Official Title: A Phase III/IV, Single Arm, Multicenter Study of Atezolizumab (Tecentriq) to Investigate Long-Term Safety and Efficacy in Previously-Treated Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Tail)

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SIGNATURE PAGE FOR STATISTICAL ANALYSIS PLAN

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Sponsor:	F. Hoffmann-La Roche Ltd
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STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE III/IV, SINGLE ARM, MULTICENTER STUDY OF ATEZOLIZUMAB (TECENTRIQ) TO INVESTIGATE LONG-TERM SAFETY AND EFFICACY IN PREVIOUSLY-TREATED PATIENTS WITH LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER (TAIL)**

PROTOCOL NUMBER: MO39171

STUDY DRUG: Atezolizumab (RO5541267)

VERSION NUMBER: 1

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[redacted], F. Hoffmann - La Roche Ltd

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List of Abbreviations

Abbreviation	Definition
AE	Adverse events
AESI	Adverse events of special interest
ALK	Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BOR	Best overall response
BUN	Blood urea nitrogen
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EGFR	Epidermal growth factor receptor
EORTC	European Organization for the Research and Treatment of Cancer
EQ-5D-5L	EuroQoL 5 Dimension questionnaire
FFPE	Formalin-fixed, paraffin-embedded
HRQoL	Health-related quality of life
iDMC	Independent Data Monitoring Committee
INR	International normalized ratio
IgG1	Immunoglobulin G, subclass 1
irAE	Immune-related adverse event
ITT	Intent-to-treat
IV	Intra-venous
KM	Kaplan Meier
LATAM	Latin America
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective response rate
OS	Overall survival

Abbreviation	Definition
PD	Progressive disease
PDMS	Protocol Deviation Management System
PFS	Progression free survival
PR	Partial response
PRO	Patient-reported outcome
PS	Performance status
PT	Preferred term
QLQ-LC13	Quality-of-Life Questionnaire – Supplemental Lung Cancer Module
RBC	Red blood cell
RBR	Research biosample repository
RECIST	Response Evaluation Criteria in Solid Tumors
RS	Raw Score
SAE	Serious adverse event
SAF	Safety population
SAP	Statistical analysis plan
SD	Stable disease
SE	Standard error
SI	System International
SOC	System Organ Class
T3	Free triiodothyronine
T4	Free thyroxine
TKI	Tyrosine kinase inhibitor
TSH	Thyroid-stimulating hormone
TTD	Time to deterioration
WBC	White blood cell

1. BACKGROUND

This Statistical Analysis Plan (SAP) describes the planned analyses and statistical methods used for Study MO39171 (TAIL).

2. STUDY DESIGN

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in

Appendix 1
Protocol Synopsis Version 3

. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 ENDPOINTS

See the Protocol Synopsis in

for a description of the outcome measures.

2.3 DETERMINATION OF SAMPLE SIZE

The sample size considerations are based upon estimation precision for the incidence of AEs. With 600 patients, the following 95% confidence intervals (CIs) (Table 1) could be provided for the different incidences of AEs, which is deemed appropriate for the purposes of the study.

Table 1: Adverse Events Incidence and Corresponding 95% Confidence Interval

Sample Size	AE Incidence	95% Clopper-Pearson Exact CI
600 patients	1%	[0.2%; 1.8%]
	2%	[0.9%; 3.1%]
	3%	[1.6%; 4.4%]
	5%	[3.3%; 6.7%]
	10%	[7.6%; 12.4%]

CI, confidence interval

2.4 ANALYSIS TIMING

The following analyses are scheduled:

- **Primary analysis** that will occur approximately 6 months after the last patient has been enrolled.
- **Final analysis** that will occur at the end of the study, i.e. when all enrolled patients have either died, withdrawn consent, are lost to follow up, or have been followed for 30 months since the last study patient is enrolled, whichever occurs first. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4 years.

3. STATISTICAL METHODS

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

3.1 ANALYSIS POPULATIONS

3.1.1 Safety Population

The primary safety population will be based on all patients who received any dose of atezolizumab during the study treatment. Patients who were enrolled to the study but who did not receive any study drug will not be included in the safety population.

3.1.2 Intent-to-treat Population (ITT)

The ITT population will be based on all enrolled patients regardless of whether they received any study drug.

3.1.3 Biomarker Evaluable Population (BEP)

Patients from the safety population with at least one result for PD-L1 expression on tumor cells (TC) in either central or local assessments available. In case both central and local assessments are available, central assessments should be used.

3.2 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.

3.3 ANALYSIS OF TREATMENT GROUP

The following analyses will be based on the Safety population.

Demographic characteristics, such as age, sex, race, ethnicity, and baseline disease characteristics, such as histology subtype, ECOG performance status, tobacco use history, number of prior cancer treatments, history of autoimmune disease and serology values will be summarized for the Safety population using means, standard deviations (SDs), medians, ranges and inter-quartile ranges for continuous variables and frequencies and percentages for categorical variables, as appropriate.

The baseline value will be defined as the last available value recorded on or prior to the first administration of any study medication.

Lung cancer history (including PD-L1 expression from local and/or central labs), CNS metastasis at baseline and details on the tumor metastasis at baseline and organs involved will also be summarized.

Prior and concurrent medical history, including but not limited to prior anti-cancer surgery, prior lines of NSCLC therapy, prior cancer immunotherapy, prior radiotherapy, prior TKI therapy, systemic therapy and medications will be summarized overall.

Subsequent anti-cancer therapies administered after progression, anti-cancer therapies administered before progression or for patients with no progression, follow-up cancer radiotherapy, on-study radiotherapy, on-study and follow-up cancer-related medical/surgical procedures will be summarized overall.

3.4 EFFICACY ANALYSIS

All efficacy analysis are descriptive and considered as secondary endpoints with the primary objective of the study being safety. The Safety population will be used for all efficacy analyses, unless otherwise stated.

3.4.1 Efficacy Endpoints

3.4.1.1 Overall Survival

OS is defined as the time (in months) from initiation of study treatment to death from any cause. Patients alive at the time of clinical cut-off date will be censored on the date the patient was last known to be alive. If no post-baseline data are available, OS will be censored at the start date of study treatment plus 1 day.

OS Rate at the 6, 12, 24 and 36-Months Timepoints

The OS rate at the 6, 12, 24 and 36-months timepoints after initiation of study treatment will be estimated using Kaplan-Meier methodology, along with 95% CI calculated with the standard error (SE) derived from the Greenwood formula. For the primary analysis, only OS rate at 6 and 12 months will be estimated.

