Official Title: A Phase III, Double-Blinded, Multicenter, Randomized Study Evaluating the Efficacy and Safety of Neoadjuvant Treatment with Atezolizumab or Placebo in Combination with Platinum-Based Chemotherapy in Patients with Resectable Stage II, IIIa, Or Select IIIb Non-Small Cell Lung Cancer

NCT Number: NCT03456063

Document Date: Statistical Analysis Plan Version 2: 09-May-2024

STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE III, DOUBLE-BLINDED, MULTICENTER, RANDOMIZED STUDY EVALUATING THE EFFICACY AND SAFETY OF NEOADJUVANT TREATMENT WITH ATEZOLIZUMAB OR PLACEBO IN COMBINATION WITH PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH RESECTABLE STAGE II, IIIA, OR SELECT IIIB NON-SMALL CELL LUNG CANCER**

PROTOCOL NUMBER:	GO40241
STUDY DRUG:	Atezolizumab
VERSION NUMBER:	2
IND NUMBER:	117296
EUDRACT NUMBER:	2017-002857-12
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted], Ph.D.
DATE FINAL:	13 July 2022
DATE AMENDED:	See electronic date stamp on the last page of this document

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

CONFIDENTIAL

This is an F. Hoffmann-La Roche Ltd document that contains confidential information. Nothing herein is to be disclosed without written consent from F. Hoffmann-La Roche Ltd.

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Key changes to the Statistical Analysis Plan, along with the rationale(s) for each change, are summarized below.

Due to an unexpected slowing down of the event-free survival (EFS) event rate, the [redacted]

Section	Description of Change	Rationale for Change
2.4	[redacted]	Protocol amendment
2.4	[redacted]	Protocol amendment

Additional minor changes have been made throughout to improve clarity and consistency.

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE 2

1. BACKGROUND 8

2. STUDY DESIGN 8

2.1 Protocol Synopsis 13

2.1.1 Primary Efficacy Outcome Measures 13

2.2 Outcome Measures 13

2.2.1 Secondary Efficacy Outcome Measures 13

2.2.2 Exploratory Outcome Measures 14

2.2.3 Pharmacokinetic Outcome Measures 14

2.2.4 Safety Outcome Measures 14

2.2.5 Immunogenicity Outcome Measures 15

2.3 Determination of Sample Size 15

2.4 Analysis Timing 17

[redacted] 17

3. STUDY CONDUCT 19

3.1 Randomization 19

3.2 Independent Review Facility 19

3.3 Data Monitoring 20

4. STATISTICAL METHODS 20

4.1 Analysis Populations 20

4.1.1 Efficacy Analysis Populations 20

4.1.2 Safety Population 21

4.1.3 Surgical Safety Population 21

4.1.4 Pharmacokinetic-Evaluable Population 21

4.1.5 ADA-Evaluable Population 21

4.2 Analysis of Study Conduct 21

4.3 Analysis of Treatment Group Comparability 21

4.4 Efficacy Analysis 22

4.4.1 Primary Efficacy Endpoint 22

4.4.1.1 Independent Review Facility-Assessed Event-Free Survival 22
4.4.2 Secondary Efficacy Endpoints 23
4.4.2.1 IRF-Assessed Pathological Complete Response Rate and Major Pathological Response Rate 23
4.4.2.2 Overall Survival 23
4.4.2.3 Investigator-Assessed Event Free Survival 24
4.4.2.4 Investigator-Assessed Objective Response Rate 24
4.4.2.5 Investigator-Assessed Pathological Complete Response Rate and Major Pathological Response Rate 24
4.4.2.6 2-year and 3-year Overall Survival, 2-year and 3-year Independent Review Facility-Assessed, and Investigator-Assessed Event Free Survival 25
4.4.2.7 Investigator-Assessed Disease-Free Survival 25
4.4.2.8 Patient-Reported Outcomes 25
4.4.2.8.1 Scoring 25
4.4.2.8.2 Visit Score Summary and Change from Baseline 25
4.4.3 Exploratory Endpoints 26
4.4.3.1 Independent Review Facility-Assessed Event-Free Survival by PD-L1 Expression 26
4.4.3.2 Subgroup Analysis 26
4.4.3.3 Exploratory Analyses of Biomarkers 26
4.4.3.4 Patient Reported Outcomes 26
4.4.3.4.1 Visit Score Summary and Change from Baseline 26
4.4.3.4.2 Time to Confirmed Deterioration (TTCD) Analysis 26
4.4.3.4.3 EQ-5D-5L Health Status Data 27
4.4.3.4.4 Additional Patient-Reported Outcome Analysis 27
4.4.3.5 Additional Exploratory Pathological Response Assessments 28
4.4.3.6 NSCLC-related Death 28
4.4.4 Sensitivity Analyses 28
4.4.4.1 Missing Tumor and Disease Assessments 28
4.4.4.2 Including Clinical Progression Precluding Surgery in the EFS Analysis 29
4.4.4.3 Non-Protocol-Specified Anti-Cancer Therapy 29

4.5 Pharmacokinetic Analysis 29
4.6 Safety Analyses 30
4.6.1 Exposure of Study Medication 30
4.6.2 Adverse Events 30
4.6.3 Laboratory Data 30
4.6.4 Vital Signs 31
4.6.5 Anti-Drug Antibody 31
4.6.6 Surgical Outcomes 31
4.7 Missing Data 31
5. REFERENCES 32

LIST OF TABLES

[redacted] .. 18
[redacted] .. 19

LIST OF FIGURES

Figure 1 Study Schema for IMpower030 10
[redacted] 16

LIST OF APPENDICES

Appendix 1 Protocol Synopsis 33
Appendix 2 Schedule of Activities 37
Appendix 3 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Blood Samples 50

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
BSC	best supportive care
C30	Core 30
CI	confidence interval
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DFS	disease-free survival
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	European Quality of Life, 5-dimension, 5-level version
GHS	global health status
HR	hazard ratio
HRQoL	health-related quality of life
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
IRF	Independent Review Facility
ITT	intent to treat
IxRS	interactive voice/web response system
KM	Kaplan-Meier
LC13	lung cancer module
MPR	major pathological response
NCI	National Cancer Institute
NPT	non-protocol-specified anti-cancer therapy
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival

pCR	pathological complete response
PD-L1	programmed death-ligand 1
PET	positron emission tomography
[redacted]	
PK	pharmacokinetic
PORT	post-operative radiotherapy
PRO	patient-reported outcome
QLQ	Quality-of-Life Questionnaire
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse events
SAP	Statistical Analysis Plan
TC	tumor cell
TEAE	treatment-emergent adverse event
TTCD	time to confirmed deterioration
VAS	visual analogue scale
WT	wild-type

1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and the statistical methods for Study GO40241 (IMpower030), "A Phase III, Double-Blinded, Multicenter, Randomized Study Evaluating the Efficacy and Safety of Neoadjuvant Treatment with Atezolizumab or Placebo in Combination with Platinum-Based Chemotherapy in Patients with Resectable Stage II, IIIA, or Select IIIB non-small cell lung cancer (NSCLC)." The background for the study can be found in the study protocol.

The analyses described in this SAP will supersede those specified in the study protocol for the purposes of a regulatory filing.

2. STUDY DESIGN

IMpower030 is a global Phase III multicenter, double-blinded, randomized study designed to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy versus placebo plus platinum-based chemotherapy followed by adjuvant/postoperative atezolizumab or best supportive care in patients with histologically or cytologically confirmed resectable Stage II, IIIA, or select IIIB (T3N2 only) NSCLC. The primary endpoint for the study is independent review facility (IRF)-assessed event-free survival (EFS).

Enrollment into the study requires patients to be eligible for R0 resection with curative intent at screening as well as meet all eligibility criteria. Male and female patients aged ≥18 years with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 with a pathologically documented Stage II, IIIA, or select IIIB (T3N2 only) (TNM Version 8) NSCLC of squamous or non-squamous histology are potentially eligible. Patients with NSCLC with an activating mutation in the epidermal growth factor receptor (EGFR) or with an anaplastic lymphoma kinase (ALK) fusion oncogene will be excluded from study entry. A full list of inclusion and exclusion criteria can be found in Appendix 1.

Eligible patients will be randomized in a 1:1 ratio to one of the following treatment arms:

- **Arm A**: Atezolizumab + platinum-based chemotherapy for 4 cycles, followed by surgical resection and then adjuvant/postoperative atezolizumab for 16 cycles
- **Arm B**: Placebo + platinum-based chemotherapy for 4 cycles, followed by surgical resection and then postoperative best supportive care (BSC) and observation follow-up (Note: BSC is defined as symptomatic management and supportive measures for the patients' recovery from neoadjuvant therapy and surgery based on institutional standards and/or investigator judgement. This may include, but is not limited to, antibiotics, analgesics, fluids, physical therapy, counseling, diet, etc. Anti-cancer therapy is not allowed. For questions and clarifications regarding allowable BSC measures, please contact the Medical Monitor).

