populations with anti-PD-1 treatment (PEPS2, CHECKMATE-817), suggest an earlier analysis can demonstrate overall survival benefit; therefore the Sponsor has added an efficacy interim analysis with adequate power for the primary efficacy endpoint (overall survival). The statistical details have been updated accordingly which may provide the community with evidence from a randomized, controlled study approximately 12 months earlier than planned. (Sections 2.3, 2.4, 3.3 and 4.9)
- OS and Investigator-assessed PFS according to RECIST v1.1 in patients with PD-L1 expression defined by the SP263 immunohistochemistry (IHC) assay has been added as a secondary analysis. Both SP142 and SP263 assays have predictive value for PD-L1 status and therefore help identify potential subsets of patients who benefit more from PD-L1 treatment (Section 2.2.2 and 4.4.2)
- Protocol amendment version 3 introduced a change in the PRO visits. As some patients had already taken a PRO visit at week 3, this SAP defines that for those patients with the PRO visit to consider should be within a window of 30 days prior to the Tumor Assessment visit to address the issue of unequal timepoints in the longitudinal analysis of PRO data (Section 4.4.3). The schedule of assessments is updated accordingly.
- Update of the protocol synopsis to be aligned with SAP V2.0
- Structural updates were made throughout the document to address the newest Sponsor SAP template; this includes:
    - ORR and BOR are described in the same section (Section 4.4.2.2)
    - Removal of any programming code, dataset specifications, computing environment, data conventions and list of outputs
    - Removal of appendixes that are readily referenced through external sources:
        - PD-L1 IHC Scoring Criteria; Vennapusa et al, 2017
        - EORTC QLQ-C30 and QLQ-LC13: Scoring Rules; Fayers et al, 2001

This amendment represents cumulative changes to the original analysis plan. Additional minor changes and administrative changes have been made to improve clarity and consistency.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

List of Abbreviations

Abbreviation	Definition
AE	adverse events
AESI	adverse events of special interest
BOR	best overall response
CI	confidence interval
CR	complete response
CSR	clinical study report
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organization for the Research and Treatment of Cancer
EQ-5D-5L	EuroQoL 5 Dimension questionnaire
FDA	Food and Drug Administration
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee
IV	Intra-Venous
ITT	Intent-to-treat
KM	Kaplan Meier
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NSCLC	Non-Small Cell Lung Cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
PK	pharmacokinetic
PR	partial response
PRO	patient reported outcome
PS	performance status
PT	preferred term
QLQ-C30	Quality-of-life Questionnaire Core 30
QLQ-LC13	Quality-of-Life Questionnaire Lung Cancer Module
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	restricted mean survival time
RPFST	rank preserving structural failure time

Abbreviation	Definition
SAP	statistical analysis plan
SD	stable disease
SI	System International
SOC	System Organ Class
TTD	time to deterioration

1. BACKGROUND

Lung cancer remains the leading cause of cancer deaths worldwide; it is the most common cancer in both men and women and accounted for approximately 13% of all new cancers in 2008 (Jemal et al. 2011).

Non−small cell lung cancer (NSCLC) is the predominant subtype of lung cancer, accounting for approximately 85% of all cases (Molina et al. 2008, Howlader et al. 2014). Half of all newly diagnosed NSCLC patients present with advanced disease (stage IIIb and IV) (Davidoff et al. 2010) which directly contributes to poor survival prospects.

The overall 5-year survival rate for advanced disease is 2%-4%, depending on geographic location (Cetin et al. 2011). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor performance status (PS), and a history of unintentional weight loss. More than half of the patients with NSCLC are diagnosed with distant disease.

The majority of patients with newly diagnosed NSCLC present with locally advanced or metastatic disease (Carnio et al. 2014). In addition, the average age at diagnosis of lung cancer in the U.S. is about 70 years (Avery et al. 2009, Gajra et al. 2014)). As a result, a significant proportion of patients with lung cancer have intercurrent illnesses or comorbid conditions that can potentially affect their ability to receive standard therapy for lung cancer.

Patients with lung cancer with a poor PS, irrespective of age, have an increased incidence of adverse effects with standard chemotherapy and have a poorer overall survival (OS) (Sweeney et al. 2001, Ruckdeschel et al. 1986). An estimated 30% to 40% of patients diagnosed with NSCLC have a poor PS-defined as a score of 2 or higher on the Eastern Cooperative Oncology Group (ECOG) scale-because of their disease burden, comorbidities, or both (Govindan et al. 2004).

Survival is shorter in patients with advanced NSCLC and a PS of 2 than in those with a better PS of 0-1, regardless of therapy (Azzoli et al, 2010). Patients with a PS of 2 do not tolerate chemotherapy as well, and treatment approaches should be different (Gridelli et al. 2006).

There is currently a highly unmet medical need for novel safe treatment options that deliver an improved therapeutic index in newly diagnosed advanced, recurrent or metastatic NSCLC deemed unsuitable for platinum-containing therapy due to poor performance status and/or comorbidities.

Atezolizumab (MPDL3280A) is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptors, PD-1 and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells.

Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans.

On 18 Oct 2016, U.S. FDA approved atezolizumab for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy.

This Statistical Analysis Plan (SAP) specifies the planned analyses and statistical methods used for Study MO29872 (IPSOS) and supersedes those analyses specified in the protocol.

2. STUDY DESIGN

This randomized, Phase III, multicenter, open-label study is designated to evaluate the efficacy and safety of atezolizumab compared with a single agent chemotherapy regimen by investigator choice (vinorelbine or gemcitabine) in treatment-naïve patients with locally advanced or metastatic NSCLC who are deemed unsuitable for platinum doublet chemotherapy due to poor performance status (ECOG PS of 2-3).

However, patients who are ineligible for platinum doublet chemotherapy but have ECOG performance status 0 or 1 may be enrolled if they are ≥ 70 years of age. They may be included if deemed unsuitable for platinum doublet chemotherapy by the investigator due to a) substantial comorbidities, b) contraindication(s) for platinum based antineoplastic drugs.

Eligible patients will be stratified by (a) histologic subtype (non-squamous/squamous), (b) PD-L1 IHC status (positive/negative/unknown; see Section 3.1) and (c) brain metastases (yes/no) and then randomized at a 2:1 ratio to receive either atezolizumab or single agent chemotherapy.

Atezolizumab at a fixed dose of 1200 mg will be administered intravenously on Day 1 of each 21-day cycle.

Patients randomized to receive single agent chemotherapy approved in their country (vinorelbine or gemcitabine), based on investigator's choice will receive chemotherapy according to the label. Doses and dose modifications for the selected single agent chemotherapy should be made according to the local guidelines and Summary of Product Characteristics (SmPC) management.

Given the unique toxicities associated with chemotherapy (i.e., alopecia, neutropenia, febrile neutropenia) and the pre-medications required (i.e., steroid, anti-emetics, and potentially growth factor support), this will be an open-label study.

No crossover will be allowed between treatment arms. However, it is not possible to prevent use of other immunotherapies after discontinuing study drug.

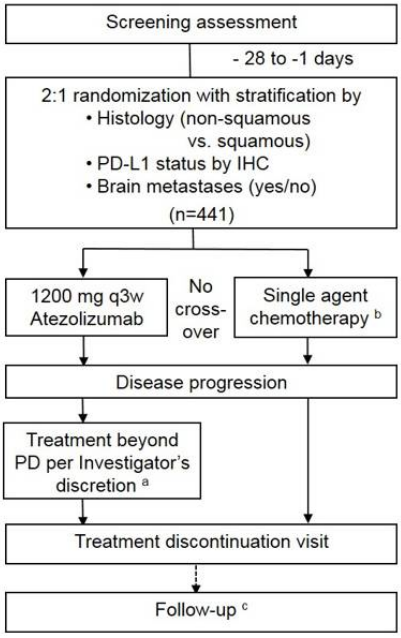
At any time-point after RECIST v1.1 criteria for progressive disease are met, patients in the experimental arm who show evidence of clinical benefit, will be permitted to continue treatment with atezolizumab until loss of clinical benefit, unacceptable toxicity, patient or physician decision to discontinue, or death.