3.4.1.2 Progression-Free Survival

PFS according to RECIST 1.1 is defined as the time (in months) from initiation of study treatment to the first documented disease progression as determined by the investigator per RECIST 1.1, or death from any cause, whichever occurs first. 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 start date of study treatment plus 1 day, if no post-baseline tumor assessment available or at study enrollment plus 1 day for patients who were not treated.

3.4.1.3 Best Overall Response

BOR according to RECIST v1.1, for a subject is defined as the most favorable outcome, at any visit after the start date of study treatment and up to the first documented disease progression per RECIST v1.1. Confirmation of response according to RECIST v1.1 is 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, thissingle response must have been assessed no less than 6 weeks (at least 42 days) after start date of study treatment.

A patient is assigned a BOR of PD if he has a response assessment of PD at any visit, and not a BOR of CR, PR, or SD otherwise the best overall response will be Non-Evaluable (NE).

3.4.1.4 Objective Response Rate

ORR, according to RECIST v1.1, is defined as the proportion of patients with a confirmed BOR, either CR or PR, 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 ORR and its 95% CI will be calculated using the Clopper-Pearson method.

3.4.1.5 Duration of Response

DOR according to RECIST 1.1 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 experienced disease progression 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 CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day.

3.4.1.6 Objective Response Rate, Progression Free Survival, and Duration of Objective Response per Modified RECIST

ORR, PFS, and DOR analyses using modified RECIST criteria. The investigator-assessed ORR is defined as the proportion of patients whose confirmed best overall response is either a PR or CR per modified RECIST. An estimate of ORR and its 95% CI will be calculated for the ITT population using the Clopper-Pearson method.

For patients experienced an objective response (CR or PR per modified RECIST) during the study as assessed by the investigator, DOR is defined as the duration from the first tumor assessment that supports the patient's objective response (CR or PR, whichever is first recorded) to disease progression or death due to any cause, whichever occurs first. Patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the last tumor assessment date. DOR will be assessed using Kaplan-Meier methodology.

PFS by modified RECIST is defined as the time from first treatment taken 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 were met:

a) Modified RECIST criteria for progression were met at a tumor assessment and no subsequent tumor assessment was performed.
b) Modified RECIST criteria for progression were met at a tumor assessment, and at the subsequent tumor assessment, the criteria for confirmed progression by modified RECIST were also met.

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

PFS and DOR per modified RECIST will be summarized using the Kaplan-Meier methodology.

3.4.2 Patient-Reported Outcomes

Patient-reported outcomes (PROs) of lung cancer-related symptoms (i.e., cough, dyspnea, pain in chest, pain in arm/shoulder) will be assessed using the EORTC QLQ LC13 (Bergman et al. 1994). Summary statistics (mean, SD, median, and range) of linear transformed scores will be reported for all the items and the dyspnea subscale of the EORTC QLQ-LC13 according to the EORTC scoring manual guidelines. The mean change of the linear transformed scores from baseline will also be assessed as well as the proportion of patients with improved, stable, or worsened outcomes.

Completion and compliance rates will be summarized at each time point will be calculated as the number of patients who completed the assessment divided by the number of patients expected to complete the assessment at each time. Reasons for missing assessments, if available, will be summarized using frequencies and percentages.

The analysis of PRO measures will be conducted on the safety 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.

The percentage for baseline will be calculated based on safety population. Only patients with a baseline assessment and at least one non-missing post-baseline assessment will be included in the analyses.

Time to Confirmed Symptom Deterioration (TTCSD):

Time to confirmed symptom deterioration using the EORTC symptom scores is defined as the time from baseline to the first confirmed clinically meaningful deterioration in the EORTC symptom score. 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 death within 3 weeks from the last assessment. A ≥ 10-point change in the EORTC scale score is perceived by patients as clinically significant (Osoba et al. 1998).

TTCSD 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 multi-item subscale (Questions 33-35 on the QLQ-LC13)
- Arm and/or shoulder pain (Question 41 on the QLQ-LC13)
- Composite of the 3 symptoms: cough, dyspnea (multi-item subscales QLQ-LC13) and chest pain

If no baseline or post-baseline assessment is performed, patients will be censored at the start date of study treatment plus 1 day. Patients without deterioration at the time of clinical cut-off date will be censored at the last time they were known to have not deteriorated.

TTD of the pre-specified symptoms will be summarized using the Kaplan-Meier method. The median time and two-sided 95% CI for the median will also be provided.

3.4.3 Exploratory Efficacy Endpoints

3.4.3.1 PFS from Start of New Anti-Cancer Therapy

For patients who started a new anti-cancer therapy, PFS from start of new cancer therapy is defined as the time (in months) from start of new anti-cancer treatment to the first occurrence of disease progression on next-line treatment or death from any cause, whichever occurs first.

Patients who are alive and who have not experienced disease progression on next-line treatment at the time of clinical cut-off date will be censored at the last date known to be alive.

The same analysis as the analysis of PFS RECIST 1.1 will be repeated for PFS from start of new anti-cancer therapy.

3.4.3.2 ORR from Start of New Anti-Cancer Therapy

For patients who started a new anti-cancer therapy, ORR from start of new cancer therapy is defined as the proportion of patients with a best response of CR or PR, following the start of new anticancer therapy. Patients not meeting this criterion will be considered non-responders. The same analysis as the analysis of ORR will be repeated for ORR from start of new anti-cancer therapy.

3.4.3.3 Progression-Free Survival 2

PFS2 is defined as the time (in months) from initiation of study treatment to the first occurrence of disease progression on next-line treatment or death from any cause, whichever occurs first. Patients who are alive and who have not experienced disease progression on next-line treatment at the time of clinical cut-off date will be censored at the last date known to be alive.

The same analysis as the analysis of PFS RECIST 1.1 will be repeated for PFS2.

3.4.3.4 Sensitivity Analysis

If there is a difference between the number of patients in the ITT and the SAF population, the outputs for OS and PFS will be repeated on the ITT population using the date of enrollment as start date. Patients without any post-enrollment data will be censored at the date of enrollment plus 1 day.

3.4.4 Subgroup Analyses

The OAK-LIKE Subgroup is defined as patients with the next characteristics:

- ECOG Performance status of 2: no
- Patients with previous anti-PD-1, anti-PD-L1, or ant-CTLA-4 therapy: no
- Presence of untreated CNS metastases at baseline: no
- Renal impairment (creatine clearance < 30 mL/min (CKD-EPI)): no
- Liver
    - AST and ALT ≤ 2.5 times the upper limit of normal (ULN), with alkaline phosphatase ≤ 2.5 ULN OR
    - AST and ALT ≤ 1.5 x ULN, with alkaline phosphatase > 2.5 x ULN
- HIV-positive: no
- HBV/HVC status: not active

- History of autoimmune disease: no
- Concomitant steroid treatment ongoing at baseline: no

OS and PFS results across subgroups will be examined in the following subgroups. Subgroups with ≤10 patients will not be included.