Selection of the platinum-based neoadjuvant chemotherapy regimen will be at the discretion of the investigator (based on histology subtypes) and will be determined and documented at the time of randomization. The following platinum-based chemotherapy options are permitted for this study:

For Non-Squamous NSCLC

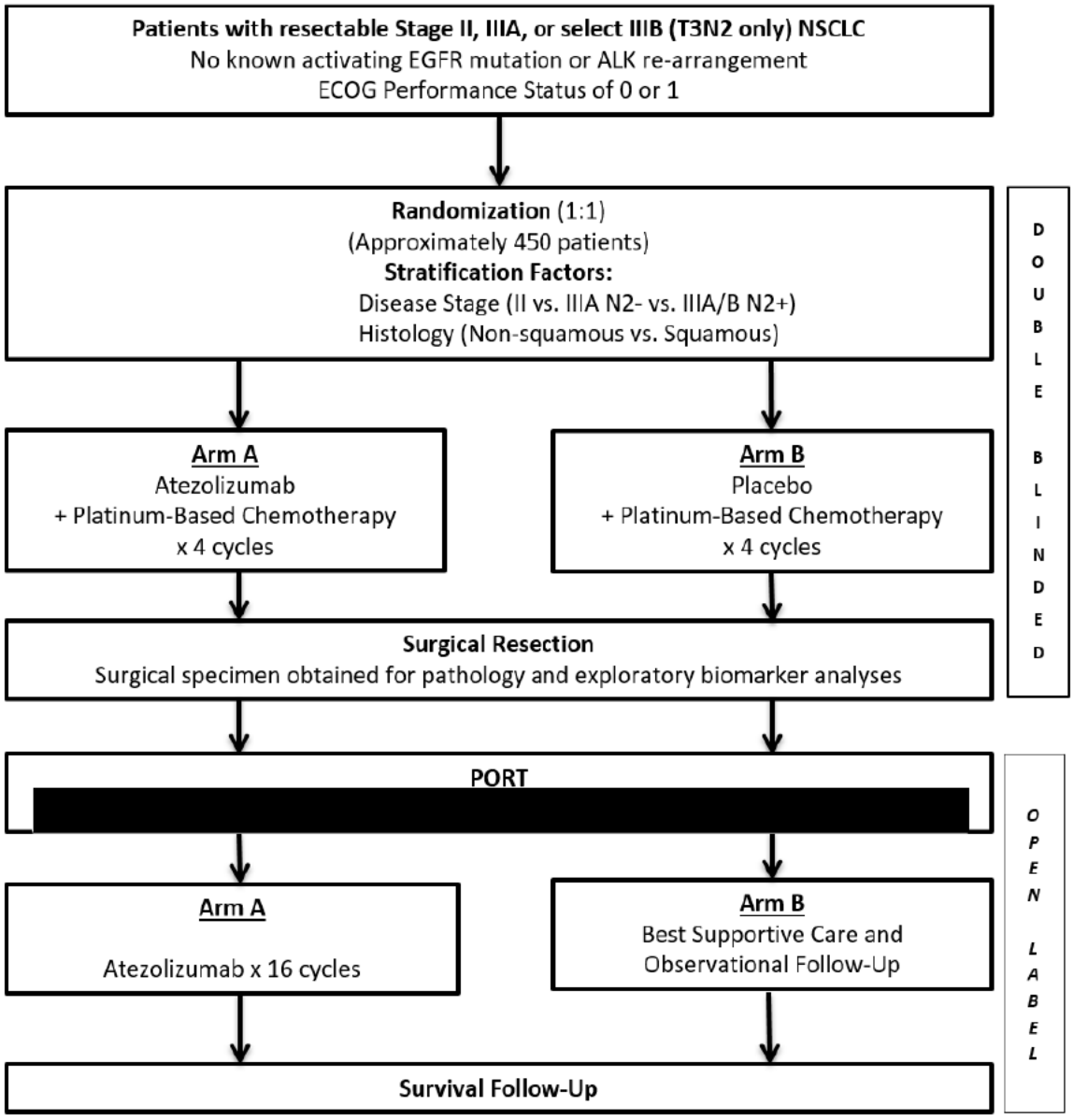
- Cisplatin + Pemetrexed
- Carboplatin + Pemetrexed
- Carboplatin + Nab-Paclitaxel

For Squamous NSCLC

- Cisplatin + Gemcitabine
- Carboplatin + Nab-Paclitaxel

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 2.

Figure 1 Study Schema for IMpower030



ALK=anaplastic lymphoma kinase; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor; NSCLC=non-small cell lung cancer; PORT=post-operative radiation therapy.

Upon completion of neoadjuvant therapy, patients will undergo surgical resection of their tumor. Surgical specimens will be assessed for pathological response (major pathological response [MPR] and pathological complete response [pCR]) by an independent central pathology laboratory as well as by the investigator site pathology laboratory. In addition, exploratory biomarker analysis of surgical specimens (primary tumor tissue and dissected lymph nodes) will be performed.

Prior to surgery, the attending surgeon and medical oncologist will reassess the surgical plan for the patient. The pre-surgery visit should occur [redacted] after the last dose of neoadjuvant treatment [redacted] The surgical procedure should be performed [redacted] after the pre-surgery visit as best as possible per clinical judgement of both the attending surgeon and medical oncologist. Any anticipated delay beyond this time window should be discussed with the Medical Monitor.

Patients who are found to have disease progression at scheduled tumor assessments (after Cycle [redacted] and Cycle [redacted] or at any time during neoadjuvant treatment and are still deemed resectable and non-metastatic will proceed to receive surgery if amenable and will remain eligible for all on-study treatment and evaluations.

Patients who discontinue neoadjuvant treatment early because of disease progression and do not proceed to surgery will be discontinued from further in-clinic study procedures and will proceed to receive other treatment as determined by the investigator. These patients will still remain in the study for survival follow-up.

For patients who are responding to neoadjuvant therapy but cannot proceed to surgery (e.g., because of pulmonary embolism or myocardial infarction), the Medical Monitor must be informed. For these patients, if they are assigned to Arm A, atezolizumab monotherapy will be offered, with continued follow-up as per protocol. Patients randomized to Arm B will continue to be monitored and followed up as per protocol.

After surgery and local pathology response assessment, the adjuvant phase of this study will be open-label. The medical oncologist and/or attending surgeon will meet with the patient 14–21 days after surgery to assess their recovery and inform the patient of their post-surgery treatment plan for the study. [redacted] Patients randomized to Arm A will receive atezolizumab as post-operative adjuvant therapy and patients randomized to Arm B will receive BSC and observation follow-up visits. If PORT is not needed, Arm A patients receiving adjuvant atezolizumab should receive the first dose of atezolizumab (Cycle 5) within 60 days after surgery; initial dosing beyond 60 days should be discussed with the Medical Monitor. If PORT is needed, Arm A patients should receive adjuvant atezolizumab [redacted] For Arm B patients that do not require PORT, observation follow-up visits should occur within 60 days after surgery. Patients will continue to receive adjuvant atezolizumab (Arm A) or undergo scheduled in-clinic observation follow-up visits (Arm B) until one of the following occurs: administration of 16 cycles of atezolizumab as adjuvant therapy (Arm A), completion of all scheduled observation follow-up assessment visits

(Arm B), unacceptable toxicity (Arm A only), disease recurrence, death, or patient and/or physician decision to discontinue study treatment or observation follow-up visits.

All patients will undergo scheduled tumor assessment scans of the chest and abdomen by both computed tomography (CT) and positron emission tomography (PET) at screening and then by CT after Cycles [redacted] and [redacted] of neoadjuvant treatment. [redacted]

If a disease follow-up assessment shows evidence of disease recurrence, it should be confirmed pathologically and/or by unequivocal radiographic evidence from the scan. If a scan shows equivocal findings (e.g., mediastinal nodes measuring < 1.5 cm in the short axis, lung parenchymal lesions or visceral lesions measuring < 1 cm in the longest diameter), a biopsy should be performed. If a biopsy is not feasible or safe, then confirmatory scans must be performed again within 4 to 8 weeks. If a biopsy for disease recurrence confirmation is performed, any leftover biopsy tissue is strongly encouraged to be submitted for exploratory biomarker research (optional consent required for exploratory research). The biopsy should be performed prior to starting the next anti-cancer therapy. If the biopsy does not show evidence of disease recurrence (e.g., non-malignant infiltrates), then the patient may continue with scheduled study treatment, assessments, and/or follow-up. In the absence of disease recurrence, disease follow-up assessments should continue until disease recurrence, withdrawal of consent, death, loss to follow-up, or study termination by the Sponsor, whichever occurs first.