Tumor assessments will be performed at baseline, every 6 weeks (± 5 days; approximately every two cycles) following randomization for 48 weeks, and every 9 weeks (± 5 days) thereafter, with additional scans as clinically indicated. Assessments will continue until disease progression per RECIST v1.1. Patients randomized to atezolizumab who continue to receive atezolizumab following disease progression will undergo assessments until treatment discontinuation. Tumor assessments should continue regardless of whether patients discontinue study treatment or start new anti-cancer therapy in the absence of disease progression unless they withdraw consent.

In all patients, response will be assessed by the investigator using RECIST v1.1 until disease progression. Patients randomized to receive atezolizumab will additionally be assessed by modified RECIST criteria until treatment discontinuation.

Follow-up data capture, including subsequent anticancer therapies, will continue for each patient until death, withdrawal of consent, loss to follow-up, or study termination by Sponsor, whichever occurs first.

Figure 1 Study Design



IHC = immunohistochemistry; NSCLC = non-small cell lung cancer; PD = disease progression; PD-L1 = programmed cell death-ligand 1; q3w = every 3 weeks.

a Patients in the experimental arm with atezolizumab who show evidence of clinical benefit, may continue atezolizumab treatment after disease progression (RECIST v 1.1) if they meet criteria specified in Protocol Section 3.1.

b Single agent chemotherapy (vinorelbine, oral or intravenous, or gemcitabine, intravenous) based on investigator's choice will be administered per relevant local guidelines and SmPC management. Chemotherapy cycles may be 3-weekly or 4-weekly.

c Follow-up information, including subsequent anticancer therapies and any treatment related adverse events, will be collected via telephone calls and/or clinic visits every 2 months (± 5 days) until death, withdrawal of consent, loss to follow-up, study termination by the Sponsor, or protocol-defined end of study, whichever comes first.

The primary efficacy endpoint is overall survival (OS).

This study is event-driven, with a recruitment period of approximately 24 months. The required number of 380 events for the final analysis of the primary endpoint of OS is expected to occur approximately 42 months after the first patient has been enrolled.

One efficacy interim analysis of OS will be performed.

An independent Data Monitoring Committee (iDMC) will be set up to evaluate safety data on an ongoing basis, as well as the efficacy interim analysis.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the schedule of assessments in Appendix 2.

2.2 ENDPOINTS

2.2.1 Primary Efficacy Endpoint

The primary efficacy outcome measure for this study is OS, defined as the time from randomization to death from any cause.

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy outcome measures for this study are the following:

- OS rates at 6, 12, 18 and 24 months
- Objective Response Rate (ORR), defined as best overall response (partial response plus complete response, confirmation being required), as determined by the investigator using RECIST v1.1
- Progression-Free Survival (PFS), defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first
- Duration of Response (DOR), defined as the time from the first occurrence of a documented objective response to the time of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first
- OS and Investigator-assessed PFS according to RECIST v1.1 in patients with PD-L1 expression defined by the SP142 and SP263 immunohistochemistry (IHC) assay

2.2.3 Safety Endpoints

The safety outcome measures for this study are the following:

- Incidence, nature and severity of adverse events (AEs) based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0).
- Changes in vital signs, physical findings, and clinical laboratory results during and following study drug administration.

2.2.4 Patient-Reported Outcome Endpoints

The patient-reported outcome (PRO) measures for this study are the following:

- Change from baseline in PROs of lung cancer symptoms, patient functioning, health-related quality of life (HRQoL) as assessed by European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) and its supplementary Lung Cancer module (LC13)
- Time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, dyspnea (single-item and multi-item subscales), chest pain, arm/shoulder pain, or fatigue using EORTC QLQ-C30 and QLQ-LC13

2.2.5 Pharmacokinetic Endpoints

Not applicable.

2.2.6 Exploratory Endpoints

The exploratory endpoints will not be included in the CSR.
The exploratory outcome measures for this study are the following:

- ORR, PFS and DOR as determined according to modified RECIST v1.1
- Disease Control Rate (DCR) defined as the rate of patients with complete response or partial response as best response or stable disease as determined by the investigator per RECIST v1.1

- Utility scores of the EQ 5D 5L questionnaire

2.3 DETERMINATION OF SAMPLE SIZE

The primary purpose of this study is to investigate the effect of atezolizumab on duration of OS relative to the current treatment practice.

Assuming a 10% withdrawal rate and accrual duration of 24 months, approximately 441 patients will be randomized in a 2:1 ratio to atezolizumab (294 patients) or chemotherapy (147 patients). A total of 380 OS events will provide 90% power to detect a significant improvement in median OS with atezolizumab compared to chemotherapy from 7 months to 10 months (i.e. hazard ratio [HR] 0.7) using a log-rank test at an overall two-sided alpha level of 5% (using a two-look Lan-DeMets group sequential design with an interim analysis at 80% of information fraction and O'Brien-Fleming type boundary at two-sided 5% level of significance). Operating characteristics are provided in Table 1.

Table 1: Operating Characteristics

Sample Size Calculation Parameters	Values
Randomization ratio (atezolizumab vs chemotherapy)	2:1
Overall type 1 error (2-sided)	5%
Power	90%
Accrual duration	24 months
Duration until OS interim analysis	30 months
Duration until OS final analysis	42 months
Drop-out rate	10%
Median control	7 months
Median atezolizumab	10 months
Hazard ratio	0.7
Number of events at interim analysis	304
Number of events at final analysis	380
Number of patients	441

Note: this is assuming validity of proportional hazards assumption, overall two-sided $\alpha = 0.05$ (using a 2-look Lan-DeMets group sequential design with an interim at 80% of information fraction and O'Brien-Fleming type boundary at two-sided 5% level of significance).

2.4 ANALYSIS TIMING

There will be one interim OS analysis after approximatively 304 deaths have occurred, corresponding to 80% of the planned 380 events, expected to occur approximately 30 months after the first patient is randomized.

The final analysis of OS will occur when approximately 380 deaths have been observed, expected to occur approximately 42 months after the first patient is randomized. For both interim and final OS analyses, the exact timing of the analysis will depend on the actual number and timing of OS events.

To control the Type 1 error for OS, a Lan-DeMets group sequential design with an O'Brien-Fleming type boundary will be used (Table 2). The information fraction and stopping boundaries at the time of each analysis will be re-calculated using the actual number of events included in the analysis, and the nominal alpha level will be re-calculated accordingly so that the overall alpha level across both analyses is maintained at 5%.

Table 2: Timing and Stopping Boundaries for Interim and Final Analyses for Overall Survival

Interim and Final Analysis for OS			
Analysis Timing	Time from First Patient in (months)	Information Fraction (No. of events)	Stopping Boundary HR (p-value[1])
Interim Analysis	30	80% (304)	0.76 ($p \leq 0.0244$)
Final Analysis	42	100% (380)	0.80 ($p \leq 0.0428$)

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Randomization to atezolizumab and chemotherapy arms will occur in a 2:1 ratio using permuted-block randomization method. Randomization will be stratified by the following factors:

- Histologic subtype (non-squamous vs. squamous)
- PD-L1 IHC status (positive vs. negative vs. unknown) as defined in Table 3.
- Brain metastases (yes vs. no)

Table 3: PD-L1 Status Assessed by SP142 Assay

PD-L1 IHC Positive:	Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma (IC3) OR Presence of discernible PD-L1 staining of any intensity in ≥ 50% tumor cells (TC3)
PD-L1 IHC Negative:	Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering <10% of tumor

	area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma AND Presence of discernible PD-L1 staining of any intensity in <50% tumor cells
PD-L1 IHC Status unknown:	PD-L1 IHC status could not be determined (e.g. not enough tumor)

3.2 INDEPENDENT REVIEW FACILITY

Not applicable.

3.3 DATA MONITORING

An iDMC will monitor study conduct and review aggregate safety data by treatment arm on a periodic basis. Members of the iDMC will be independent of the Sponsor and will follow a charter that outlines their roles and responsibilities. The iDMC will meet approximately every 6 months from the point of first patient in (FPI) until study unblinding, to review study conduct and unblinded safety data prepared by an independent Data Coordinating Center (iDCC).

Following each data review, the iDMC will provide recommendations to the Sponsor as to whether the study should continue as planned, or be amended, or whether the study should be stopped on safety grounds (i.e., evidence of harm). The Sponsor's Data Review Board (DRB; a group consisting of employees of the Sponsor empowered to make critical decisions) will make a decision based on the iDMC's recommendations. The final decision will rest with the Sponsor.