- OAK-LIKE
- Demographics:
  - Age (<, >= 65 years),
  - Sex,
  - Region (EMEA, Asia, LATAM),
  - Smoking status (never, current/previous)
- Baseline disease characteristics:
  - Histologic subtype (squamous, non-squamous),
  - ECOG performance status at baseline (0/1, 2),
  - Brain metastases at baseline (yes, no)
  - Liver metastases at baseline (yes, no),
  - History of autoimmune disease (yes, no),
  - Prior anti-PD-1 therapies (yes, no),
  - Renal impairment (eGFR<, >= 60 mL/min/m2),
  - EGFR positive at baseline (yes, no),
  - ALK positive at baseline (yes, no),
  - Active hepatitis B or C at baseline (positive, negative),
- PD-L1 status (Central):
  - PD-L1 Expression on TC (<1%, ≥1%, [1-50[%, ≥50%)
- PD-L1 status (Local):
  - PD-L1 Expression on TC (<1%, ≥1%, [1-50[%, ≥50%)
- PD-L1 (BEP):
  - PD-L1 Expression on TC (<1%, ≥1%, [1-50[%, ≥50%)
  - Yes vs No
- PD-L1 (OAK-LIKE/BEP):
  - PD-L1 Expression on TC (<1%, ≥1%, [1-50[%, ≥50%)
  - Yes vs No

Summaries of OS and PFS, including Kaplan-Meier estimates of median OS and PFS, OS rate at 6, 12, 24 and 36 months, PFS rate at 6, 12 and 24 months will be produced separately for each level of the subgroup. For the primary analysis, only the rate at 6 and 12 months will be estimated.

3.5 SAFETY ANALYSES

Safety summaries will be produced on the safety population.

3.5.1 Exposure of Study Medication

Treatment exposure, including treatment duration and number of doses received will be summarized as both continuous and categorical variables.

3.5.2 Primary Safety Endpoints

The primary endpoints are the following AE categories:

- Serious AE related to study drug
- Immune-related AE related to study drug

Incidence rates will be provided along with the corresponding 95% Pearson-Clopper CIs. Additionally, both categories will be summarized by SOC, PT and NCI CTCAE grade.

3.5.3 Adverse Events

Verbatim description of adverse events will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to the NCI CTCAE v4.0. Summary tables will include only the treatment emergent adverse events up to the data cutoff date.

The following Adverse Events will be summarized:

- All Adverse Events
- Treatment Related Adverse Events
- Grade ≥3 adverse events
- Serious Adverse Events
- Adverse events leading to Atezoliumab discontinuation
- Adverse events leading to Atezoliumab discontinuation or interruption
- Adverse Events with Fatal Outcome
- Adverse Events of Special Interest
- Treatment Related Adverse Events of Special Interest
- Serious Adverse Events of Special Interest
- Immune-Related Adverse Events

The AE tables will include the number and percentage of patients with at least one AE, by MedDRA primary System Organ Classes (SOC) and MedDRA Preferred Terms (PT) and by NCI CTCAE grade. A patient with more than one occurrence of the same adverse event in a particular SOC/PT will be counted only once in the total of those experiencing adverse events in that particular SOC/PT. For immune-related AE related to study drug, similar summary will be provided by AESI category and PT. Summary tables displaying number of patients with at least one AE by PT will also be provided.

Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation and causes of death will be summarized by treatment arm.

3.5.4 Time to first onset of AE

The time to first onset of specific AE (AESI) (in months) will be analyzed and be summarized using Kaplan Meier methodology.

The time to first onset of any specific AE is defined as the time (in months) from initiation of study treatment until the date of first onset of a specific AE. Patients without any occurrence of specific AE will not be counted.

The analysis described above will be conducted for the following categories of AEs:

- AESI,
- Immune-related AE

3.5.5 Long-Term Safety

The incidence of AEs recorded 30 days after last treatment taken will be summarized and will display number of patients with at least one AE by SOC/PT, for the following AE:

- SAEs
- AESIs

3.5.6 Duration of AEs

The time to resolution of specific AEs (in months) for AESI and irAE by Category will be analyzed and summarized using Kaplan Meier methodology.

- The start date will be the onset date recorded
- If AE is ongoing (no end-date), then the end date will be imputed at the cutoff date and the event will be censored.
- If a patient has ≥ 2 AE events, the worst grade will be taken into account
- If a patient has ≥ 2 AE events with the same grade, the longest will be taken into account

3.5.7 Subgroup Analyses

Safety summary tables and summary of AE by SOC/PT will be repeated for the following subgroups:

- OAK-LIKE Population
- Demographics:
    - Age (<, >=65 years),
    - Age (<, >=80 years),
    - Region (Europe, Asia, LATAM)
- Baseline disease characteristics:
    - Histologic subtype (squamous, non-squamous),
    - ECOG performance status at baseline (0/1, 2),
    - Brain metastases at baseline (yes, no)
    - Liver metastases at baseline (yes, no),
    - History of autoimmune disease (yes, no),
    - Prior anti-PD-1 therapy (yes, no),
    - Renal impairment (eGFR<, >= 60 mL/min/m2),
    - EGFR positive at baseline (yes, no),
    - ALK positive at baseline (yes, no),
    - Active hepatitis B or C at baseline (positive, negative),

3.5.8 Laboratory Data

Laboratory parameters will be summarized by using shift table of baseline versus worst post-baseline category (grade for gradable parameters as per NCI CTCAE version 4.0 and low/normal/high for non-gradable parameters). The first abnormal category for patients with High and Low for the same laboratory test (at different visits) will be considered. A “Missing” category will be reported for subjects with missing grades or missing reference range indicators at baseline and/or post-baseline and subjects with no laboratory assessments.
In addition, a summary table will be provided for clinically relevant laboratory shifts from baseline defined as shifts from Grade 0, 1, or 2 at baseline to Grade 3 or 4 post-baseline.

All laboratory values will be listed. Separate listings will be generated to include all abnormal laboratory values for hematology, biochemistry, coagulation and thyroid function.

3.5.9 Vital Signs and ECOG Performance Status

Vital Signs of each patient, actual value and change from baseline for vital signs parameters will be summarized using descriptive statistics. ECOG PS will be summarized in a shift table of baseline versus worst post-baseline value.

3.6 MISSING DATA

For the flagging of a treatment emergent adverse event or concomitant medication with partial start and/or end date: the AE/medication will be assumed to be treatment-emergent/concomitant if it could possibly have started or been taken after the first dose of study drug.

