Official Title: A Phase III, Open-Label, Randomized Study To Investigate The Efficacy And Safety Of Atezolizumab (Anti–PD-L1 Antibody) Compared With Best Supportive Care Following Adjuvant Cisplatin-Based Chemotherapy In Patients With Completely Resected Stage IB–IIIA Non–Small Cell Lung Cancer

NCT Number: NCT02486718

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STATISTICAL ANALYSIS PLAN

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) COMPARED WITH BEST SUPPORTIVE CARE FOLLOWING ADJUVANT CISPLATIN-BASED CHEMOTHERAPY IN PATIENTS WITH COMPLETELY RESECTED STAGE IB–IIIA NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29527
STUDY DRUG:	TECENTRIQ® (Atezolizumab)
VERSION NUMBER:	1
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted] Ph.D.
DATE FINAL:	See electronic date stamp below.

Date and Time(UTC)	Reason for Signing	Name
30-Jun-2020 16:57:42	Company Signatory	[redacted]

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1. BACKGROUND

This Statistical Analysis Plan (SAP) details the planned analyses and statistical methods for Study GO29527 (hereinafter IMpower010), "A Phase III, Open-Label, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti–PD-L1 Antibody) Compared with Best Supportive Care following Adjuvant Cisplatin-Based Chemotherapy in Patients with Completely Resected Stage IB–IIIA Non–Small Cell Lung Cancer."

During the study conduct, the planned analyses in this study, including the analysis populations for the efficacy endpoints of disease-free survival (DFS) and overall survival (OS), the type I error rate control scheme, the required number of events, and/or the sample size to achieve targeted power may be modified on the basis of results from other TECENTRIQ® (atezolizumab) studies. A Modification Plan describing such potential modifications based on results generated outside of IMpower010 (with the exception of cumulative population-level PD-L1 expression prevalence data in the combined treatment arms based on ongoing study monitoring) and therefore, not resulting in bias, is included in Appendix 5. The analyses described in this SAP will supersede those specified in Protocol GO29527 for the purposes of a regulatory filing.