Patients may undergo an optional tumor biopsy sample upon disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1 during the neoadjuvant treatment phase for exploratory biomarker research (optional consent required). These data may be used to explore whether the radiographic findings are consistent with the presence of tumor or for patients treated with atezolizumab if the appearance of recurrence was caused by tumor immune infiltration. In addition, these data may be analyzed to evaluate the association between changes in tumor tissue and clinical outcome and to understand further the potential mechanisms of resistance and recurrence to atezolizumab compared with such mechanisms after treatment with neoadjuvant chemotherapy alone. This exploratory biomarker evaluation will not be used for any treatment-related decisions.

Patients will complete patient-reported outcomes (PROs), specifically the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30) and lung cancer module (QLQ-LC13) to assess disease and/or treatment-related symptoms (e.g., dyspnea, pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, hemoptysis, functioning, and health-related quality of life [HRQoL]) at specified timepoints throughout the duration of the study

(neoadjuvant, adjuvant/monitoring, and long-term survival follow-up). Patients will also complete the European Quality of Life, 5-dimension, 5-level version (EQ-5D-5L) in its entirety, including the visual analogue scale (VAS) to document health status for pharmacoeconomic analyses.

Safety assessments will include the incidence, nature, and severity of adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs), immune-mediated adverse events, and laboratory abnormalities, graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Protocol-specified vital signs will be measured.

Patient samples, including archival and fresh tumor tissues as well as serum, plasma and whole blood, will be collected for future exploratory biomarker assessments.

All patients will undergo safety, tolerability, and exploratory assessments on Day 1 of each cycle in the blinded neoadjuvant treatment phase (both arms) and in the open-label adjuvant and observation follow-up phase (every cycle [i.e., every 3 weeks] for Arm A, and every 6 weeks for Arm B). After treatment or observation follow-up discontinuation, patient follow-up will be periodically performed for survival status, PROs, and any additional anti-cancer treatment.

An external independent Data Monitoring Committee (iDMC) will evaluate safety data, review the interim analysis of IRF-assessed EFS data, and assess study conduct during the study (see Section 3.3).

2.1 PROTOCOL SYNOPSIS

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

2.1.1 Primary Efficacy Outcome Measures

Independent Review Facility -assessed EFS, defined as the time from randomization to the first documented disease progression per RECIST v1.1 that precludes surgery, local or distant disease recurrence (including occurrence of new primary NSCLC), or death from any cause, whichever occurs first.

2.2 OUTCOME MEASURES

2.2.1 Secondary Efficacy Outcome Measures

- Overall survival (OS)
- Pathological complete response assessed by central pathology laboratory at the time of surgical resection
- Major pathological response, assessed by central pathology laboratory at the time of surgical resection

- Investigator-assessed EFS
- Investigator-assessed objective response according to RECIST v1.1
- Investigator-assessed MPR and investigator-assessed pCR at the time of surgical resection
- Two-year and 3-year OS, 2-year and 3-year IRF-assessed and investigator-assessed EFS for each treatment arm
- Investigator- quality of life assessed disease-free survival (DFS) during the adjuvant setting in patients completing R0 surgical resection
- Change from baseline in HRQoL score as assessed through use of the two-item global health status/ (GHS)/QoL subscale (Questions 29 and 30) of the EORTC QLQ-C30, at each assessment timepoint during the study through the completion of adjuvant treatment and observation follow up assessments

2.2.2 Exploratory Outcome Measures

- Independent Review Facility -assessed EFS by programmed death-ligand 1 (PD-L1) expression using the Ventana SP263 PD-L1 immunohistochemistry (IHC) assay (tumor cell [TC] $\geq$ 1%, and $\geq$ 50%)
- Subgroup analysis of pCR, MPR, EFS, DFS and OS
- Biomarker analysis exploring the association of biomarkers from tissue and blood samples (e.g., PD-L1, circulating tumor DNA [ctDNA], tumor mutational burden [TMB], and others) with study treatment response, efficacy (including pathological response), and/or adverse events
- Change from baseline of treatment or disease-related symptoms in the EORTC QLQ-C30 and QLQ-LC13 questionnaires
- Time to confirmed deterioration (TTCD) analysis in patient-reported lung cancer symptoms of cough, fatigue, and pain and in GHS/QoL and physical functioning as evaluated by prespecified items of the EORTC QLQ-C30 and QLQ-LC13 questionnaires
- Health status utility scores as evaluated by the EQ-5D-5L
- Additional exploratory pathological response assessments

2.2.3 Pharmacokinetic Outcome Measures

- Serum concentration of atezolizumab at specified timepoints (see Appendix 2).

2.2.4 Safety Outcome Measures

- Incidence, nature, and severity of adverse events, including serious adverse events and immune-mediated adverse events, with severity determined according to NCI CTCAE v5.0
- Changes from baseline in vital signs, physical findings, and targeted clinical laboratory results
- Surgical outcomes, such as surgical delays, surgery cancellations, surgery type, blood loss, fibrosis, intraoperative complications, and post-operative complications

2.2.5 Immunogenicity Outcome Measures

- Incidence of anti-drug antibody (ADA) response to atezolizumab and potential correlation with pharmacokinetic, safety, and efficacy parameters.

2.3 DETERMINATION OF SAMPLE SIZE

A total of approximately 450 patients will be randomized into this study.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

Assumptions for the Number of Events Required to Demonstrate Efficacy for IRF Assessed EFS in the stage IIB-IIIB-WT population:

- 1:1 randomization ratio
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Assumptions for the Number of Events Required to Demonstrate Efficacy for IRF Assessed EFS in the ITT-WT population:

- 1:1 randomization ratio
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

2.4 ANALYSIS TIMING

[redacted]

[redacted]

[redacted]







3. STUDY CONDUCT

3.1 RANDOMIZATION

For patients who are eligible for study randomization, the study site will obtain the patient's randomization number and treatment assignment from the interactive voice/web response system (IxRS).

Patients will be randomized in a 1:1 ratio to one of two treatment arms for the neoadjuvant treatment phase: Arm A (atezolizumab + platinum-based chemotherapy) or Arm B (placebo + platinum-based chemotherapy).

Randomization will be stratified by the following factors:

- Stage (II vs. IIIA N2− vs. IIIA/B N2+)
- Histology (non-squamous vs. squamous)

A permuted-block randomization is applied to ensure a balanced assignment to each treatment arm within levels of the stratification factors.

3.2 INDEPENDENT REVIEW FACILITY

An Independent Review Facility will be used to conduct an independent assessment of tumor response and progression of disease per RECIST v1.1 and local or distant

disease recurrence as assessed for all patients according to a prespecified IRF charter. This assessment will be used for analyses of IRF-assessed EFS.

Following surgical resection, resected specimens will be grossed and sectioned into slides at the local pathology laboratory per study pathology manual instructions for pathological response assessment of the primary tumor. After local pathology assessment, the same set of slides or recut slides from the same tissue block cassettes will be sent to a central pathology laboratory for the assessment of MPR and pCR as well as other pathological assessments according to Manual for Pathological Response Evaluation.

3.3 DATA MONITORING

An independent Data Monitoring Committee will evaluate safety data, review the interim analysis of IRF-assessed EFS data, and assess study conduct during the study. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC roles and responsibilities.

Unblinded safety data will be reviewed on a periodic basis. The first safety review will occur at approximately 6 months from the time of enrollment of the first patient or when approximately 22 patients have been randomized to the study, whichever occurs later. Subsequent safety review will occur approximately every 6 months during the study until the statistically significant IRF-assessed EFS analysis at the interim analysis by iDMC or final analysis of IRF-assessed EFS by the Sponsor, whichever occurs first.

The iDMC will be responsible for evaluating IRF-assessed EFS data at the time of the prespecified analysis. The efficacy analyses will be conducted in accordance with the methods that are specified in the SAP.

All summaries and analyses for the iDMC review will be prepared by an independent Data Coordinating Center (iDCC). After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC Charter. Final decisions will rest with the Sponsor.

Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards/Ethics Committees (IRBs/ECs). Details of the iDMC's conduct will be further described in the charter.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

4.1.1 Efficacy Analysis Populations

The randomized population or ITT population is defined as all randomized patients, regardless of receipt of the assigned treatment. ITT-WT population is defined as ITT

patients without a known EGFR activating mutation or a known ALK fusion oncogene, respectively. Stage IIB-IIIB-wild type (Stage IIB-IIIB-WT) population is defined as Stage IIB-IIIB patients in the ITT-WT population per American Joint Committee on Cancer (AJCC) v8.