Imputation of partial/missing death date will be done as follows:

- If the date is completely missing, then the day of “Last known to be alive” +1 will be used
- If only day is missing and year and month are same as “Last known to be alive”, then the day of “Last known to be alive”+1 will be used otherwise the 1st day of the month will be used
- If day and month are missing and year is same as “Last known to be alive”, then the “Last known to be alive”+1 will be used, otherwise 1st of January will be used

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Appendix 1
Protocol Synopsis Version 3

TITLE:	**A PHASE III/IV, SINGLE ARM, MULTICENTER STUDY OF ATEZOLIZUMAB (TECENTRIQ) TO INVESTIGATE LONG-TERM SAFETY AND EFFICACY IN PREVIOUSLY-TREATED PATIENTS WITH LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER (TAIL)**
PROTOCOL NUMBER:	MO39171
VERSION NUMBER:	3
EUDRACT NUMBER:	2017-001409-34
IND NUMBER:	Not applicable
TEST PRODUCT:	Atezolizumab (RO5541267)
PHASE:	Phase III/IV
INDICATION:	Non-small cell lung cancer (NSCLC)
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the long-term safety and efficacy of atezolizumab in patients with locally advanced or metastatic NSCLC who have progressed following standard systemic chemotherapy (including if given in combination with anti-PD-1 therapy, after anti-PD-1 as monotherapy, or after tyrosine kinase inhibitor [TKI] therapy). Patients with a previously detected sensitizing EGFR mutation or ALK fusion oncogene must have received targeted therapy (TKI) followed by at least one line of standard systemic chemotherapy prior to receiving atezolizumab. Overall, patients should not have received more than two lines of standard systemic chemotherapy. Patients will also be eligible if they discontinued first-line or second-line therapy due to intolerance.

Table 1 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoints
• To evaluate the long-term safety of atezolizumab in previously treated patients with advanced NSCLC	• Incidence of serious adverse events (SAEs) related to atezolizumab treatment • Incidence of immune-related adverse events (irAEs) related to atezolizumab treatment
Main Secondary Objective	**Corresponding Endpoint**
• To evaluate the efficacy of atezolizumab in previously treated patients with advanced NSCLC	• Overall survival (OS) rate at 2 years, defined as the proportion of patients remaining alive 2 years after initiation of study treatment

Other Secondary Objectives	Corresponding Endpoints
• To further evaluate the efficacy of atezolizumab in previously treated patients with advanced NSCLC	• OS, defined as the time from initiation of study treatment to death from any cause • Progression-free survival (PFS), defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause, whichever occurs first. PFS will be calculated based on disease status evaluated by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) and also by disease status evaluated by the investigator according to modified RECIST • OS rate at 3 years, defined as the proportion of patients remaining alive 3 years after initiation of study treatment • Objective response rate (ORR), defined as the percentage of patients who attain complete response (CR) or partial response (PR) according to RECIST v1.1 and also by disease status evaluated by the investigator according to modified RECIST • Duration of response (DOR), defined as the time from initial response to disease progression or death among patients who have experienced a CR or PR (unconfirmed) during the study. Duration of response will be calculated based on disease status evaluated by the investigator according to RECIST v1.1 and also by disease status evaluated by the investigator according to modified RECIST
Exploratory Objectives	**Corresponding Endpoints**
• To further evaluate the long-term safety and efficacy of atezolizumab in previously treated patients with advanced NSCLC	• Safety and efficacy of atezolizumab in subgroups of the study population differentiated according to: Presence of CNS metastases at baseline (yes vs. no) ECOG performance status (0 or 1 vs. 2) Histologic subtype (squamous vs. non-squamous) History of or current autoimmune disease (yes vs. no) Prior anticancer treatment • Progression-free survival from start of new anti-cancer therapy, defined as the time from initiation of new anti-cancer therapy to objective tumor progression on next-line treatment or death from any cause • Objective response rate from start of new anti-cancer therapy, defined as the percentage of patients who attain complete response (CR) or partial response (PR) • Progression-free survival 2 (PFS2), defined as the time from initiation of study treatment to objective tumor progression on next-line treatment or death from any cause

Exploratory Biomarker Objectives	Corresponding Endpoints
• To assess the role of PD-L1 and other biomarkers in the progression and fundamental biology of advanced NSCLC • To evaluate PD-L1 and other biomarkers (e.g., cancer-related genes) as prognostic biomarkers	• Safety and efficacy of atezolizumab in subgroups of the study population differentiated according to: Expression of PD-L1 protein in tumor tissue Presence/absence of other biomarkers in tumor tissue • Correlations between PD-L1 expression and other biomarkers
Patient-Reported Outcome Objectives	**Corresponding Endpoint**
• To evaluate health status utility and HR QoL of atezolizumab in previously treated patients with advanced NSCLC	• EQ-5D-5L index-based and VAS scores • EORTC QLQ-LC13 score

EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire—Supplemental Lung Cancer Module; EQ-5D, EuroQol 5-Dimension Questionnaire; HR QoL, health-related quality of life; VAS, visual analog scale.

Study Design

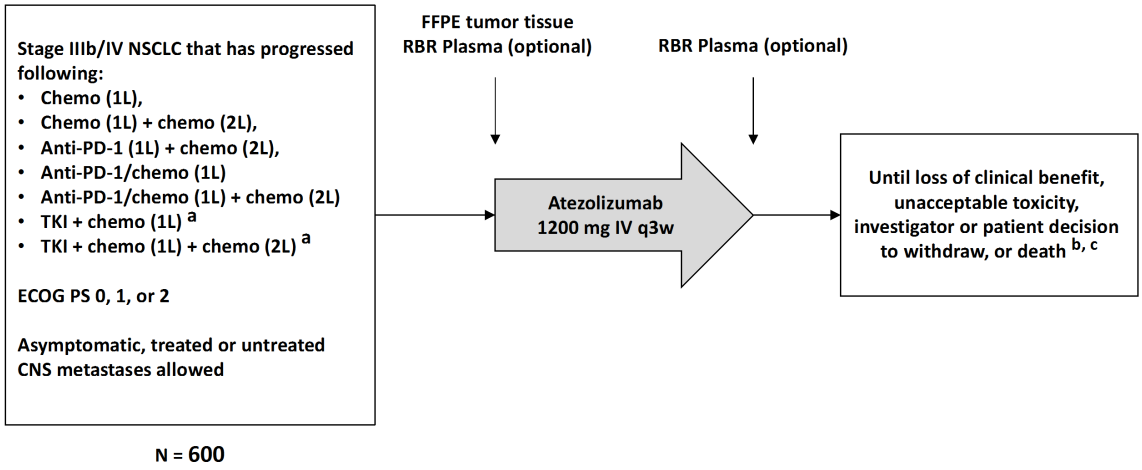
Description of Study

Study MO39171 is a phase III/IV, single-arm, multicenter study of the long-term safety and efficacy of atezolizumab treatment in patients with Stage IIIb or Stage IV NSCLC who have progressed following standard systemic chemotherapy (including if given in combination with anti-PD-1 therapy, after anti-PD-1 as monotherapy, or after TKI therapy). Patients with a previously detected sensitizing EGFR mutation or ALK fusion oncogene must have received targeted therapy (TKI) followed by at least one line of standard systemic chemother apy prior to receiving atezolizumab. Overall, patients should not have received more than two lines of standard systemic chemotherapy. Patients will also be eligible if they discontinued first-line or second-line therapy due to intolerance.