Any outcomes of the iDMC safety reviews that affect the study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards/Ethics Committees (IRBs/ECs).

There is one interim analysis planned for the primary endpoint OS. The interim analysis will be carried out by the iDCC and provided to the iDMC. The iDMC will review these data and will recommend or not recommend to release the trial results and to unblind the study to the sponsor. The DRB of the sponsor will either accept or reject this recommendation. Details are specified in the iDMC charter.

4. STATISTICAL METHODS

The analyses outlined in this SAP supersede those specified in the protocol.

4.1 ANALYSIS POPULATIONS

4.1.1 Efficacy Analysis Population

Intent-to-treat (ITT) Population: all randomized patients irrespective of whether the assigned treatment was actually received. For analyses on ITT, patients will be grouped according to the treatment assigned at randomization. The ITT population will be the population for the analysis of efficacy parameters.

4.1.2 Safety-Evaluable Population

Safety-Evaluable Population: all randomized patients who received any amount of study treatment. For analyses on Safety-Evaluable Population, patients will be grouped according to whether any amount of atezolizumab was received, including the case when atezolizumab was received in error. The Safety-Evaluable Population will be the population for the analysis of safety parameters.

4.2 ANALYSIS OF STUDY CONDUCT

Study enrollment, patient disposition, reasons for discontinuation from the study treatment and reason for study termination will be summarized for all patients in the ITT population.

Major protocol deviations, including violations of inclusion/exclusion criteria and deviations during study conduct will be reported and summarized in the ITT population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

The following analyses will be based on the ITT population.

Demographic variables such as age, sex, race/ethnicity, stratification variables and other relevant baseline characteristics including disease history will be summarized using means, standard deviations (SDs), medians, ranges and inter-quartile ranges for continuous variables and frequencies and percentages for categorical variables, as appropriate. Summaries will be presented overall and by treatment arm.

The baseline value of any non-efficacy variable will be defined as the last available value recorded on or prior to the first administration of any study medication The baseline value of efficacy variable related to tumor assessment will be defined as the last available value recorded prior to randomization.

Previous and concurrent medical history will be summarized overall and by treatment arm. Prior cancer therapy, prior cancer radiotherapy, prior cancer surgery, follow-up cancer therapy, follow-up cancer radiotherapy, on-study radiotherapy, on-study and follow-up cancer-related medical/surgical procedures will be summarized overall and by treatment arm.

4.4 EFFICACY ANALYSIS

Efficacy analysis will be conducted on ITT population and presented by treatment arms assigned at randomization, unless otherwise stated.

Hypothesis tests will be two-sided unless otherwise indicated. The overall type I error (α) for this study is 0.05 (two-sided). There will be no multiplicity adjustments for testing of secondary endpoints.

4.4.1 Primary Efficacy Endpoint

The primary efficacy objective of this study is the comparison of OS between the two treatment arms (atezolizumab versus chemotherapy).

For OS, patients without a date of death will be censored on the date a patient was last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization plus 1 day.

The following analyses will be performed:

- Treatment comparisons will be based on the stratified log-rank test. The stratification factors will be the predefined randomization stratification factors: histologic subtype (non-squamous/squamous), PD-L1 IHC status (positive/negative/unknown) and brain metastases (yes/no) and will be obtained from the interactive Web/phone response system IxRS.

- The hazard ratio (HR) will be estimated using a stratified Cox regression model with the same stratification variables used for the stratified log-rank test, and the 95% CI for the HR will be provided.

- Kaplan-Meier methodology will be used to estimate median OS for each treatment arm and to construct survival curves for each treatment arm. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS for each treatment arm (Brookmeyer and Crowley 1982).

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 OS Rate at the 6, 12, 18, 24-Months Timepoints

OS rate at 6, 12, 18 and 24 months will be estimated for each treatment arm using Kaplan-Meier methodology, along with 95% CI calculated with the standard error derived from the Greenwood formula.

4.4.2.2 Objective Response Rate

An objective response rate (ORR) is defined as a Best Overall Response (BOR) of either CR or PR, as determined by the investigator with use of RECIST v1.1. Patients not meeting these criteria, including patients without any post-baseline tumor assessments, will be considered non-responders. A confirmation of response is also required.

A minimum interval of 6 weeks (42 days) will be considered for Stable Disease (SD) to be assigned as best overall response, i.e. in the case the single response is SD, PR or CR, this single response must have been assessed no less than 6 weeks (at least 42 days) after start date of study treatment. Patients will be classified as missing or unevaluable if no post-baseline response assessment is available or all post- baseline response baseline assessments are unevaluable.

An estimate of ORR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs between the two arms will be determined using the normal approximation to the binomial distribution.
The ORR will be compared between the two arms using a Chi-square test.

4.4.2.3 Progression-Free Survival

PFS is defined as the time from randomization to the first documented disease progression as determined by the investigator with the use of RECIST v1.1 or death from any cause, whichever occurs first. Data for patients who are alive and who have not experienced disease progression at the time of clinical cut-off date will be censored: i) at the date of the last tumor assessment, if post-baseline tumor assessment available, ii) at the date of randomization plus 1 day, if no post-baseline tumor assessment available.

The same analysis as the primary analysis of OS will be repeated for PFS.

4.4.2.4 Duration of Response

DOR is defined as the time from the first tumor assessment that supports the patient's objective response (CR or PR, whichever is first reported) to documented disease progression as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first, among patients who have a best overall response as CR or PR.

Patients who are alive and have not progressed at the time of clinical cut-off date will be censored at the time of the last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a complete or partial response, DOR will be censored at the date of the first occurrence of a complete or partial response plus 1 day.

Because the determination of DOR is based on a non-randomized subset of patients, formal hypothesis testing will not be performed. Comparisons between treatment arms will be made for descriptive purposes. The same methodologies detailed for the OS analysis will be used for the DOR analysis.

4.4.2.5 Overall Survival and Investigator-Assessed Progression-Free Survival for SP142 and SP263 PD-L1 Subpopulation

OS and investigator-assessed PFS in patients with PD L1 expression on tumor cells defined by the SP142 and SP263 IHC assay will be analyzed and included in the Clinical Study Report (CSR). This will be analyzed through use of the same methods described for the OS and PFS analysis.

4.4.3 Patient-Reported Outcomes

Through the use of the EORTC QLQ-C30 and EORTC QLQ-LC13, lung cancer symptom data will be collected along symptoms commonly associated with cancer treatments, and disease and treatment impact on patients' functioning and health-related quality of life.

The analysis of PRO measures will be conducted on ITT population, and will include all assessments until progressive disease as per RECIST 1.1. All assessments performed strictly after progressive disease as per RECIST 1.1 will only be listed. In addition, only the assessments within 30 days prior to the scheduled tumor assessment date will be analyzed.

The EORTC QLQ-C30 and QLQ-LC13 data will be scored according to the EORTC scoring manual (Fayers 2001). Missing data will be assessed and reported by timepoint. In the event of incomplete data, for all questionnaire subscales, if >50% of the constituent items are completed, a pro-rated score will be computed consistent with the scoring manuals and published validation reports. For subscales with ≤50% of the items completed, the subscale will be considered as missing. PRO completion and compliance rates will be summarized at each timepoint by treatment arm on the ITT population. Summary statistics at each visit and change from baseline of linear-transformed scores will be reported for all the items and the subscales.

For analysis of functioning domains and Global Health Status/Health-related quality of life scale, a patient will be classified as improved if a 10-point or greater increase is observed in the average change from baseline scores at available timepoints for that patient. Similarly, a patient will be classified as worse if a decrement of 10 points or worse is observed in the average change from baseline scores at available timepoints for an individual patient. For analysis of symptom domains and single items, the classification into improved/worse categories is the reverse, such that a patient will be classified as improved if a decrement of 10-point or worse is observed in the average change from baseline scores at available timepoints and will be classified as worse if a 10-point or greater increase is observed. For

analysis of symptom domains and single items, a positive change indicates worsening (i.e., greater symptom severity) and a negative change indicates symptom improvement. Improvement and worsening rates between treatments will be compared using the Chi-Square test. Bar Charts will be generated for both improvement and worsening separately for each PRO measure. All scales for a specific PRO measure will be displayed on the same bar chart, as well as the two treatment arms.