4.1.2 Safety Population

The safety population will consist of all randomized patients who received at least one dose of study treatment. For safety analyses, patients will be grouped according to whether any amount of atezolizumab was received, including cases where atezolizumab was received in error.

4.1.3 Surgical Safety Population

The surgical safety population consists of the safety population that has undergone protocol-mandated surgery. For surgery outcome analyses, patients will be grouped according to whether any amount of atezolizumab was received, including where atezolizumab was received in error.

4.1.4 Pharmacokinetic-Evaluable Population

The pharmacokinetic-evaluable population (PEP) is defined as all randomized patients who received any amount of atezolizumab and have evaluable pharmacokinetic (PK) samples.

4.1.5 ADA-Evaluable Population

The ADA-evaluable population is defined as all randomized patients who received at least one dose of atezolizumab and who have at least one post-baseline ADA result.

4.2 ANALYSIS OF STUDY CONDUCT

Study enrollment and reasons for discontinuation from the study will be summarized by treatment arm for the ITT population. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will also be summarized by treatment arm for the ITT population. Study treatment administration and the reasons for study treatment discontinuation will be tabulated for the safety population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic variables such as age, sex, race/ethnicity, and baseline characteristics such as ECOG performance status, disease stage, and histology will be summarized by treatment arm for the IIB-IIIB-WT and/or ITT-WT population. Descriptive statistics (mean, standard deviation, median, and range including minimum and maximum) will be presented for continuous data and frequencies and percentages will be presented for categorical data. Baseline measurements are the last available data obtained prior to patients receiving the first dose of study treatment, unless otherwise noted.

4.4 EFFICACY ANALYSIS

Independent Review Facility assessed EFS and OS analyses will be performed on Stage IIB-IIIB-WT patients and ITT-WT patients (i.e., the Stage IIB-IIIB patients per AJCC v8 and all randomized patients without a known EGFR activating mutation or an ALK fusion oncogene, respectively). The secondary and exploratory efficacy endpoints, except IRF assessed pCR, IRF assessed MPR and OS, will be analyzed in the Stage IIB-IIIB-WT and/or the ITT-WT populations depending on the results of the primary endpoint analysis. Patients will be grouped by their assigned treatment at randomization by the IxRS.

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Independent Review Facility-Assessed Event-Free Survival

The IRF-assessed EFS, is defined as the time from the date of randomization to any of the following events, whichever occurs first: disease progression per RECIST v1.1 that precludes surgery; local or distant disease recurrence (including occurrence of new primary NSCLC); or death due to any cause.

Patients who have not experienced disease progression that precludes surgery, local or distant disease recurrence (including occurrence of new primary NSCLC), or death at the time of analysis will be censored at the time of last tumor or disease follow-up assessment. Patients with missing baseline scan imaging will be censored at the date of randomization. Patients with no post-baseline tumor assessment will be censored at the date of randomization. Patients who do not go through planned surgeries and have disease progressions per RECIST v1.1 post the planned but not done surgery will be counted as having events at the time of disease progression per RECIST v1.1.

[redacted]

For the efficacy analysis population, the comparisons in IRF-assessed EFS between two treatment arms will be based on a stratified log-rank test. The stratification factors are Stage (II vs. IIIA N2- vs. IIIA/B N2+) and histology (non-squamous vs. squamous) at randomization. The null and alternative hypotheses can be phrased in terms of the survival functions $S_A(t)$ and $S_B(t)$ in Arm A and Arm B, respectively.

$$H_0: S_A(t) = S_B(t) \text{ versus } H_1: S_A(t) \neq S_B(t)$$

The HR will be estimated using a stratified Cox regression model with the same stratification factors used in the stratified log-rank test, and the 95% confidence interval (CI) will be provided. Results from an unstratified analysis will also be provided. Kaplan-Meier (KM) methodology will be used to estimate the median IRF-assessed EFS in each treatment arm, and a KM curve will be constructed to provide a visual description

of the difference between the treatment arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median IRF-assessed EFS for each treatment arm (Brookmeyer and Crowley 1982).

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 IRF-Assessed Pathological Complete Response Rate and Major Pathological Response Rate

Independent Review Facility assessed pCR rate is defined as the proportion of patients with an absence of invasive neoplastic cells at microscopic examination of the primary tumor and all sampled lymph nodes after surgery, as determined by the central pathology laboratory. Patients not meeting these criteria, including patients who did not have surgical resection, or patients who did not have their entire tumor bed submitted, will be considered as non-responders.

Independent Review Facility assessed MPR is defined as $\leq$ 10% residual viable tumor (unweighted) in the primary tumor at the time of surgical resection in the primary tumor, assessed by the central pathology laboratory. It considers the averaged percentage of viable tumor cells on each slide that is prepared and available (Hellmann et al. 2014; Pataer et al. 2012). Major pathological response rate is defined as the proportion of patients who have MPR. Patients not meeting these criteria, including patients who did not have surgical resection, will be considered as non-responders.

The pCR and MPR rates between treatment arms will be compared using a Cochran-Mantel-Haenszel test stratified by Stage (II vs. IIIA N2$-$ vs. IIIA/B N2$+$) and histology (non-squamous vs. squamous). An unstratified χ^2 test will also be provided as a sensitivity analysis. The difference in pCR and MPR rates will be provided with 95% CI, using the normal approximation to the binomial distribution. The Clopper-Pearson method will be used to construct the 95% CI for pCR and MPR rates for each treatment arm.

[redacted]

4.4.2.2 Overall Survival

Overall survival is defined as the time from the date of randomization to the date of death due to any cause. Patients who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization.

The analysis methodology (as described in Section 4.4.1.1) used for IRF-assessed EFS will be applied for OS. [redacted]

4.4.2.3 Investigator-Assessed Event Free Survival

Investigator-assessed EFS is defined as the time from the date of randomization to any of the following events, whichever occurs first: progression of disease that precludes surgery per RECIST v1.1, as assessed by the investigator; local or distant disease recurrence (including occurrence of new primary NSCLC), as assessed by the investigator; or death due to any cause. Investigator-assessed EFS will be assessed using the same statistical methodology as the primary endpoint, IRF-assessed EFS in Section 4.4.1.1.

4.4.2.4 Investigator-Assessed Objective Response Rate

objective response rate (ORR) is defined as the proportion of patients with a best overall response of complete response or partial response as determined by the investigator per RECIST v1.1 (confirmation not required) during the neoadjuvant treatment phase in the same analysis population as for IRF-assessed EFS. Patients not meeting these criteria before the surgery, including patients without at least one post-baseline tumor assessment before the surgery, will be considered non-responders.
Investigator-assessed ORR will be analyzed using the same methods as the secondary endpoints in Section 4.4.2.1.

4.4.2.5 Investigator-Assessed Pathological Complete Response Rate and Major Pathological Response Rate

The definition of investigator-assessed pCR and MPR rate is the same as that of the IRF-pCR and MPR except that this will be assessed by the investigator site pathologist after surgical resection of the primary tumor. Investigator-assessed pCR and MPR rates will be analyzed using the same methods as described in Section 4.4.2.1 .

4.4.2.6 2-year and 3-year Overall Survival, 2-year and 3-year Independent Review Facility-Assessed, and Investigator-Assessed Event Free Survival

The 2-year and 3-year OS rates are defined as the probability that a patient will be alive 2 years and 3 years after randomization, respectively. The 2-year and 3-year IRF-assessed EFS and investigator-assessed EFS rates are defined as the probability that a patient will be event-free 2 years and 3 years after randomization, respectively. The KM method will be used to estimate the 2-year and 3-year survival rate for each treatment arm. The 95% CI for the difference in survival rates between the two treatment arms will be estimated through use of the normal approximation method, and standard errors will be computed through use of the Greenwood method.

4.4.2.7 Investigator-Assessed Disease-Free Survival

Disease-free survival is defined as the time from the first date of no disease (i.e., date of surgery) to local or distant recurrence (including occurrence of new primary NSCLC) as assessed by investigator, or death due to any cause, whichever occurs first. Disease-free survival will be analyzed only for patients who underwent protocol-mandated surgery and had no evidence of NSCLC disease (R0 surgical resection). After surgery, patients without documented disease recurrence or death will be censored at the date of last assessment. Patients without post-surgery assessments but known to be alive will be censored at the date of surgery. Disease-free survival will be analyzed using the same methods as described in Section 4.4.1.1 .