The study will consist of a Screening Period (Day –28 to Day –1), a Treatment Period, a Treatment Discontinuation Visit occurring ≤ 30 days after the last dose of study medication, and a Follow-Up Period. Day 1 (baseline) will be defined as the first day the patient receives atezolizumab. It is anticipated that the trial will enroll 600 patients at 140 sites globally.

Enrolled patients will receive atezolizumab at a fixed dose of 1200 mg administered intravenously on the first day of each cycle (Figure 1). One cycle of therapy will be defined as 21 days (± 3 days). Atezolizumab treatment will continue until investigator-assessed loss of clinical benefit, unacceptable toxicity, investigator or patient decision to withdraw from therapy, or death (whichever occurs first).

Figure 1 Study Schema



Chemo, standard systemic chemotherapy; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; FFPE, formalin-fixed paraffin-embedded; IV, intravenous; L, line; NSCLC, non-small cell lung cancer; RBR, Research Biosample Repository; TKI, tyrosine kinase inhibitor.

a. Patients with a previously detected sensitizing EGFR mutation or ALK fusion oncogene must have received targeted TKI therapy (no restrictions on number or sequence) followed by at least one line of standard systemic chemotherapy prior to receiving atezolizumab. Patients will also be eligible if they discontinued first-line or second-line therapy due to intolerance.

b. Response will be assessed by the investigator using RECIST v1.1 and modified RECIST. Patients who continue atezolizumab treatment beyond radiographic disease progression assessed per RECIST v1.1 will be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 6 weeks, and will be assessed by modified RECIST criteria until treatment discontinuation. If the scan frequency is every 9 weeks, a follow-up scan is recommended at 9 weeks or earlier if clinically indicated.

c. In those patients for whom tumor assessments are performed as part of local clinical practice and are available for report after PD or atezolizumab treatment discontinuation, best overall response (BOR) and PFS will be assessed from the first date of the new anticancer therapy to the end of the study per RECIST v1.1 and modified RECIST.

The primary objective of the study is to evaluate the long-term safety of atezolizumab. Long-term safety will be assessed by monitoring the nature, severity, duration, frequency and timing of atezolizumab-related SAEs and atezolizumab-related irAEs. An irAE is defined as any adverse event of special interest (AESI) associated with systemic corticosteroid use within 30 days of the onset date. All-causality AEs, all-causality SAEs, AEs and SAEs leading to atezolizumab interruption or discontinuation, and AESIs will also be reported, as well as causes of death, vital signs, physical findings and clinical laboratory results.

Secondary objectives will assess the efficacy of atezolizumab. The main efficacy objective will be to evaluate the OS rate 2 years after the first dose of atezolizumab. Other efficacy objectives will include evaluation of OS, OS rate at 3 years, PFS, ORR, and DOR (additional efficacy assessments may occur on an exploratory basis). All antitumor response assessments will be based on RECIST v1.1 and modified RECIST.

Exploratory objectives will include evaluation of the safety and efficacy of atezolizumab in patient subgroups differentiated by: presence or absence of CNS metastases at baseline; ECOG performance status; histological subtype; history of or current autoimmune disease; and prior anticancer treatment. Other exploratory and PRO outcomes will include objective response rate and progression-free survival (PFS2) following start of new anticancer therapy, HR QoL as measured on the EORTC LQ-LC13, health utility score as measured on the EQ-5D-5L instrument, and expression of PD-L1 protein and cancer-related genes in tumor samples obtained before treatment. Finally, exploratory biomarkers may be assessed in tissue to assist in the potential development of new diagnostic assays and to assess biomarkers in terms of prognosis, response/resistance and safety.

Following discontinuation of study treatment, safety assessments will be conducted for 30 days after the last study drug administration or until initiation of other anti-cancer therapy (whichever occurs

first). Thereafter, follow-up information on disease progression (unless this has already occurred), anti-cancer therapy and survival will be collected via telephone contact, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, end of study (30 months after last patient in), patient withdrawal or study termination by the Sponsor, whichever occurs first.

In those patients for whom tumor assessments are performed as part of local clinical practice and are available for report after PD or atezolizumab treatment discontinuation, overall response rate (ORR) and progression-free survival (PFS) will be assessed from the first date of the new anticancer therapy to the end of the study. These data will be used in an exploratory fashion to assess whether prior atezolizumab treatment positively influences response to subsequent anticancer therapies.

An Independent Data Monitoring Committee (iDMC) will be established to review all AEs, irAEs, SAEs, AESIs and other cumulative safety data.

A Schedule of Assessments for this study is provided in Appendix 1.