Time to Deterioration (TTD):

TTD with use of the EORTC is defined as the time from randomization to the first confirmed clinically meaningful deterioration in EORTC symptom scores. Confirmed clinically meaningful deterioration in lung cancer symptoms is defined as a ≥ 10-point increase above baseline in a symptom score that must be held for at least two consecutive assessments or an initial ≥ 10-point increase above baseline followed by either (a) death within 6 weeks from the last assessment through Week 48 or (b) death within 9 weeks from the last assessment from Week 48 thereafter. A ≥ 10-point change in the EORTC scale score is perceived by patients as clinically significant (Osoba et al. 1998).

TTD will be documented for each of the following EORTC-based symptom scores:

- Cough (Question 31 on the EORTC QLQ-LC13)
- Chest pain (Question 40 on the QLQ-LC13)
- Dyspnea single item (Question 8 on the QLQ-C30)
- Dyspnea multi-item subscale (Questions 33-35 on the QLQ-LC13)
- Arm and/or shoulder pain (Question 41 on the QLQ-LC13)
- Fatigue (Questions 10, 12, 18 on the QLQ-C30)
- Composite of the 3 symptoms: cough, dyspnea (multi-item subscales QLQ-LC13) and chest pain

Patients who do not have an confirmed deterioration at the time of clinical data cut-off will be censored i) at the last non-missing assessment date if post-baseline assessment ii) on the date of randomization + 1 day if no post-baseline assessment.

TTD of the prespecified symptoms will be summarized using the KM method. Comparison of TTD using the EORTC QLQ-C30 and EORTC QLQ-LC13 measures between treatment arms will be performed using the stratified log-rank test; the stratified HRs and 95% CIs will also be reported.

4.4.4 Exploratory Efficacy Endpoints

Results from exploratory analyses will not be included in the CSR .

4.4.4.1 ORR, PFS and DOR as Assessed by the Investigator Using Modified RECIST

The endpoints assessed with modified RECIST will be limited to the atezolizumab arm.

PFS by modified RECIST is defined as the time from randomization to disease progression as determined by the investigator per modified RECIST or death from any cause, whichever occurs first. A patient is considered to have disease progression by modified RECIST if either of the following conditions is met:

a) Modified RECIST for progression is met at a tumor assessment and no subsequent tumor assessment is performed.

b) Modified RECIST for progression is met at a tumor assessment, and at the subsequent tumor assessment, the criteria for confirmed progression by modified RECIST are also met.

For patients who meet criterion a), the date of progression is the date of the tumor assessment that met the criteria for progression per modified RECIST. For patients who meet criterion b), the date of progression is the date of the tumor assessment at which the modified RECIST for progression is first met. Patients who do not meet either of the above conditions are not considered to have disease progression by modified RECIST.

ORR by modified RECIST is defined as the proportion of patients whose best overall response is either a PR or CR per modified RECIST.

DOR by modified RECIST is defined for patients who experienced an objective response (best overall response of CR or PR per modified RECIST) as assessed by the investigator as the time from the first tumor assessment that supports the patient's objective response (CR or PR, whichever is recorded first) to disease progression or death from any cause, whichever occurs first. Data for patients who are alive and who have not experienced disease progression at the time of clinical cut-off date will be censored at the last available tumor assessment date.

Similar methodologies outlined for the primary and secondary efficacy endpoint analyses will be used for the analyses of PFS, ORR, and DOR as assessed by the investigator using modified RECIST in the experimental arm.

4.4.4.2 Disease Control Rate

Disease Control Rate (DCR) is defined as the proportion of patients with a best overall response, either CR or PR or SD, as determined by the investigator using RECIST v1.1 Patients not meeting this criterion, including those without any post-baseline assessment, will be considered non-responders.

An estimate of DCR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. CIs for the difference in DCRs between the two arms will be determined using the normal approximation to the binomial distribution. The DCR will be compared between the two arms using a Chi-square test.

4.4.4.3 Utility scores of the EQ 5D 5L questionnaire

EQ-5D-3L data will be used to generate health status and utility scores for use in economic models.

4.4.5 Sensitivity Analyses

4.4.5.1 Unstratified Analysis

The primary analysis on OS, PFS, DOR and TTD will be repeated by using the unstratified Cox model and the unstratified log-rank test.

4.4.5.2 Overstratification

Due to the potential risk of over-stratification (Akazawa et al. 1997), if at least 1 stratum has less than 10 OS events, the stratification factor which contains the level with the smallest number of patients will be removed from the stratified analyses and added to the next level.

The removal of stratification factors will continue until there is no stratum with less than 10 OS events in the analysis population. With the final set of stratification factors, stratified analyses of OS will be conducted using similar methods described in Section 4.4.1.

4.4.5.3 Mistratification

The primary analysis on OS will be repeated by using the stratification factors as per eCRF/Laboratory data.

4.4.5.4 Imbalance between Treatment Arms

If strong baseline imbalances are observed between treatment arms, the stratified Cox regression analysis for OS endpoints including such prognostic factors as covariates in the model will be performed to investigate the potential impact of such imbalances on the treatment effect.

4.4.5.5 Non-Proportional Hazard

The proportional hazards assumption will be tested with the Schoenfeld residuals. If there is evidence of non-proportionality, the following analysis could be conducted to assess a potential delayed clinical effect for atezolizumab.

Restricted Mean Survival Time
The restricted mean survival time (RMST) will be computed for OS using the area under the curve from baseline to several timepoints (defined a posteriori). RMST will be computed for each treatment arm and the difference with its 95% CI will be displayed (Uno 2014).

4.4.5.6 Non-Protocol-Specified Anti-Cancer Therapy

Following approval of atezolizumab in previously treated, locally advanced or metastatic NSCLC, and quickly evolving development of immunotherapies (IM) may lead to increased treatment options for patients in the NSCLC, either via trial participation or newly approved medicines in this class. Usage of such treatments by patients progressing on this first-line trial could result in biased estimate of the treatment effect on OS. To account for this possibility of bias the following sensitivity analyses might be conducted, if deemed appropriate:

- Rank-preserving structural failure time (RPSFT) provides an estimate of the OS time for the control group had IM not occurred (Robins and Tsiatis 1991). It estimates OS measured from the time of IM by applying an estimate of the benefit of the IM. The total overall survival time (sum of time to IM and the estimated survival time after NPT started) will then be analyzed using the same methodology as for the primary analysis of OS. The key assumption is that all IM have the same effect, so if a patient from atezolizumab takes more IM the effect is assumed to be the same (not to change) from the one he is already carrying from atezolizumab. However, for a patient in the control arm, it is equivalent to a treatment switch.

4.4.5.7 Missing Tumor Assessment

The impact of missing scheduled tumor assessments on PFS will be assessed by the following sensitivity analysis:

- Patients who missed two or more consecutive scheduled assessments immediately prior to the date of disease progression per RECIST v1.1 or death will be censored at the last available tumor assessment with response not ‘Not Evaluable’. Missing tumor

assessment will be assessment reported as ‘Not performed’ or with overall response as ‘Not evaluable’ on the ‘RECIST 1.1 Response Assessment’ eCRF page.

Statistical methodologies analogous to those used in the analysis of PFS as specified in Section 4.4.2 will be used for this sensitivity analysis.

4.4.5.8 Unconfirmed ORR

Due to possible rapid patient progression in pateints with poor performance status, Objective Response Rate not requiring the confirmation of response will also be analyzed. This will be analyzed through use of the same methods described for the ORR requiring confirmation of response.

4.4.6 Subgroup Analyses

The consistency of OS and PFS results in subgroups will be examined the following subgroups:

- PD-L1 expression by IHC (SP142 or SP263)
- Demographics, including but not limited to: SLD (Median), Number of metastatic sites (<3 vs ≥3), age, sex and race
- Baseline disease characteristics: histologic subtype (squamous versus non-squamous), ECOG performance status, brain metastases at baseline, liver metastases at baseline, smoking status

Other subgroups might be added if deemed relevant.
Summaries of OS and PFS, including the unstratified HR estimated from a Cox proportional hazards model and KM estimates of median OS and PFS, will be produced separately for each level of the subgroup for the comparisons between both treatment arms and displayed in a forest plot.