4.4.2.8 Patient-Reported Outcomes

4.4.2.8.1 Scoring

The EORTC QLQ-C30 and EORTC QLQ-LC13 will be scored according to the EORTC scoring manual, 3rd edition (Fayers et al. 2001). A high score for a functional scale represents a high level of functioning and a high score for the GHS/QoL scale represents a high HRQoL. However, a high score for a symptom scale or item represents a high level of symptomatology problems. A score change of ≥10 points is considered to be clinically meaningful by patients for lung cancer–related symptoms, GHS/QoL, and physical functioning subscale score (Osoba et al. 1998).

For the EORTC QLQ-C30 multi-item subscales, no imputation will be performed to replace missing scores. If <50% of items within the multi-item subscale are missing at a given timepoint, the multi-item score will be calculated on the basis of the non-missing items. If ≥50% of items are missing or if a single-item measure is missing, the subscale is considered missing. The dyspnea subscale should be used only if all 3 items have been answered.

4.4.2.8.2 Visit Score Summary and Change from Baseline

Visit summary and change from baseline analyses will be performed for HRQoL scores, as assessed through the two-item GHS/QoL subscale (Questions 29 and 30) of the EORTC QLQ-C30 at each assessment timepoint during the study through the

completion of adjuvant treatment and observation follow-up assessments. Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum) of score(s) and score change(s) from baseline to each time point will be presented by treatment arm.

4.4.3 Exploratory Endpoints

4.4.3.1 Independent Review Facility-Assessed Event-Free Survival by PD-L1 Expression

Independent Review Facility -assessed EFS by PD-L1 expression on TCs defined by the SP263 IHC assay (including ≥ 1%, and ≥ 50% of tumor cells) will be analyzed using the unstratified analysis methods described in Section 4.4.1.1. The analysis will be conducted on patients whose SP263 test results are available.

4.4.3.2 Subgroup Analysis

The effects of demographics (e.g., age, sex and race/ethnicity), baseline prognostic characteristics (e.g., tumor stage, histology at baseline), NSCLC pathologic downstaging after neoadjuvant treatment (N2 to N0, vs others), and biomarker status (e.g., SP263 TC ≥ 1%, 1–49% and ≥ 50%) on pCR, MPR, EFS, investigator assessed DFS and OS will be examined. The difference in pCR and MPR rates by subgroups will be provided with 95% CI, using the normal approximation to the binomial distribution. Summaries of EFS, DFS, and OS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan Meier estimates of median survival time will be produced separately for each level of the categorical variables.

4.4.3.3 Exploratory Analyses of Biomarkers

Exploratory biomarker analysis will be performed in an effort to understand the association of biomarkers with study treatment response, efficacy (including pathological response), and/or adverse events. The tumor biomarkers from tissue and blood samples include, but are not limited to, PD-L1, CD-8, T-effector gene expression, tumor mutational burden, and ctDNA. Methods for assessment include, but are not limited to, IHC and qRT-PCR. These results may be reported separately from the Clinical Study Report.

4.4.3.4 Patient Reported Outcomes

4.4.3.4.1 Visit Score Summary and Change from Baseline

Visit summary and change from baseline analyses will be performed for the EORTC QLQ-C30 and QLQ-LC13 questionnaires. Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum) of score(s) and score change(s) from baseline to each time point will be presented by treatment arm.

4.4.3.4.2 Time to Confirmed Deterioration (TTCD) Analysis

Time to confirmed deterioration will be performed for each of the following scores:

- Cough (Question 1, QLQ-LC13)
- Fatigue (Questions 10, 12, 18, QLQ-C30)

- Pain (Questions 9 and 19, QLQ-C30)
- GHS/QoL (Questions 29, and 30, QLQ-C30)
- Physical functioning (Questions 1 to 5, QLQ-C30)
- Dyspnea subscale (Questions 33, 34, and 35, QLQ-LC13)

Time to confirmed deterioration for cough symptom and dyspnea using the EORTC QLQ-LC13 and fatigue, pain, GHS/QoL and physical functioning using the EORTC QLQ-C30, is defined as the time from date of randomization until the first confirmed clinically meaningful deterioration on each respective score. Confirmed clinically meaningful deterioration in symptoms is defined as a clinically meaningful increase from baseline in a symptom score that must be held for at least two consecutive assessments or an initial clinically meaningful increase from baseline followed by death. Confirmed clinically meaningful deterioration in GHS/QoL and physical functioning is defined as a clinically meaningful decrease from baseline in GHS/QoL and physical functioning scale scores that must be held for at least two consecutive assessments or an initial clinically meaningful decrease from baseline followed by death within three weeks. A score change of $\geq$10 points is considered to be clinically meaningful by patients for lung cancer–related symptoms, GHS/QoL, and physical functioning subscale score (Osoba et al. 1998). If no baseline or post-baseline assessment is performed, patients will be censored at the randomization date. Patients without confirmed deterioration at the time of analysis will be censored at the last time they were known to have not deteriorated, i.e., the last assessment. There will be no imputation for missing baseline or post-baseline data for the TTCD analysis. Time to confirmed deterioration using the EORTC scale will be analyzed via the same method as described in Section 4.4.1.1.

Time to event analyses of the pre-specified symptoms, GHS/QoL, and physical functioning will be summarized using the KM method. The estimated KM plots will be provided for each score previously described (EORTC QLQ-C30 and QLQ-LC13 scores). The median time and two-sided 95% CI for the median will also be provided.

4.4.3.4.3 EQ-5D-5L Health Status Data

The EQ-5D-5L will be scored according to its manual, and results will be reported separately from the Clinical Study Report.

4.4.3.4.4 Additional Patient-Reported Outcome Analysis

Completion rates will be summarized by listing the number and proportion of patients among those expected to complete the EORTC QLQ-C30 and QLQ-LC13 questionnaires at each timepoint. Reasons for non-completion will be summarized, if available.

4.4.3.5 Additional Exploratory Pathological Response Assessments

To further elucidate the role of pathological response on clinical outcomes among subgroups, additional exploratory pathological response assessments will be performed. These include assessing pathological response in lymph nodes by central pathology assessment, as well as the potential role of digital pathology in the assessment of pathological response. Additional assessments include assessing pathological response by PD-L1 expression as well as the degree of pathological response by histology as there may be different cutoffs for predicting survival (Qu et al. 2019). Lastly, other exploratory assessments include rate of MPR (centrally and locally assessed) in patients who have had surgery and the MPR rate calculated by a weighted method which take into account both the assessed viable tumor percentage and the area of the tumor (bed) of each slide (estimated size of viable tumor divided by the size of the tumor bed, Travis et al. 2020). In this approach, the weight of each slide is calculated as the percentage of its tumor area over the total tumor (bed), the weighted percentage of viable tumor for each slide is calculated by multiplying the weight of each slide with the estimated percentage of viable tumor within the tumor (bed) for each slide, and the weighted MPR is calculated as the sum of the weighted percentages of viable tumor from all obtained slides. The results of these additional exploratory pathological response assessments will be reported separately from the Clinical Study Report (CSR).

4.4.3.6 NSCLC-related Death

NSCLC-related Death is defined as the time from the date of randomization to the date of death due to NSCLC recurrence only. Patients who are not reported as having died at the time of analysis due to NSCLC recurrence will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization. It will be assessed using the same statistical methodology as the primary endpoint, IRF-assessed EFS in Section **4.4.1.1.** This analysis may not be included in the CSR

4.4.4 Sensitivity Analyses

4.4.4.1 Missing Tumor and Disease Assessments

The impact of missing scheduled tumor and disease assessments on IRF-assessed EFS will be assessed depending on the number of patients who missed assessments scheduled immediately prior to the date of disease recurrence or disease progression per RECIST v1.1 (except disease progression per RECIST v1.1 that do not preclude surgeries) or the data cutoff. If $>$5% of patients missed two or more assessments scheduled immediately prior to the date of recurrence or disease progression per RECIST v1.1 (except disease progression per RECIST v1.1 that do not preclude surgeries) or the data cutoff in any treatment arm, the following sensitivity analysis will be performed:

- Patients who missed two or more scheduled assessments immediately prior to the date of recurrence or disease progression per RECIST v1.1 or the data cutoff will be

censored at the last tumor assessment or disease follow-up assessment prior to the first of these missed visits.

Statistical methodologies analogous to those used in the primary analysis of IRF-assessed EFS as specified in Section 4.4.1.1 will be used for this sensitivity analysis.

4.4.4.2 Including Clinical Progression Precluding Surgery in the EFS Analysis

Patients who did not have RECIST1.1 progression but had clinical progression that precluded surgery will be not counted as an EFS event per protocol definition. In this analysis, patients who did not undergo surgery due to progressive disease, regardless of having met the RECIST1.1 definition for progressive disease, will be considered as an EFS event.