Number of Patients

This study will enroll approximately 600 patients with Stage IIIb or Stage IV NSCLC who have progressed following standard systemic chemotherapy (including if given in combination with anti-PD-1 therapy or after anti-PD-1 as monotherapy). Patients with a previously detected sensitizing EGFR mutation or ALK fusion oncogene must have received targeted therapy followed by one line of standard systemic chemotherapy prior to receiving atezolizumab. Overall, patients should not have received more than two lines of standard systemic chemotherapy. Patients will also be eligible if they discontinued first-line or second-line therapy due to intolerance. The recruitment of 600 patients is expected to take place over approximately 18 months. Patients who discontinue the study prior to study treatment initiation will not be replaced.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Age ≥ 18 years
3. Able to comply with the study protocol, in the investigator's judgment
4. Histologically or cytologically documented Stage IIIb or Stage IV NSCLC that has progressed following standard systemic chemotherapy (including if given in combination with anti-PD-1 therapy, after anti-PD-1 as monotherapy, or after TKI therapy). Patients with a previously detected sensitizing EGFR mutation or ALK fusion oncogene must have received targeted therapy (TKI), followed by at least one line of standard systemic chemotherapy, prior to receiving atezolizumab. Overall, patients should not have received more than two lines of standard systemic chemotherapy. Patients who have discontinued first-line or second-line therapy due to intolerance are also eligible
   - Staging must be according to the UICC/AJCC system, 7th edition (Detterbeck et al. 2009)
   - Pathological characterization may be conducted on tumor specimens from earlier stage disease, but the tumor samples must be sufficient to distinguish squamous or non-squamous histology
   - Chemotherapy regimens will be counted based on interval disease progression, and not on the number of agents or the number of switches in agents (e.g., a first-line or second-line therapy that consists of several cycles of a platinum doublet and subsequent maintenance therapy that introduces or switches to a new chemotherapy agent without interval disease progression will all be considered one chemotherapy regimen)
   - Patients with a previously-detected sensitizing EGFR mutation must have experienced disease progression (during or after treatment) on an EGFR TKI (erlotinib, gefitinib, osimertinib, etc.)
   - Patients with a previously detected ALK fusion oncogene must have experienced disease progression (during or after treatment) with crizotinib, alectinib, or another ALK inhibitor
   - Prior radiation therapy is allowed, provided that the patient has recovered from any toxic effects thereof. Combined radiation/chemotherapy treatment constitutes a single regimen
   - Combined radiation/chemotherapy treatment (chemoradiation) counts as one prior chemotherapy regimen if < 6 months have elapsed between the last dose and the date of recurrence

- Adjuvant/neoadjuvant chemotherapy is not counted as a line of treatment
- Debulking surgery and anticancer agents used for pleurodesis are not counted as lines of therapy

5. The last dose of prior systemic anticancer therapy must have been administered ≥ 21 days prior to study treatment initiation
6. The last dose of prior anti-PD-1 therapy must have been administered
   - Nivolumab must have been discontinued ≥ 14 days and pembrolizumab ≥ 21 days prior to study treatment initiation, providing that these treatments were not administered in a clinical trial setting
7. Measurable disease, as defined by Response Evaluation Criteria for Solid Tumors, Version 1.1 (RECIST v1.1)
8. Patients with asymptomatic CNS metastases (treated or untreated), as determined by CT or MRI evaluation during screening and prior radiographic evaluation, are eligible
9. ECOG performance status 0, 1, or 2 [Appendix 7]
10. Life expectancy ≥ 12 weeks
11. Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 2 weeks prior to the first study treatment:
    - Absolute neutrophil count ≥ 1500 cells/μL (without granulocyte colony-stimulating factor support within 2 weeks prior to the first study treatment)
    - White blood cell count > 2500/μL
    - Lymphocyte count ≥ 500/μL
    - Platelet count ≥ 100,000/μL (without transfusion within 2 weeks prior to the first study treatment)
    - Hemoglobin ≥ 9.0 g/dL (patients may be transfused or receive erythropoietic treatment to meet this criterion)
    - Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase ≤ 2.5 times the upper limit of normal (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

    - Serum bilirubin ≤ 1.5 ×ULN. Patients with known Gilbert's Syndrome who have serum bilirubin level ≤ 3 × ULN may be enrolled.
    - Calculated creatinine clearance ≥ 15 mL/min (Cockcroft-Gault formula)
    - International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 ×ULN. This applies only to patients who are not receiving therapeutic anticoagulation agents
    - Patients receiving therapeutic anticoagulation agents must be on a stable dose
    - HIV-positive patients are allowed, so long as they are on stable anti-retroviral therapy, have a CD4 count ≥ 200 cells/μL, and have an undetectable viral load at the time of screening
12. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year 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, 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 acceptable methods of contraception

13. Patients must have recovered (i.e., improvement to Grade 1 or better) from all acute toxicities from previous therapy, excluding alopecia and toxicities related to prior anti-PD-1-therapy

Exclusion Criteria

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

1. Symptomatic CNS metastases
2. 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 study treatment initiation
3. Leptomeningeal disease
4. Uncontrolled pericardial effusion or ascites requiring recurrent drainage procedures
5. Pregnant or lactating, or intending to become pregnant during the study
   - Women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non-drug-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 2 weeks prior to initiation of study drug
6. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)
7. Significant cardiovascular disease, such as New York Heart Association cardiac disease ≥ Class III, myocardial infarction within 3 months, unstable arrhythmias, or unstable angina
   - Patients with known coronary artery disease or left ventricular ejection fraction < 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
8. Significant renal disorder requiring dialysis or indication for renal transplant
9. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days prior to study treatment initiation
10. Major surgical procedure within 4 weeks prior to study treatment initiation or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis
11. Inability to understand the local language(s) for which the EORTC QLQ-LC13 and EuroQol EQ-5D-5L questionnaires are available
12. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
13. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
14. History of autoimmune disease (Appendix 5) are allowed if controlled and on stable treatment (i.e., same treatment, same dose) for the last 12 weeks, with the exception of:
   - Patients taking concurrent abatacept or belatacept treatment, unless therapy has been withdrawn for > 8 weeks
   - Patients with a history of serious or life threatening immune-related events
   - No more than 1 concomitant autoimmune disease at the time of study entry is allowed unless one of them is:

     Autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone

     Controlled Type I diabetes mellitus on a stable dose of insulin regimen

     A medical history of such entities as atopic disease or childhood arthralgias, where the clinical suspicion of autoimmune disease is low. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis)
15. Prior allogeneic stem cell or solid organ transplantation
16. History of idiopathic pulmonary fibrosis, including pneumonitis, drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan

- History of radiation pneumonitis in the radiation field (fibrosis) is permitted

17. Active tuberculosis
    - In patients who have a potentially high likelihood of latent tuberculosis (e.g., recent contact with an infectious carrier, residence in a locale with high TB burden), absence of *Mycobacterium tuberculosis* infection must be confirmed before enrollment according to local practice standards

18. Administration of a live, attenuated vaccine within 4 weeks prior to study treatment initiation
    - Influenza vaccination should be given during influenza season only (e.g., approximately October to March in the Northern Hemisphere).
    - Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to study treatment initiation or at any time during the study

19. Prior treatment with CD137 agonists or immune checkpoint blockade therapies other than anti-PD-1 therapy, including anti−PD-L1 therapeutic antibodies
20. Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to initiation of study treatment
    - Prior cancer vaccines and cellular immunotherapy are permitted

21. Specifically for patients without autoimmune disease: treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor [TNF] agents) within 2 weeks prior to study treatment initiation, or anticipated requirement for systemic immunosuppressive medications during the trial
    - For patients with CNS metastases, use of prednisone at a stable dose (or dose equivalent) of ≤ 20 mg/day is acceptable
    - 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 and topical steroids for cutaneous diseases are allowed

End of Study and Length of Study

The end of study and final analysis will occur when all enrolled patients have either died, withdrawn consent, are lost to follow up, or have been followed for 30 months since the last study patient is enrolled, whichever occurs first.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4 years.