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable.

4.6 SAFETY ANALYSES

Safety summaries will be produced by treatment group on the Safety-Evaluable Population.

4.6.1 Exposure of Study Medication

Given the variety of schedule assessments (various cycle length [3 versus 4 week cycles], day of administration etc…) and dosings for the chemotherapy, only the treatment duration will be summarized by treatment arm (atezolizumab versus chemotherapy). Treatment duration (as both continuous and categorical variables) will be summarized for each treatment arm with descriptive statistics.

Number of doses received as well as number of doses missed will be summarized separately for each drug and each schedule. For vinorelbine, as patient might switch from one schedule to another during the study, the initial schedule will be used to classify a patient. For gemcitabine, no change of schedule is expected during the study. For vinorelbine, route at first administration, switch of route, switch of schedule will also be summarized.

4.6.2 Adverse Events

Verbatim description of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0). Adverse events will be summarized by MedDRA term, appropriate MedDRA levels (system organ class [SOC] and preferred term [PT]), and when specified by NCI CTCAE grade. For each patient, if multiple incidences of the same adverse events occur, the maximum severity reported will be used in the summaries. Only adverse events occurring on or after the first dose of any study treatment will be included in the summary tables of adverse events.

The following adverse events will be summarized:

- AE
- Common AEs (Occurring in ≥10% of patients)
- AE related to study drug
- AE with NCI CTCAE grade 3 and 4
- AE with fatal outcome (Grade 5)
- Serious AE
- Serious AE related to study drug
- AE leading to discontinuation of study drug
- AE leading to modification of study drug
- AE of special interest (AESI)
- AESI related to study drug

All deaths and causes of deaths will be summarized by treatment arm.

4.6.3 Laboratory Data

Laboratory data will be summarized descriptively over time including change from baseline by treatment arm.

Laboratory data will be classified according to NCI CTCAE 4.0. Highest NCI CTCAE grade post-baseline will also be reported and shift tables from baseline to worst post-baseline will be presented by treatment arm. Values outside normal ranges will be summarized.

Potential Hy's law patients will be listed. Potential Hy's law cases are defined as elevated ALT or AST ($> 3 \times$ ULN) with concomitant elevated total bilirubin ($> 2 \times$ ULN)).

4.6.4 ECOG PS

ECOG PS will be summarized in a shift table of baseline versus worst post-baseline value.

4.6.5 Electrocardiogram

Electrocardiogram Abnormalities will be summarized for Screening and the worst assessment for the Post-Baseline visits.

4.7 BIOMARKER ANALYSIS

Exploratory analyses for biomarker are not covered in this SAP.

4.8 MISSING DATA

See Section **Error! Reference source not found.** and Section 4.4.2 for methods of handling missing data for the primary and secondary efficacy endpoints.

4.9 INTERIM ANALYSES

4.9.1 Planned Interim Analysis

There will be one interim analysis of OS after 304 deaths (80% of information fraction) have occurred. The final analysis of OS will be conducted when 380 deaths have occurred in the ITT population. A group sequential design (Lan-DeMets with O'Brien-Fleming stopping boundaries) will be used to control the overall type I error rate (Lan and DeMets, 1983). Details of the timing and alpha spending function are included in Section 2.4.

The information fraction at the time of each analysis will be re-calculated using the actual number of events included in the analysis, and the nominal alpha level re-calculated accordingly.

An iDMC will be used to evaluate interim safety data on a regular basis and interim efficacy data at a pre-specified timepoint. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an external iDCC. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities

4.9.2 Safety Monitoring

The iDMC will review the safety data periodically during the study. Full details are provided in the iDMC charter.

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Appendix 1
Protocol Version 5 Synopsis

TITLE:	**A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB COMPARED WITH CHEMOTHERAPY IN PATIENTS WITH TREATMENT-NAÏVE ADVANCED OR RECURRENT (STAGE IIIB NOT AMENABLE FOR MULTIMODALITY TREATMENT) OR METASTATIC (STAGE IV) NON-SMALL CELL LUNG CANCER WHO ARE DEEMED UNSUITABLE FOR PLATINUM-CONTAINING THERAPY**
PROTOCOL NUMBER:	MO29872
VERSION NUMBER:	5
EUDRACT NUMBER:	2015-004105-16
IND NUMBER:	Not applicable
NCT NUMBER:	NCT03191786
TEST PRODUCT:	Atezolizumab (RO5541267)
PHASE:	Phase III
INDICATION:	Non-small cell lung cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of atezolizumab compared with single agent chemotherapy with respect to antitumor effects in patients with treatment-naïve locally advanced or metastatic non-small cell lung cancer (NSCLC) who are deemed unsuitable for any platinum-doublet chemotherapy. Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab compared with single agent chemotherapy in patients with treatment-naïve locally advanced or metastatic NSCLC who are deemed unsuitable for any platinum-doublet chemotherapy, as measured by overall survival (OS).

Secondary Efficacy Objectives

The secondary efficacy objectives for this study are:

- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy as measured by OS rates at 6, 12, 18 and 24 months
- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator assessed ORR using RECIST v1.1
- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator assessed progression-free survival (PFS) using RECIST v1.1

- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator assessed duration of response (DOR) using RECIST v1.1
- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by OS and Investigator-assessed PFS according to RECIST v1.1 in patients with PD-L1 expression defines by SP263 assay

SAFETY OBJECTIVE

The safety objective for this study is:

- To evaluate the safety and tolerability of atezolizumab compared with single agent chemotherapy

Patient-reported Outcome Objectives

The patient-reported outcome (PRO) objective for this study is

- To evaluate and compare PROs of lung cancer symptoms, patient functioning, and health-related quality of life (HRQoL) between treatment arms as measured by the European Organisation for Research and treatment of Cancer (EORTC) Quality-of-life Questionnaire Core 30 (QLQ C30) and its Lung Cancer Module (QLQ LC13)

Exploratory Objectives

The exploratory objectives for this study are:

- To evaluate the efficacy of atezolizumab compared with single agent chemotherapy with respect to antitumor effects as measured by investigator-assessed ORR, PFS and DOR according to modified RECIST (immune--mediated response criteria; imRC)
- To evaluate and compare investigator-assessed disease control rates (DCR) between the two treatment arms using RECIST v1.1
- To generate utility scores for use in economic models for reimbursement by collecting patient's health status data using the EuroQoL-5 Dimensions 5-level (EQ-5D-5L) questionnaire

Study Design

Description of Study

This is a Phase III, global, multicenter, open-label, randomized, controlled study designed to evaluate the efficacy and safety of atezolizumab compared with a single agent chemotherapy regimen by investigator choice (vinorelbine or gemcitabine) in treatment-naïve patients with locally advanced or metastatic NSCLC who are deemed unsuitable for any platinum-doublet chemotherapy due to poor performance status (Eastern Cooperative Oncology Group performance status [ECOG PS] of 2-3).

However, patients ≥ 70 years of age who have an ECOG PS of 0 or 1 may be included if they are deemed unsuitable for platinum doublet chemotherapy by the investigator due to:

a) substantial comorbidities
b) contraindication(s) for platinum-doublet chemotherapy.

Eligible patients will be stratified by (a) histologic subtype (non-squamous vs squamous), (b) PD-L1 immunohistochemistry (IHC) status (positive/negative/unknown) and (c) brain metastases (yes/no) and then randomized at a 2:1 ratio to receive either atezolizumab or single agent chemotherapy.

Eligible patients must therefore provide a tumor tissue specimen for central assessment of PD-L1 expression by IHC at a central laboratory. The study will enroll all patients whose tissue is evaluable for PD-L1 analysis, regardless of PD-L1 expression status.

Given the unique toxicities associated with chemotherapy (i.e., alopecia, neutropenia, febrile neutropenia) and the pre-medications required (i.e., steroid, anti-emetics, and potentially growth factor support), this will be an open-label study.

No crossover will be allowed between treatment arms.

Atezolizumab at a fixed dose of 1200 mg will be administered intravenously on Day 1 of each 21-day cycle.

Patients randomized to receive single agent chemotherapy (vinorelbine [oral or intravenous] or gemcitabine [intravenous]), based on investigator's choice will receive chemotherapy per relevant local guidelines and summary of product characteristics (SmPC) management. Doses and dose

modifications for the selected single agent chemotherapy should be made per relevant local guidelines and SmPC management.