It will be analyzed using the same methods as described in Section 4.4.1.1. These results may be reported separately from the CSR.

4.4.4.3 Non-Protocol-Specified Anti-Cancer Therapy

The impact of non-protocol-specified anti-cancer therapy (NPT) on investigator-assessed EFS and IRF-assessed EFS will be assessed. A sensitivity analysis will be performed for the comparison between the two treatment arms in which patients who receive NPT before an EFS event will be censored at the last tumor assessment date or disease follow-up assessment on or before receipt of NPT.

The impact of subsequent NPT on OS will be assessed depending on the number of patients who received NPT. If $>$10% of patients received an NPT in either treatment arm, the following analyses may be performed to compare treatment arms:

- The discount method uses a “discounted” survival time after switching for patients who switch treatments based on a user-specified assumption for the effect on OS. The duration from initiation of NPT to death or censoring date will be discounted in accordance with a range of possible effects on OS of the subsequent NPT after treatment switching occurred (e.g., 10%, 30%, 50%).

After adjustments are made for the effect of NPT on OS, the methods that outlined for the primary efficacy endpoint analyses will be used for these analyses (see Section 4.4.1).

4.5 PHARMACOKINETIC ANALYSIS

Atezolizumab serum concentration data (C_{min} [minimum blood plasma concentration] and C_{max} [maximum blood plasma concentration]) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and standard deviations as appropriate.

Additional pharmacokinetic analyses will be conducted based on the availability of data as appropriate.

4.6 SAFETY ANALYSES

Safety analysis will be performed on the safety populations. The safety population will consist of all randomized patients who received any amount of study treatment. For safety analyses, patients will be grouped according to whether any amount of atezolizumab was received, including cases where atezolizumab was received in error. The surgical safety population will consist of the safety population that has undergone protocol-mandated surgery.

4.6.1 Exposure of Study Medication

Study treatment exposure, including treatment duration, number of cycles, and dose intensity, will be summarized for each treatment arm using descriptive statistics.

4.6.2 Adverse Events

Verbatim description of AE terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be determined by the investigator according to NCI CTCAE v5.0. Treatment-emergent adverse events (TEAEs) will be summarized by mapped term, appropriate thesaurus level, NCI CTCAE grade, and treatment arm. For safety analyses, “treatment emergent” is defined as AEs occurring on or after the first dose of study drug treatment or a pre-existing condition that worsened on or after the first dose of study drug treatment up to the data cutoff date, regardless of relationship to study drug as assessed by the Investigator.

Multiple occurrences of the same event in a single patient will be counted once at the maximum grade. The TEAEs will be summarized as: AEs, common AEs, SAEs, treatment-related SAEs, surgical-related AEs, severe AEs (Grade 3-4), Grade 5 AEs, adverse events of special interest, AESI that require the use of systemic corticosteroids, and AEs that lead to study drug discontinuation or interruption. Adverse events will be summarized combining the neoadjuvant and adjuvant phases, and may be separately reported as combined, and by neoadjuvant and adjuvant phases.

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

4.6.3 Laboratory Data

Laboratory data will be graded in accordance with NCI CTCAE v5.0. The proportion of patients with a clinically relevant shift from baseline (i.e., a change from Grade 0, 1, 2 at baseline to Grade 3 or 4 post baseline) in lab safety parameters will be summarized by treatment arm.

4.6.4 Vital Signs

Changes in selected vital signs from baseline will be summarized by treatment arms.

4.6.5 Anti-Drug Antibody

Serum levels and incidence of ADAs against atezolizumab will be summarized. The analyses of pharmacokinetics, key efficacy, and safety by ADA status will be conducted to explore the potential impact of immunogenicity.

4.6.6 Surgical Outcomes

Incidence and reasons of surgical cancellations will be summarized by treatment arm and by disease stage at randomization using the safety population.

Incidence, length and reasons of surgical delays will be summarized by treatment arm and by disease stage at randomization using the surgical safety population.



4.7 MISSING DATA

Refer to Section 4.4.1 and Section 4.4.2 for methods on how to handle missing data for the primary and secondary efficacy endpoints.

For PRO (patient-reported outcome) data, the EORTC QLQ-C30 and QLQ-LC13 questionnaires will be scored according to the EORTC scoring manual guidelines (Fayers et al. 2001). Missing scores will not be imputed.

5. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics, 1982;38:20-41.

Fayers PM, Aaronson NK, Bjordal K, et al. The EORTC QLQ-C30 scoring manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer, 2001.

Gordon Lan KK, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983 Dec 1;70(3):659-63.

Hellmann MD, Chaft JE, William WN Jr, et al. Pathological response after neoadjuvantchemotherapy in resectable non(small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. Lancet Oncol 2014;15:e42−50.

Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139−44.

Pataer A, Kalhor N, Correa AM, et al. Histopathologic response criteria predict survival of patients with resected lung cancer after neoadjuvant chemotherapy. J Thorac Oncol 2012;7:825−32.

Qu Y, Emoto K, Eguchi T, et al. Pathologic assessment after neoadjuvant chemotherapy for NSCLC: importance and implications of distinguishing adenocarcinoma from squamous cell carcinoma. J Thorac Oncol 2019;14:482-93.

Travis WD, Dacic S, Wistuba I, et al. IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy. J Thorac Oncol 2020; 15: 709-740.

Wassmer G, Brannath W. Group sequential and confirmatory adaptive designs in clinical trials. Cham: Springer International Publishing; 2016 Jul 4.

Appendix 1 Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, DOUBLE-BLINDED, MULTICENTER, RANDOMIZED STUDY EVALUATING THE EFFICACY AND SAFETY OF NEOADJUVANT TREATMENT WITH ATEZOLIZUMAB OR PLACEBO IN COMBINATION WITH PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH RESECTABLE STAGE II, IIIA, OR SELECT IIIB NON–SMALL CELL LUNG CANCER**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 117296 EU CT Number: 2023-504209-35-00 NCT Number: NCT03456063 EudraCT Number: 2017-002857-12

STUDY RATIONALE

This study will evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy, when compared with placebo with platinum-based chemotherapy. Specific objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" in the neoadjuvant treatment phase refers to the combination of treatments assigned to patients as part of this study (i.e., atezolizumab or placebo with platinum-based chemotherapy).

OBJECTIVES AND ENDPOINTS

Primary Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy followed by adjuvant atezolizumab	• IRF assessed EFS, defined as the time from randomization to the first documented disease progression per RECIST v1.1 that precludes surgery, local or distant disease recurrence (including occurrence of new primary NSCLC), or death from any cause, whichever occurs first

EFS = event-free survival; IRF = Independent Review Facility; NSCLC = non-small-cell lung cancer; RECIST = Response Evaluation Criteria in Solid Tumors.

OBJECTIVES AND ENDPOINTS (CONT.)

Secondary Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy	• IRF assessed pCR, defined as the absence of any viable primary tumor cells at the time of surgical resection in the primary tumor and all sampled lymph nodes as assessed by central pathology laboratory • IRF assessed MPR, defined as $\leq$10% residual viable tumor cells at the time of surgical resection in the primary tumor as assessed by central pathology laboratory • MPR and pCR at the time of surgical resection, as assessed by the investigator site pathology laboratory • Objective response, defined as a complete response or partial response, as determined by the investigator according to RECIST v1.1 (confirmation not required)
• To evaluate the efficacy of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy followed by adjuvant atezolizumab	• OS, defined as the time from randomization to death from any cause during the course of the study • Investigator assessed EFS • DFS, defined as the time from the first date of no disease to local or distant recurrence (including occurrence of new primary NSCLC) or death due to any cause, whichever occurs first, as determined by the investigator during the adjuvant treatment and observation follow-up • 2-year and 3-year OS, IRF assessed EFS and investigator assessed EFS during the study
• To evaluate PROs of HRQoL associated with atezolizumab in combination with platinum-based chemotherapy as neoadjuvant treatment followed by adjuvant atezolizumab	• Change from baseline in HRQoL scores as assessed through use of the two-item GHS/QoL subscale (Questions 29 and 30) of the EORTC QLQ-C30 at each assessment timepoint during the study through the completion of adjuvant treatment and observation follow-up assessments

DFS = disease-free survival; EFS = event-free survival; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; HRQoL = health-related quality of life; IRF = Independent Review Facility; MPR = major pathological response; NSCLC = non-small-cell lung cancer; OS = overall survival; pCR = pathological complete response; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire Core 30; RECIST = Response Evaluation Criteria in Solid Tumors.