The primary analysis will occur approximately 6 months after the last patient has been enrolled.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product (IMP) for this study is atezolizumab.

The dose of atezolizumab in this study will be 1200 mg (equivalent to an average body weight-based dose of 15 mg/kg) administered by intravenous infusion every 3 weeks (21 [± 3] days).

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. For detailed information on drug preparation, storage and administration, refer to the Atezolizumab Investigator's Brochure.

The initial dose of atezolizumab will be administered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated AEs, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before, during (every 15 [± 5] minutes) if clinically indicated, and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated, and 30 minutes (± 10 minutes) after the infusion if clinically indicated or patient experienced symptoms during previous infusions.

Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The management of infusion-related reactions will be according to severity as follows:

- In the event that a patient experiences a mild (Grade 1) National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) infusion-related event, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate
- In the event that a patient experiences a moderate infusion-related event (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the patient should have his or her infusion immediately interrupted and should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the infusion-related event
- For severe or life-threatening infusion-related events (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening infusion-related events will not receive further infusion and will be further managed as clinically indicated until the event resolves

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Please refer to the Pharmacy Manual for detailed instructions on drug preparation, storage and administration.

Non-Investigational Medicinal Products

Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine and/or famotidine or another H2 receptor antagonist, as per standard practice (equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists.
- Systemic corticosteroids and tumor necrosis factor−α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab, but may be administered at the discretion of the treating physician after consultation with the Medical Monitor (see Exclusion Criterion 21 and Prohibited Therapy. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician after consultation with the Medical Monitor. The use of inhaled corticosteroids for COPD and mineralocorticoids (e.g., fludrocortisone) and low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as an appetite stimulant is acceptable while the patient is enrolled in the study.
- Colony-stimulating factors, such as granulocyte colony-stimulating factor and erythropoietin, should only be used according to manufacturers' labels and the ASCO and ASCO/ASH guidelines.
- Influenza vaccination should be given during influenza season only (approximately October to March in the Northern Hemisphere). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to study treatment initiation or at any time during the study.
- Patients who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy should continue their use.

All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

Prohibited Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, unless otherwise specified, is prohibited. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, or investigational agents (except for maintenance therapies outlined in Section 4.1.1 and 4.1.2 of the protocol)
  - After completion of Cycle 1, certain forms of radiotherapy may be considered for palliation if patients are deriving benefit (e.g., treatment of known bone metastases)
  - Patients experiencing a mixed response requiring local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) for control of three or fewer lesions may still be eligible to continue study treatment. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression. Such cases must be discussed with and approved by the Sponsor

- Traditional herbal medicines are not recommended because the ingredients of many herbal medicines are not fully studied, and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity
- Patients should not receive abatacept or belatacept treatment (those who were receiving it must stop it > 8 weeks before study entry)

Patients are not allowed to receive immunostimulatory agents, including but not limited to interferon (IFN)-α, IFN-γ, or IL-2, during the entire study. These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.

With the exception of autoimmune disease patients, patients should not receive immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of atezolizumab.

Systemic corticosteroids and anti−TNF-α agents may attenuate potential beneficial immunologic effects of treatment with atezolizumab, but may be administered at the discretion of the treating physician after consultation with the Medical Monitor. If feasible, alternatives to these agents should be considered.

Patients with CNS metastases are allowed to receive anticonvulsants and steroid treatments if the dose of prednisone is stable and ≤ 20 mg/day (or equivalent).

In addition, all patients (including those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.

The above list of medications is not necessarily comprehensive. The investigator should consult the prescribing information for any concomitant medication and contact the Medical Monitor if questions arise regarding medications not listed above.

Statistical Methods

Primary Analysis

All safety analyses will be run on the Safety Analysis set, defined as all enrolled patients who had at least one administration of atezolizumab.

The incidence of SAEs related to atezolizumab and the incidence of irAEs related to atezolizumab will be summarized by incidence rates and 95% Pearson-Clopper confidence intervals.

Determination of Sample Size

No formal sample size calculation linked to hypothesis testing is done for this descriptive study. The sample size considerations are based upon estimation precision for the incidence of AEs. With 600 patients, the following 95% CIs (Table 2) could be provided for the different incidences of AEs, which is deemed appropriate for the purposes of the study.

Table 2. Adverse Event Incidence and Corresponding 95% Confidence Intervals

Sample Size	AE Incidence	95% Clopper-Pearson Exact CI
600 patients	1%	1% [0.2% ; 1.8%]
	2%	2% [0.9% ; 3.1%]
	3%	3% [1.6% ; 4.4%]
	5%	5% [3.3% ; 6.7%]
	10%	10% [7.6% ; 12.4%]

CI, confidence interval.

Interim Analyses

This study will have no formal interim analyses. However, regular safety reviews of data will be performed by an Independent Data Monitoring Committee (iDMC). The frequency of these reviews will be stated in the iDMC charter.

In addition, to adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim analysis for reporting and publication of safety and efficacy results.

Appendix 2
Schedule of Assessments

	Screening Period		Treatment Period	Treatment Discontinuation	Follow-Up Period
	Day –28 to Day –1	Day –14 to –1	Day 1 (± 5 days) of each 3-week treatment cycle	≤ 30 days from last dose or at initiation of new anti-cancer therapy (whichever occurs first)	
Informed consent [a]	x				
Review of eligibility criteria	x				
Medical history and demographics [b]	x				
Weight	x		x	x	
Height	x				
Complete physical examination [c]	x			x	
Limited physical examination [c, d]			x [d]		
ECOG Performance Status [e]	x		x [d]	x	
Vital signs [f]	x		x	x	
12-lead ECG [g]	x		as clinically indicated		
HIV, HBV, HCV serology [h]	x		as clinically indicated		
Hematology [i]		x	x [d]	x	
Coagulation (aPTT, INR)		x		x	
Thyroid function testing [j]		x	Cycle 2, Day 1, then every other cycle		
Serum chemistry [k]		x	x [d]	x	
Urinalysis [l]		x	x [d]	x	
Pregnancy test [m]		x	Every 3 cycles		