At any time-point after RECIST v1.1 criteria for progressive disease are met, patients in the experimental arm who show evidence of clinical benefit, will be permitted to continue treatment with atezolizumab if they meet all of the following criteria:

- Evidence of clinical benefit (i.e., in the absence of symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results [if available], clinical status, and of laboratory values)
- Absence of unacceptable toxicity
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial progression.

Tumor assessments will be performed at baseline, every 6 weeks (± 5 days) following randomization for 48 weeks, and every 9 weeks (± 5 days) thereafter, with additional scans as clinically indicated. Assessments will continue until disease progression per RECIST v1.1. Patients randomized to atezolizumab who continue to receive atezolizumab following disease progression will undergo tumor assessments until treatment discontinuation. Tumor assessments should continue regardless of whether patients discontinue study treatment or start new anti-cancer therapy in the absence of disease progression unless they withdraw consent.

In all patients, response will be assessed by the investigator using RECIST v1 until disease progression. Patients randomized to receive atezolizumab will additionally be assessed by modified RECIST criteria until treatment discontinuation.

Follow-up data capture, including subsequent anticancer therapies, will continue for each patient until death, withdrawal of consent, loss to follow up, or study termination by Sponsor, whichever occurs first.

In addition to PD-L1 analysis, exploratory research will be performed on histological tumor tissue samples pre-treatment.

Patients will undergo blood sample collection for exploratory biomarker analyses using plasma and PBMCs as per schedule of assessments.

Tissue and plasma samples will be analyzed for example by methods like IHC, quantitative reverse transcriptase PCR (qRT-PCR), next-generation sequencing (NGS) and/or other methods to study tumor biomarkers and changes thereof on DNA, RNA and/or protein (or other analytes). These exploratory biomarker evaluations will not be used for any treatment-related decisions. Exploratory analyses aim to study tumor-associated alterations to further understand disease pathobiology (including but not limited to mechanisms of disease progression, pseudo-progression, acquired resistance), to evaluate surrogate biomarkers and to potentially allow for the development of blood-based and tissue-based diagnostic tests to help predict which patients may benefit from atezolizumab.

Primary imaging data used for tumor assessment may be collected by the Sponsor to enable centralized, independent review of response endpoints, if needed.

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 and assessed by immune mediated adverse events (imAEs) and immune mediated adverse reactions (imARs) methods. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. An external independent Data Monitoring Committee (iDMC) will be assembled and will be responsible for monitoring the safety of patients in the study in accordance with a pre specified iDMC charter.

During the study, assessments will be performed according to the Schedule of Assessments.

Number of Patients

Approximately 120 sites globally will participate in the study, and 441 patients are expected to be randomized.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Male or female, age ≥ 18 years
3. Able to comply with the study protocol, in the investigator's judgment
4. Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC as per the American Joint Committee on Cancer (AJCC) 7th edition
5. No sensitizing epidermal growth factor receptor (EGFR) mutation (L858R or exon 19 deletions) or anaplastic lymphoma kinase (ALK) fusion oncogene detected
6. No prior systemic treatment for advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC as per the AJCC 7th edition
7. Life expectancy ≥ 8 weeks
8. Deemed unsuitable for any platinum-doublet chemotherapy by the investigator due to poor performance status (ECOG PS of 2-3)

   - However, patients ≥ 70 years of age who have an ECOG PS of 0 or 1 may be included due to:
     a) substantial comorbidities
     b) contraindication(s) for any platinum-doublet chemotherapy
9. Representative formalin-fixed paraffin-embedded (FPPE) tumor tissue block obtained during course of disease (archival tissue) or at screening (tumor blocks are highly preferred for central analysis of PD-L1 expression and exploratory biomarkers)
10. Patients with treated, asymptomatic central nervous system (CNS) metastases are eligible, provided they meet all of the following criteria:
    a) Measurable disease outside CNS
    b) Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)
    c) No ongoing requirement for corticosteroids as therapy for CNS disease; anticonvulsants at a stable dose allowed
    d) No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to randomization
    e) No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

    - Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to randomization, if all other criteria are met, including clinical confirmation of no evidence of interim disease progression.
11. Measurable disease (by RECIST v1.1)

    - Previously irradiated lesions can only be considered as measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of disease.
12. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to randomization:
    a) Absolute neutrophil count (ANC) ≥ 1500 cells/μL without granulocyte colony-stimulating factor support
    b) White blood cell (WBC) counts > 2500/μL
    c) Lymphocyte count ≥ 500/μL
    d) Serum albumin ≥ 2.5 g/dL
    e) Platelet count ≥ 100,000/μL without transfusion (without transfusion within 2 weeks of laboratory test used to determine eligibility)
    f) Hemoglobin ≥ 9.0 g/dL, patients may be transfused or receive erythropoietic treatment to meet this criterion

g) International normalized ratio (INR) or activated partial thromboplastin time (aPTT) ≤ 1.5 × upper limit of normal (ULN). This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation must have an INR or aPTT within therapeutic limits for at least 1 week prior to randomization

h) Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase ≤ 2.5 × ULN with the following exceptions:

- Patients with documented liver metastases: AST and/or ALT ≤ 5 × ULN
- Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN

i) Serum bilirubin ≤ 1.5 × ULN. Patients with known Gilbert's syndrome who have serum bilirubin level ≤ 3 × ULN may be enrolled

j) Serum creatinine ≤ 1.5 × ULN

13. For female patients of childbearing potential randomized to the atezolizumab treatment arm: agreement (by patient and/or partner) to remain abstinent (refrain from heterosexual intercourse) or to use highly effective form(s) of contraceptive methods that result in a failure rate of < 1% per year when used consistently and correctly during the treatment period and for at least 5 months after the last dose of atezolizumab.

- A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, and established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.

14. Female patients of childbearing potential and male patients with partners of childbearing potential treated in the comparative single agent chemotherapy arm should continue contraception use for at least 6 months after the last dose of study treatment. Such methods include: combined (estrogen and progestogen containing) hormonal contraception, progestogen-only hormonal contraception associated with inhibition of ovulation together with another additional barrier method always containing a spermicide, intrauterine device (IUD): intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner (on the understanding that this is the only one partner during the whole study duration), and sexual abstinence. Male patients should not donate sperm during this study and for at least 6 months after the last dose of comparative single agent chemotherapy treatment.

- Oral contraception should always be combined with an additional contraceptive method because of a potential interaction with the study drug. The same rules are valid for male patients involved in this clinical study if they have a partner of childbirth potential. Male patients must always use a condom.

15. Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- **Cancer-Specific Exclusion Criteria**

1. Patients younger than 70 years who have an ECOG PS of 0 or 1.
2. Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation of the brain during screening and prior radiographic assessments

a) Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for > 2 weeks prior to randomization

b) Leptomeningeal disease

c) History of CNS metastases intracranial haemorrhage

3. Uncontrolled tumor-related pain
   a) Patients requiring pain medication must be on a stable regimen at study entry.
   b) Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment. Patients should have recovered from the effects of radiation. There is no required minimum recovery period.
   c) Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
4. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently). Patients with indwelling catheters (e.g., PleurX®) are allowed.
5. Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L or calcium > 12 mg/dL or corrected serum calcium > ULN)
6. History of other malignancy within 5 years prior to screening, with the exception of those with a negligible risk of metastasis or death (e.g. expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated with curative intent, breast ductal carcinoma in situ treated surgically with curative intent)
7. NCI CTCAE (v4.0) Grade 3 or higher toxicities due to any prior therapy (e.g., radiotherapy) (excluding alopecia), which have not shown improvement and are strictly considered to interfere with current study medication
8. Patients who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 6 months from randomization since the last chemotherapy, radiotherapy, or chemoradiotherapy

- **General Medical Exclusion Criteria**

9. Women who are pregnant or lactating, or intending to become pregnant during the study. Women of childbearing potential including women who have had a tubal ligation, must have a negative serum pregnancy test result within 14 days prior to initiation of study drug
10. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis
    - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study
    - Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen are eligible for this study
11. Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
    a) Rash must cover less than 10% of body surface area (BSA)
    b) Disease is well controlled at baseline and only requiring low potency topical steroids
    c) No acute exacerbations of underlying condition within the last 12 months requiring treatment with either psoralen plus ultraviolet radiation (PUVA), methotrexate, retinoids, biologic agents, oral calcineurin inhibitors or high potency or oral steroids
12. History of idiopathic pulmonary fibrosis (IPF), organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted
13. Known positivity for human immunodeficiency virus (HIV)

- Testing is not required in the absence of clinical symptoms and signs suggestive of HIV infection.
- Patients with a past history of/or symptoms of HIV are eligible only if serological tests are negative.