OBJECTIVES AND ENDPOINTS (CONT.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy followed by adjuvant atezolizumab	• Occurrence and severity of adverse events, including serious adverse events and immune-mediated adverse events, with severity determined according to NCI CTCAE v5.0 • Incidence and length of surgical delays, incidence of operative and post-operative complications, and/or reasons for surgical cancellations
Pharmacokinetic Objectives	**Corresponding Endpoint**
• To characterize the PK profile of atezolizumab when given in combination with platinum-based chemotherapy • To characterize the PK profile of atezolizumab alone	• Serum concentration of atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to atezolizumab	• Incidence of ADAs against atezolizumab during the study

ADA = anti-drug antibody; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PK = pharmacokinetic.

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020) in Section 3 of the protocol.

OVERALL DESIGN AND STUDY POPULATION

This is a global Phase III multicenter, double-blinded, randomized study designed to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of neoadjuvant treatment with atezolizumab in combination with platinum-based chemotherapy versus placebo plus platinum-based chemotherapy followed by adjuvant/post-operative atezolizumab or best supportive care (BSC) in patients with histologically or cytologically confirmed resectable Stage II, IIIA, or select IIIB (T3N2 only) non–small-cell lung cancer (NSCLC).

Several key aspects of the study design and study population are summarized below.

Phase:	Phase III	**Population Type:**	Adult patients
Control Method:	Placebo	**Population Diagnosis or Condition:**	Histologically or cytologically confirmed resectable Stage II, IIIA, or select IIIB (T3N2 only) NSCLC
Interventional Model:	Parallel group	**Population Age:**	Age ≥ 18 years at time of signing Informed Consent Form
Test Compound:	Atezolizumab (RO5541267)	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not Applicable	**Study Intervention Assignment Method:**	Randomization and stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 450

NSCLC = non–small-cell lung cancer.

STUDY TREATMENT

INVESTIGATIONAL MEDICINAL PRODUCTS

Test Product (Investigational Drug) (Patients in Arm A only)

- Atezolizumab (1200 mg IV) on Day 1 of each 21–day cycle (every 3 weeks) for 4 cycles during the neoadjuvant treatment phase
- Atezolizumab (1200 mg IV) every 3 weeks for 16 cycles during the post-operative adjuvant phase
- Nab-paclitaxel (100 mg/m^2 IV) on Days 1, 8, and 15 of each 21day cycle for 4 cycles during the neoadjuvant treatment phase

Comparator (Patients in Arm B only)

- Placebo (IV) on Day 1 of each 21–day cycle for 4 cycles during the neoadjuvant treatment phase
- Nab-paclitaxel (100 mg/m^2 IV) on Days 1, 8, and 15 of each 21–day cycle for 4 cycles during the neoadjuvant treatment phase

AUTHORIZED AUXILLIARY MEDICINAL PRODUCTS / NON-INVESTIGATIONAL MEDICINAL PRODUCTS

- Carboplatin (IV, initial target AUC of 6 mg/mL/min) on Day 1 of each 21-day cycle for 4 cycles during the neoadjuvant treatment phase
- Cisplatin (75 mg/m^2 IV) on Day 1 of each 21-day cycle for 4 cycles during the neoadjuvant treatment phase
- Pemetrexed (500 mg/m^2 IV) on Day 1 of each 21-day cycle for 4 cycles during the neoadjuvant treatment phase
- Gemcitabine (1250 mg/m^2 IV) on Days 1 and 8 of each 21-day cycle for 4 cycles during the neoadjuvant treatment phase

DURATION OF PARTICIPATION

Participation will continue until withdrawal or death due to any cause.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee
Other Committees:	Not applicable

Appendix 2 Schedule of Activities

Assessment			Neoadjuvant Treatment					Adjuvant Treatment/ Observation FU			
	[redacted]										
Informed consent [a, g]	x										
ALK and/or EGFR assessment (if status is unknown) [h]	x										
Baseline tumor tissue sample [i]	x										
Surgical tumor tissue and lymph node sample [j]						x					

Assessment			Neoadjuvant Treatment					Adjuvant Treatment/ Observation FU			
Pathological response assessment						x					
Demographic data	x										
Medical history and baseline conditions	x										
Thoracic surgery evaluation	x			x							
Patient-reported outcomes [k]				x			x		x	x	
Vital signs [l]	x		x					x		x	
Weight	x		x					x		x	

Assessment			Neoadjuvant Treatment					Adjuvant Treatment/ Observation FU			
Height	x										
Complete physical examination [m]	x										
Limited physical examination [n]			x					x	x		
ECOG Performance Status	x									x	
ECG [p]	x		x					x	x		
Hematology [q]		x	x [r]					x		x	
Chemistry [s]		x	x [r]					x		x	
Pregnancy test [t]		x	x					x		x [t]	

Assessment			Neoadjuvant Treatment					Adjuvant Treatment/ Observation FU			
Coagulation (INR, aPTT)		x								x	
TSH, free T3 (or total T3), free T4 [u]	x		x [r, u]					x [u]		x	
Viral serology [v]	x										
Urinalysis [w]	x		x [w]					x [w]	x [w]		
Blood, plasma, serum, sample for biomarkers	x [x]		x [x]	x [x]			x [x]	x [x]	x [x]	x [x]	x [x]
Serum samples for PK and ADA analyses			x [x]					x [x]		x [x]	

Assessment			Neoadjuvant Treatment					Adjuvant Treatment/ Observation FU			
Blood for RBR (optional) [y]			x [y]								

Assessment			Neoadjuvant Treatment					Adjuvant Treatment/ Observation FU			
Optional consent for exploratory research on disease recurrence biopsy								x [z]	x [z]	x [z]	
Optional tumor biopsy at the time of disease progression			x [z]							x [z]	
Optional tumor biopsy at other timepoints [aa]				Any time during study treatment, observation FU or survival FU (at investigator's discretion)							
Tumor response and disease FU assessments	x [bb]		x [cc]					x [dd]	x [dd]		x [dd]

Assessment			Neoadjuvant Treatment					Adjuvant Treatment/ Observation FU			
	[redacted]										
Concomitant medications [ee]	x		x	x		x	x	x	x	x	
Adverse events [ff]	x		x	x			x	x	x	x	x
Study treatment administration [gg]			x					x			
Survival FU and anti-cancer treatment											x [hh]

ADA = anti-drug antibody; ALK = anaplastic lymphoma kinase ; BSC = best supportive care; CT = computed tomography (scan); ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EGFR = epidermal growth factor; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5 Dimension Questionnaire, 5-level version; FU = follow-up; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LDH = lactate dehydrogenase; MPR = major pathological response; MRI = magnetic resonance imaging; NSCLC = non-small-cell lung cancer; pCR = pathological complete response; PET = positron emission tomography; PK = pharmacokinetic; PORT = post-operative radiotherapy; PRO = patient-reported outcome; Q3W = every 3 weeks; Q6W = every 6 weeks; QLQ-C30 = quality of life questionnaire for cancer; QLQ-LC13 = quality of life questionnaire for lung cancer; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results of standard of care tests or examinations performed prior to obtaining informed consent and within [redacted] days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] [redacted]

[c] [redacted]

[d] [redacted]

[e] Patients randomized to Arm A will receive adjuvant treatment with atezolizumab Q3W for 16 cycles and will be scheduled for disease FU assessments. Patients randomized to Arm B on BSC will be required to come in for observation FU visit assessments Q6W for up to 8 visits and will be scheduled for disease FU assessments as well. [redacted]

[f] Patients who discontinue study treatment will return to the clinic for a treatment or observation FU discontinuation visit not more than [redacted] days after the last dose of study treatment or last observation FU visit (for Arm B patients). The visit at which response assessment shows disease progression or recurrence may be used as the treatment or observation FU discontinuation visit.

[g] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than [redacted] days before initiation of study treatment.

[h] For patients with non-squamous or mixed histology with observed non-squamous component that have unknown EGFR and/or ALK status, test results are required at screening. ALK and/or EGFR status may be assessed locally or at a central laboratory (in China, will be assessed centrally only). Additional tissue material and/or a plasma sample is required for central testing of EGFR and/or ALK. See laboratory manual for details.

[i] Archival or newly collected tumor tissue sample suitable for central PD-L1 testing is required (results of PD-L1 testing are not required for patient to be randomized into the study). Additional tissue material, if available, is strongly encouraged to be submitted for exploratory biomarker research. Samples and associated pathology report should be submitted before or within [redacted] weeks after randomization. Refer to Section 4.5.6 of the protocol for tissue sample requirements.

[j] Tumor tissue and lymph node tissue obtained from surgical resection is required for pathological response analysis. Assessments on surgical specimen will be done for MPR, pCR, and exploratory biomarker analysis (if adequate tissue remains). Refer to Section 4.5.6 of the protocol for tissue sample requirements.