	Screening Period		Treatment Period	Treatment Discontinuation	Follow-Up Period
	Day –28 to Day –1	Day –14 to –1	Day 1 (± 5 days) of each 3-week treatment cycle	≤ 30 days from last dose or at initiation of new anti-cancer therapy (whichever occurs first)	
Tumor assessment [n]	x [o]		Every 6 weeks for 48 weeks, thereafter every 9 weeks until PD (regardless of atezolizumab discontinuation) or until loss of clinical benefit for patients treated beyond progression [p]		
EGFR/ALK testing [q]	x				
Submission of pre-treatment tumor tissue (biomarker) [r, s]		x [u]			
Plasma for RBR (optional) [t]		x [u]		PD	
EORTC QLQ-LC13 & EQ-5D-5L [v]			Day 1 of first 3 cycles, then with tumor assessments		
Concomitant medications [w]	x		x	x	
Adverse events [x]	x		x	x	x
Study drug infusion			x		
Survival and new anti-cancer therapy [y]				x	x

Abbreviations: aPTT: activated partial thromboplastin time; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer; INR: international normalized ratio; PD: progressive disease; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events

Note: Unless otherwise indicated, assessments scheduled on the study treatment days should be performed prior to initiation of study treatment infusion.

a. Written informed consent is required for performing any study-specific tests or procedures. 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. Medical history includes surgical and cancer histories. Cancer history includes stage, date of diagnosis, prior anti-cancer treatment, EGFR/ALK status and, if available, PD-L1 status. Reproductive status and smoking history should also be captured. Demographic information includes age, sex, and self-reported race/ethnicity.

c. A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded 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 Adverse Event eCRF.

d. Limited physical examination, ECOG performance status (Appendix 7), and local laboratory assessments may be obtained ≤ 96 hours before Day 1 of each cycle. It is not necessary to repeat these assessments again prior to Cycle 1 if they have been conducted for screening within this time period.

e. See Appendix 7.

f. Vital signs include respiratory rate, heart rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Treatment cycle Day 1 vital sign assessments will be done prior to study treatment.

g. ECG recordings will be obtained during screening and when clinically indicated. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG recording.

h. Refer to Section 4.5.7. HIV testing is not required in the absence of clinical symptoms and signs suggestive of HIV infection; patients with a positive serological test may be enrolled so long as they are stable on anti-retroviral therapy, have a CD4 count ≥ 200 cells/μL, and have an undetectable viral load at the time of screening.

i. Hematology consists of CBC (including RBC count), hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. A manual differential may be done if clinically indicated.

j. Includes thyroid-stimulating hormone (TSH), free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), free thyroxine (also known as T4).

k. Serum chemistry includes glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.

l. Urinalysis includes specific gravity, pH, glucose, protein, ketones, and blood.

m. 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 performed every 3 treatment cycles can be conducted with serum or urine.

n. The same radiographic procedure should be used throughout the study for each patient. A CT (with contrast) or MRI of the head must be included in screening tumor assessments for patients with known or suspected CNS disease. Results must be reviewed by the investigator before dosing at the next cycle. Patients who continue treatment beyond radiographic disease progression assessed per RECIST v1.1 should be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 6 weeks, and will be assessed by modified RECIST criteria (see Appendix 3) until treatment discontinuation. If the scan frequency is every 9 weeks, a follow-up scan is recommended at 9 weeks or earlier if clinically indicated. Investigators may perform additional scans or more frequent assessments if clinically indicated.

o. Ideally within 14 days of the start of study treatment.
p. Patients will undergo tumor assessments at baseline, every 6 weeks ± 5 days for the first 48 weeks following treatment initiation, and every 9 weeks thereafter 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 Section 3.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new anti-cancer therapy.
q. For sites where EGFR/ALK testing is not routinely performed at local laboratories, a minimum of 7 consecutively cut slides from a most recent FFPE tumor tissue block must be submitted for EGFR/ALK testing for all patients with non-squamous NSCLC. Testing is not required for patients who have squamous NSCLC. EGFR mutation and ALK testing should be considered for patients with squamous NSCLC who are never-smokers, have mixed histology or small biopsy specimen.
r. If available, pre-treatment FFPE tumor tissue (most recent sample) for PD-L1 testing and exploratory biomarkers. Most recent archival sample or a sample obtained during screening should be submitted if available (1 FFPE tissue block or 5–10 slides).
s. From patients who received anti-PD-1 therapy, sites are highly encouraged to provide archival FFPE tissue (prior anti-PD1 therapy) and an FFPE tissue biopsy obtained during screening (archival and screening tissue sample).
t. Ten milliliters (10 mL) whole blood for plasma. Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.
u. Only to be shipped if the patient is eligible for enrollment.
v. See Appendix 4.
w. Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.
x. After informed consent has been obtained, but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all SAEs and AESIs, 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 AEs, 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 this period, the investigator should report any SAEs or AESIs believed to be related to prior study drug treatment. The investigator should follow each AE 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 SAEs considered to be related to study drug or study-related procedures until a final outcome can be reported.
y. Survival and new anti-cancer therapy follow-up information will be collected via telephone contact, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, end of study (30 months after the last patient in), patient withdrawal or study termination by the Sponsor, whichever occurs first. In those patients for whom tumor assessments are performed and available for report after PD or treatment discontinuation, best overall response (BOR) will be assessed from the first date of the new anticancer therapy to the end of the study per RECIST v1.1. These data will be used in an exploratory fashion to assess whether prior atezolizumab treatment positively influences response to subsequent anticancer therapies.

Appendix 3
EORTC QLQ-LC13: Scoring Rules

The lung cancer module (EORTC QLQ-LC13) is meant for use among a wide range of lung cancer patients varying in disease stage and treatment modality (Bergman et al., 1994). The module comprises 13 questions and is designed for use among patients receiving treatment with chemotherapy and/or radiotherapy. The QLQ-LC13 includes questions assessing lung cancer-associated symptoms (cough, hemoptysis, dyspnea and site specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication.

Scoring of QLQ-LC13

The lung cancer module incorporates one multi-item scale to assess dyspnea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. Details of multi-item scales information are in **Error! Reference source not found.**.

A score for a specific scale will be calculated only if all items of the scale are non-missing; otherwise, it will be set as missing.

Table 33: Scoring the QLQ-LC13

Scale name	Scale	Number of items	Item range*	QLQ-LC13 Item numbers
Dyspnoea	LCDY	3	3	33,34,35
Coughing	LCCO	1	3	31
Haemoptysis	LCHA	1	3	32
Sore mouth	LCSM	1	3	36
Dysphagia	LCDS	1	3	37
Peripheral neuropathy	LCPN	1	3	38
Alopecia	LCHR	1	3	39
Pain in chest	LCPC	1	3	40
Pain in arm or shoulder	LCPA	1	3	41
Pain in other parts	LCPO	1	3	42
Dyspnoea at Resting	LCDYR	1	3	33
Dyspnoea at Walking	LCDYW	1	3	34
Dyspnoea at Climbing Stairs	LCDYC	1	3	35

* "Item range" is the difference between the possible maximum and the minimum response to individual items.