14. Known active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or known active hepatitis C
    - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible. HBV DNA test must be performed in these patients prior to randomization. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA
15. Active tuberculosis
16. Severe infections within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
17. Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina
    - Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction (LVEF) < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate
18. Major surgical procedure other than for diagnosis within 4 weeks prior to randomization or anticipation of need for a major surgical procedure during the course of the study
19. Prior allogeneic bone marrow transplantation or solid organ transplant
20. Any serious medical condition (including metabolic dysfunction, physical examination finding) or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study or that may affect the interpretation of the results or render the patient at high risk for treatment complications
21. Patients with an illness or condition that may interfere with capacity or compliance with the study protocol, as per investigator's judgment
22. Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to randomization

- **Exclusion Criteria Related to Atezolizumab**

23. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
24. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
25. Oral or IV antibiotic treatment. Patients will thus need to have recovered from any infection requiring antibiotics. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
26. Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine will be required during the study
    - Influenza vaccination is allowed, but should be given during influenza season. However, patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to randomization, at any time during the study or within 5 months after the last atezolizumab dose
27. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti-programmed death−1 (anti-PD-1), and anti-PD-L1 therapeutic antibodies. Patients who have had prior anti-cytotoxic T lymphocyte−associated antigen 4 (CTLA-4) treatment may be enrolled, provided the following requirements are met:
    a) Minimum of 6 weeks from the last dose of anti−CTLA-4
    b) No history of severe immune mediated adverse effects from anti-CTLA-4 (NCI CTCAE Grade 3 and 4)

28. Treatment with systemic immunostimulatory agents (including but not limited to interferons, interleukin-2 [IL-2]) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to randomization
29. Treatment with systemic corticosteroids or other immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor [anti-TNF] agents)
    - Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.
    - The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.
    - Patients with history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumor assessments done by MRI.
30. Patients not willing to stop treatment with traditional herbal medicines

- **Exclusion Criteria Related to Chemotherapy**

31. Known sensitivity and contraindications to the 2 comparative chemotherapy agents, i.e. vinorelbine (oral or intravenous) and gemcitabine (intravenous)

End of Study and Length of Study

This study is event-driven, with a recruitment period of approximately 24 months. The required number of 380 events for the final analysis of the primary endpoint of OS is expected to occur approximately 42 months after the first patient has been enrolled.

For patients randomized to the atezolizumab treatment arm, treatment may continue beyond disease progression per RECIST v1.1 until loss of clinical benefit, unacceptable toxicity, patient or physician decision to discontinue, or death. For all patients, tumor response data collection will continue until disease progression, even if the patient stops study treatment prior to disease progression. Patients randomized to receive atezolizumab who continue study treatment after disease progression continue to undergo tumor assessments until treatment discontinuation. Follow-up data capture, including subsequent anticancer therapies, will continue for each patient until death, withdrawal of consent, loss to follow-up, or study termination by Sponsor, whichever occurs first.

The end of the study is when the required number of deaths has been observed. Additionally, the Sponsor may decide to terminate the study at any time.

Investigational Medicinal Products

Test Product (Investigational Drug)

Atezolizumab, at a dose of 1200 mg, will be administered by IV infusion every 21 days.

Comparators

Single agent chemotherapy (vinorelbine [oral or intravenous] or gemcitabine [intravenous]) based on investigator's choice will be administered per relevant local guidelines and SmPC management. Doses and dose modifications for the selected single agent chemotherapy should be made per relevant local guidelines and SmPC management.

Statistical Methods

Primary Analysis

The primary efficacy analysis is the comparison of OS between the two treatment arms (atezolizumab arm and single agent chemotherapy arm).

For OS, patients without a date of death will be censored on the date a patient was last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization plus 1 day.

The null and alternative hypotheses for OS analysis can be phrased in terms of comparison of survival function S(t) for the two treatment arms:

Ho: $S_{chemo}(t) = S_{Atezo}(t)$ vs

H1: $S_{chemo}(t) \neq S_{Atezo}(t)$.

The hazard ratio (HR) will be estimated using a stratified Cox regression model including 95% confidence intervals (CIs). The stratification factors will be: histologic subtype

(non-squamous/squamous), PD-L1 IHC status (positive/negative/unknown) and brain metastases (yes/no).

An unstratified analysis will also be performed.

Kaplan-Meier methodology will be used to construct survival curves by treatment arms. The median OS and corresponding 95%CI will be provided for each treatment arm.

If non proportionality of HR is detected, then further analyses and tests will be run. Further details on this scenario will be provided in the statistical Analysis Plan (SAP).

Determination of Sample Size

. Assuming a 10% withdrawal rate and accrual duration of 24 months, approximately 441 patients will be randomized in a 2:1 ratio to atezolizumab (294 patients) or chemotherapy (147 patients). A total of 380 OS events will provide 90% power to detect a significant improvement in the primary endpoint (median OS) for treatment with atezolizumab versus chemotherapy from 7 months to 10 months (i.e. HR of 0.7) for a two-sided log-rank test at an alpha level of 5%. There is one planned interim analysis at 304 OS events. Operating characteristics (power and expected total number of events) for true underlying hazard ratio values of 0.7 are provided in the table below.

Sample Size Calculation Parameters	**Values**
Randomization ratio (Atezolizumab vs Chemotherapy)	2:1
Type 1 error (2-sided)	5%
Power	90%
Accrual duration	24 months
Duration until OS interim analysis	30 months
Duration until OS final analysis	42 months
Drop-out rate	10%
Median Control	7 months
Median Atezolizumab	10 months
Hazard ratio	0.7
Number of events at interim analysis	304
Number of events at final analysis	380
Number of patients	441

Note: This is assuming validity of proportional Hazards assumption.

Interim Analyses

An interim analysis of OS will be performed when approximately 304 events in the ITT population have been reached. A group sequential design (Lan-DeMets with O'Brien-Fleming stopping boundaries) will be used to control the overall type I error rate (Lan and DeMets 1983).

The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter. The decision to conduct the planned interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP. The iDMC charter will document potential recommendations the iDMC can make to the Sponsor as a result of the analysis and the iDMC charter will also be made available to relevant health authorities, if applicable.

Appendix 2
Schedule of Assessments

Assessment Window (Days)	Screening Period [a] Day –28 to Day –1	Treatment Period [w] Baseline (Cycle 1 Day 1)	Treatment Period [w] Cycles ≥ 2 (Day 1 ± 5 days)	Treatment Discontinuation [b] ≤ 30 Days after Last Dose	Follow-Up Period [c] -
Signed Informed Consent Form(s) [a]	x				
Tumor Tissue for ALK/EGFR analysis, central PD-L1 IHC (stratification) and exploratory biomarkers [d]	x				
Review of eligibility criteria	x				
Medical, surgical, and cancer histories, including demographic information, EGFR, and ALK mutational status [e]	x				
HIV, HBV, HCV serology [f]	x [y]				
TSH, free T3 (or total T3), free T4 [g]	x [y]	x	Cycles 5, 9, 13 etc.	x	
Concomitant medications [h]	x	x	x	x	
Tumor response assessments [i]	x [i]		x [x]		
Patient-reported outcomes [j]	x		With tumor response assessments [z]		
Complete physical examination [k]	x			x	
Limited physical examination [k]		x	x		
ECOG performance status [l]	x	x	x [m]	x	
Vital signs [n]	x	x	x	x	
12-lead electrocardiogram [o]	x	x	x	x	
Hematology [p]	x [y]	x	x	x	
Serum chemistry [q]	x [y]	x	x	x	
Urinalysis [r]	x [y]	x	x	x	

Assessment Window (Days)	Screening Period [a] Day –28 to Day –1	Treatment Period [w] Baseline (Cycle 1 Day 1)	 Cycles ≥ 2 (Day 1 ± 5 days)	Treatment Discontinuation [b] ≤ 30 Days after Last Dose	Follow-Up Period [c] -
Pregnancy test [s]	x [y]	Prior to each treatment cycle		x	x [s]
Coagulation (INR, aPTT)	x [y]			x	
Whole blood for PBMC (exploratory biomarker) [t]		x			
Plasma for exploratory biomarkers [u]		x	Week 7 and at PD		
Adverse events / adverse events of special interest [v]		x	x	x	x [v]
Study drug administration [w]		x	x		
Survival and anticancer therapy follow-up [c]					x

ALK = anaplastic lymphoma kinase; ECG = electrocardiogram; EGFR = epidermal growth factor receptor; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus, IHC = immunhistochemistry; PBMC = peripheral blood mononuclear cell; PD = disease progression; PD-L1 = programmed cell death-ligand 1; q3w = every 3 weeks; TSH = thyroid-stimulating hormone; T3 = free triiodothyronine; T4 = free thyroxine.