[k] PRO assessments EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires are required to be completed by the patient at the investigational site at the start of the clinic visit before discussion of the patient's health state, laboratory results or health record, before administration of study treatment, and/or prior to any other study assessment(s) that could bias patients' responses to ensure that the validity of the instrument is not compromised and that data quality meets regulatory requirements. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. During the neoadjuvant treatment phase, PRO assessments will be administered on Day 1 of each cycle only. For patients randomized to Arm A during the adjuvant treatment phase, PRO assessments will be administered on Day 1 of Cycle [redacted] and Day 1 of every other cycle thereafter. For patients who are unable to come to the clinic due to government restrictions or safety considerations, PROs may be completed via a telephone call; source documentation sufficient to pass an audit should be obtained which includes, among other information, that the questionnaires were administered via telephone because of government restrictions or safety considerations. During follow-up visits, PROs will be administered by site personnel to the patient via telephone in order to collect data without mandating that patients travel to the study site.

During survival FU, patients will complete the global health status (Questions 29 and 30), physical functioning (Questions 1−5) and role functioning (Questions 6 and 7) scales of the EORTC QLQ-C30, and full EQ-5D-5L questionnaires via telephone at the survival FU calls scheduled at [redacted] months only.

[l] Includes respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during the infusion and at 30 (±10) minutes after the infusion.

[m] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[n] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[o] [redacted]

[p] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[q] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Hematology labs should also be performed prior to administration of Day [redacted] of gemcitabine infusion as well as Days [redacted] of nab-paclitaxel infusion.

[r] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle [redacted], they do not have to be repeated.

[s] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, magnesium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, and LDH. Chemistry panel labs should also be performed prior to administration of Day [redacted] of gemcitabine infusion as well as Days [redacted] of nab-paclitaxel infusion.

[t] All women of childbearing potential will have a serum pregnancy test at screening, within [redacted] days prior to initiation of study treatment. Urine pregnancy tests will be performed at every cycle in the neoadjuvant phase for both treatment arms, and during every cycle in the adjuvant treatment phase for Arm A. Urine pregnancy test will also be performed at the Treatment or Observation FU Discontinuation Visit for Arm A and for Arm B if the last dose of neoadjuvant treatment was administered within 6 months of treatment or observation FU discontinuation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[u] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day [redacted] of Cycles [redacted] for both treatment arms in the neoadjuvant phase, and Day [redacted] of Cycles [redacted] in the adjuvant phase only for patients assigned to Arm A.

[v] At screening, patients will be tested for HIV, HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[w] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted. Urinalysis should be performed as clinically indicated during study treatment.

[x] See Appendix 2 of the protocol for detailed schedule. During survival FU, biomarker plasma and serum samples will be collected only at the time of disease progression or recurrence (before administration of subsequent therapy if planned).

[y] A blood sample for the RBR will be collected on Cycle [redacted], Day [redacted]. However, if this sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study. 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.

[z] Patients will undergo an optional tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of radiographic disease progression per RECIST v1.1 during the neoadjuvant treatment phase or to submit tissue samples obtained from pathological confirmation of disease recurrence (for exploratory biomarker research) during the adjuvant treatment/monitoring phase. Biopsies should be performed prior to the next anti-cancer therapy. Patients must sign a separate Optional Biopsy Informed Consent Form to undergo optional biopsies. See Section 4.5.6 of the protocol for tissue sample requirements.

[aa] Biopsies collected at the investigator's discretion are preferred at the time of clinical events (e.g., clinical response). Patients must sign a separate Optional Biopsy Informed Consent Form to undergo optional biopsies. See Section 4.5.7 of the protocol for details.

[bb] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within [redacted] days (for CT or MRI scan) or [redacted] days (for PET scan) prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include PET scan (whole body, or skull base to thighs) and CT scan (with oral or IV contrast) of the chest, abdomen, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance or severe allergy), a non-contrast CT scan of the chest and abdomen may be performed along with the PET (whole body, or skull base to thighs). A CT scan with contrast or MRI scan of the head must be done at screening to rule out CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

[cc] Patients will undergo tumor assessments after completion of Cycles [redacted] following treatment initiation per RECIST v1.1 during the neoadjuvant treatment phase. All measurable and evaluable lesions should be reassessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). The investigator must review the scan results after Cycle [redacted] to determine if the patient is eligible to continue receiving Cycle [redacted] of neoadjuvant treatment, or if the patient should proceed with surgery (those with disease progression but still amenable to curative surgery) or other standard of care treatment (those with disease progression not amenable to curative surgery). Similarly, the investigator must review tumor assessment scans after Cycle [redacted] to assess response and confirm disease resectability.

[dd] [redacted] If a disease FU assessment suggests potential disease recurrence, the event should be confirmed pathologically and/or by unequivocal radiographic evidence. If a scan shows equivocal findings (e.g., mediastinal nodes measuring < 1.5 cm in the short axis, lung parenchymal lesions or visceral lesions measuring < 1 cm in the longest diameter), a biopsy should be performed. The biopsy should be performed prior to starting the next anti-cancer therapy. If the biopsy does not show evidence of disease recurrence (e.g., non-malignant infiltrates), then the patient may continue with scheduled study treatment and/or FU. If a biopsy is not feasible or safe, then confirmatory scans should be performed again within 4–8 weeks.

[redacted]

All scans will be submitted to an IRF for blinded independent review during the pre-surgery neoadjuvant treatment phase for RECIST v1.1 review as well as post-surgery disease assessment review.

[ee] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from [redacted] days prior to initiation of study treatment until the treatment or observation FU discontinuation visit.

[ff] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until [redacted] days after the last dose of study treatment or last observation FU visit or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until [redacted] days after the last dose of study treatment or last observation FU visit or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6 of the protocol). 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 FU, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[gg] The initial infusion of atezolizumab/placebo will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. For carboplatin, cisplatin, pemetrexed, gemcitabine, and nab-paclitaxel, study treatment will be administered according to the local prescribing information, including premedication with corticosteroids (see Section 4.3.2 of the protocol).

[hh] After treatment or observation FU discontinuation, information on survival FU and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from FU, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) in accordance with local regulations to obtain information about survival status only. [redacted]

Appendix 3 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Blood Samples

Visit	Timepoint	Sample Type
Screening (Day [redacted])	NA	• Blood for biomarkers [a] • Plasma for EGFR central testing [b]
Neoadjuvant Treatment		
Day 1 of Cycles [redacted]	Pre-dose	• Plasma and serum for biomarkers (Cycle [redacted]) • Serum for PK and ADA analyses (Cycle [redacted]) • Optional blood for RBR (Cycle [redacted]) [c]
	30 (±10) minutes after end of atezolizumab/placebo infusion	• Serum for PK analyses (Cycle [redacted])
Pre-Surgery Visit	NA	• Plasma and serum for biomarkers
Post-Surgery Visit	NA	• Blood for biomarkers [a] • Plasma and serum for biomarkers
Adjuvant Treatment (Arm A Only)		
Day [redacted] of Cycles [redacted]	Pre-dose	• Plasma and serum for biomarkers • Serum for PK and ADA analyses (Cycle [redacted] only)
	30 (±10) minutes after end of atezolizumab infusion	• Serum for PK analyses (Cycle [redacted])
Best Supportive Care and Observation FU (Arm B Only)		
Visits [redacted]	NA	• Plasma and serum for biomarkers
Arm A and Arm B		
Disease Progression/ Recurrence or Treatment/Observation FU Discontinuation Visit (≤30 days after last dose)	NA	• Plasma and serum for biomarkers • Serum for PK and ADA analyses [d]

ADA = anti-drug antibody; EGFR = epidermal growth factor receptor; FU = follow-up; NA = not applicable; NSCLC = non–small cell lung cancer; PK = pharmacokinetic; RBR = Research Biosample Repository.

Note: Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] If this sample is not collected during the scheduled visit, it may be collected at any other visit during the conduct of the clinical study.

[b] Only to be performed if EGFR activating mutation status is unknown for patients with non-squamous or mixed histology with observed non-squamous component and if there is inadequate tissue for central EGFR testing.

[c] 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. The whole blood sample for the RBR will be collected on Day [redacted] of Cycle [redacted]. However, if this sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study.

[d] Serum draws for PK and ADA analyses at disease progression or treatment discontinuation will occur in both treatment arms during the double-blinded neoadjuvant treatment phase and only in Arm A during the open-label adjuvant treatment phase.

Signature Page for Statistical Analysis Plan - GO40241 - Published
System identifier: RIM-CLIN-532975

Approval Task	[redacted] Company Signatory 09-May-2024 19:39:26 GMT+0000