Note: All assessments should be performed within ± 5 days of the scheduled visit, unless otherwise specified.

[a] Written informed consent is required for performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry (except where otherwise specified) may be used for screening assessments rather than repeating such tests.

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit ≤ 30 days after the last dose of study drug. The visit at which the decision is made to discontinue treatment (e.g., disease progression is determined or confirmed) may be used as the treatment discontinuation visit. After study drug discontinuation, patients will be treated at the discretion of the investigator according to local practice. The decision to continue treatment with atezolizumab (experimental arm only) beyond disease progression (RECIST v.1.1) is at the investigator's discretion for patients who can continue to benefit from the treatment (for criteria see protocol Section 3.1).

[c] Required follow-up information, including subsequent anticancer therapies and any treatment related AEs, will be collected via telephone calls and/or clinic visits every 2 months (± 5 days) until death, withdrawal of consent, loss to follow-up, study termination by the Sponsor, or protocol-defined end of study, whichever comes first. In case of serious side effects during the study, follow-up examinations at the study site may be required.

[d] Screening: A representative formalin-fixed paraffin-embedded (FPPE) tumor tissue block obtained during course of disease (archival tissue) or screening (tumor blocks are highly preferred; ideally, 3 cores should be submitted in case smaller core biopsies are available in order to have sufficient tumor cells available. In case the tumor block is not available, 10-15 unstained, consecutive slides not older than 60 days will be accepted. A minimum of five slides is mandated for PD-L1 analysis and patient stratification. If archival tissue (most recent sample) is unavailable, a pretreatment tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable. Tumor tissue from bone metastases or are not acceptable. Tumor tissue should be of good quality based on total and viable tumor content (at least 300 viable tumor cells across cores are needed for determination of TC/IC status at low cut-offs).

[e] Cancer history includes stage, date of diagnosis, results of EGFR mutation and ALK rearrangement testing (if available), and prior antitumor treatment. Demographic information includes sex, age, and self-reported race/ethnicity. Patients with non-squamous NSCLC and unknown EGFR or ALK status will be required to be tested at pre-screening/screening. Patients with squamous NSCLC and unknown EGFR or ALK status will not be required to be tested at pre-screening/ screening, except for patients who are never smokers or have mixed histology. EGFR and/or ALK may be assessed locally or at a central lab. Additional tissue will be required for central testing of EGFR and/or ALK. An FFPE tumor tissue block (or at least 7 slides) will be required for testing.

[f] Patients with a history of, or signs of active HIV or hepatitis B/C disease must be tested for seropositivity prior to the inclusion into the study. HIV-positive patients will be excluded from the clinical study. Patients with a positive hepatitis B surface antigen [HBsAg] test at screening will be excluded from this clinical study. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

[g] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening, on Day 1 of Cycle 1 and every four cycles thereafter (i.e., Cycles 5, 9, 13, etc.).

[h] Includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening until the treatment discontinuation visit. All such medications should be reported to the investigator, and must be recorded on the appropriate Concomitant Medications eCRF.

[i] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. It is recommended to have the screening/baseline tumor assessment done within 14 days before randomization, as close as possible to baseline. All measurable and evaluable lesions should be assessed and documented at the screening visit. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Results must be reviewed by the investigator before dosing at the next cycle. All patients should undergo a brain scan at Screening. Patients with CNS metastases newly detected at the screening scan should have received radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to randomization, if all other criteria are met, including clinical confirmation of no evidence of interim disease progression..

[j] PRO assessments (EORTC QLQ-C30, QLQ-LC13, and EQ-5D-5L) will be completed before the patient receives any information on disease status and prior to the performance of non-PRO assessments and the administration of study treatment. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site.

[k] Complete and limited physical examinations are defined in protocol Section 4.5.3.

[l] ECOG performance status, limited physical examination, local laboratory assessments may be obtained ≤ 96 hours before Day 1 of each cycle.

[m] ECOG PS is mandatory at all timepoints.

[n] Includes height, weight, respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature, an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, (or as clinically indicated), limited, symptom-

directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the AE eCRF.

[o] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. ·ECG recordings will be obtained as described in protocol Section 4.5.9.

[p] Hematology includes complete blood count [CBC], including red blood cell count [RBC] count, hemoglobin, hematocrit, white blood cell (WBC) count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count

[q] Serum chemistry panel (serum or plasma) includes glucose, blood urea nitrogen [BUN] or urea, creatinine, sodium, potassium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), calcium, phosphorus, total and direct bilirubin, ALT, AST, alkaline phosphatase, uric acid, LDH, total protein, and albumin.

[r] Dipstick permitted: pH, specific gravity, glucose, protein, ketones, blood.

[s] A serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Day 1. On study pregnancy tests must be performed prior to each treatment cycle (21 day cycle for atezolizumab and per relevant local guidelines and SmPC management for chemotherapy) while receiving the IMP. For female patients of childbearing potential, the pregnancy tests will be repeated during the treatment discontinuation visit and then every 2 months during follow-up for at least 5 months after the last dose of atezolizumab and for at least 6 months after the last dose of chemotherapy, respectively. Pregnancy tests during follow-up do not require on-site visits; results from a treating physician can be used. The pregnancy test can be conducted with serum or urine. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[t] 18 mL whole blood (ACD tubes) should be obtained pre-dose and shipped to the central laboratory for PBMC preparation, RNA isolation and gene expression analysis. Details are specified in a separate laboratory manual. If consented, residual material will be transferred to RBR.

[u] 20 mL whole blood (K3 EDTA tubes) for preparation of plasma should be obtained pre-dose. Plasma samples will be shipped to the central laboratory for exploratory biomarker analyses. If consented, residual material (including extracted RNA or DNA or other) will be transferred to RBR.

[v] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see protocol Section 5.4.2 for instructions for reporting serious adverse events). After initiation of study drug, all serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After these respective periods, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug, regardless of time after study (see protocol Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[w] Atezolizumab at a fixed dose of 1200 mg will be administered intravenously at the study site on Day 1 of each 21-day cycle. Single agent chemotherapy (vinorelbine, oral or intravenous, or gemcitabine) will be administered per relevant local guidelines and SmPC management. Chemotherapy cycles may be 3-weekly or 4-weekly. A 28-day assessment schedule will be followed for patients receiving 4-weekly chemotherapy cycles.

[x] Tumor assessments will be performed at baseline, every 6 weeks (± 5 days) following randomization for 48 weeks, and every 9 weeks (± 5 days) thereafter, regardless of dose delays, with additional scans as clinically indicated, until radiographic disease progression per RECIST v1.1 or (for patients who continue atezolizumab after radiographic disease progression), loss of clinical benefit as determined by the investigator (see protocol Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue study treatment for reasons other than disease progression or loss of clinical benefit, even if patients start new anti-cancer therapy. In all patients, response will be assessed by the investigator using RECIST v1.1 until disease progression. Patients randomized to receive

atezolizumab will additionally be assessed by modified RECIST criteria until treatment discontinuation. Follow-up tumor assessments are not required after discontinuation of atezolizumab for patients continuing atezolizumab beyond PD.

[y] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment.

[z] The EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires will be completed by the patients with each tumor assessment until disease progression per RECIST v1.1, even if patients discontinue study treatment for any reason other than progressive disease or loss of clinical benefit.