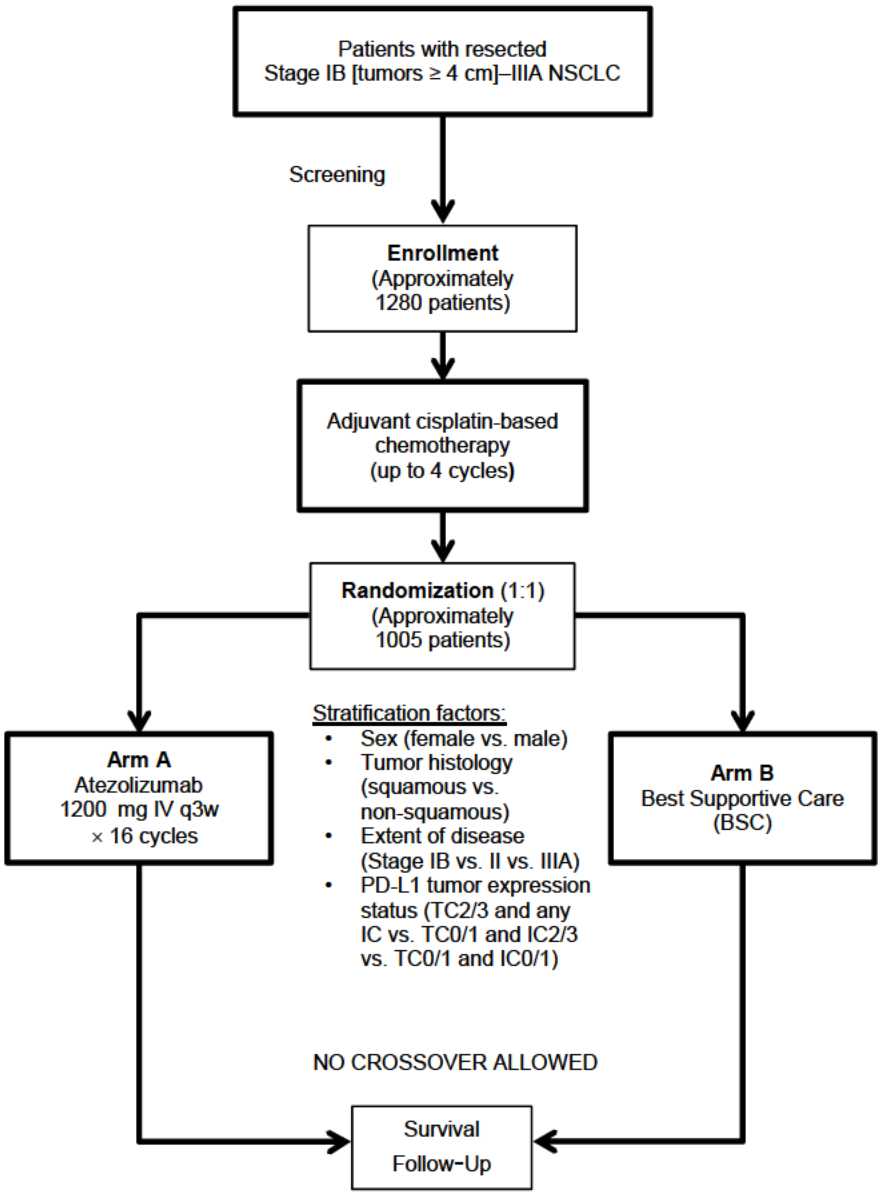
2. STUDY DESIGN

IMpower010 is a Phase III, global, multicenter, open-label, randomized study comparing the efficacy (investigator-assessed DFS and OS) and safety of atezolizumab versus best supportive care (BSC) in patients with Stage IB–Stage IIIA non–small cell lung cancer (NSCLC) following resection and adjuvant chemotherapy. The study consists of two phases, an enrollment phase and a randomized phase.

In the enrollment phase, patients who have recently undergone complete resection of their NSCLC are screened, and eligible patients are enrolled to receive one of four regimens of cisplatin-based chemotherapy (cisplatin plus vinorelbine, docetaxel, gemcitabine, or pemetrexed based on investigator choice). The randomized phase starts after patients complete their cisplatin-based chemotherapy and are still considered eligible to proceed with randomization. Figure 1 illustrates the study design.

Male and female patients aged ≥18 years with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 with a complete surgical resection of histologically or cytologically confirmed Stage IB (tumors ≥4 cm)–IIIA NSCLC are potentially eligible. At screening, tumor specimens from each potentially eligible patient is tested for programmed death–ligand 1 (PD-L1) expression by a central laboratory with use of an immunohistochemistry (IHC) assay (SP142), but patients are enrolled in the study regardless of the PD-L1 status. Patients who fulfill the eligibility criteria receive adjuvant cisplatin-based chemotherapy in the enrollment phase of the study. Patients receive up to 4 cycles of cisplatin-based chemotherapy unless unacceptable toxicity, disease relapse, or patient's decision to discontinue occurs.

Figure 1 Study Schema



IC = tumor-infiltrating immune cell; IV = intravenous; NSCLC = non–small cell lung cancer; PD-L1 = programmed death–ligand 1; q3w = every 3 weeks; TC = tumor cell.
Note: Patients will receive up to 4 cycles of cisplatin-based chemotherapy unless unacceptable toxicity, disease relapse, or patient's decision to discontinue occur.

Patients who experience disease recurrence of their primary disease at any time up to completion of chemotherapy are not eligible for the randomized phase of the study. Additionally, patients must fulfill the eligibility criteria of the randomized phase prior to randomization.

Eligible patients go on to be randomized in a 1:1 ratio to receive either atezolizumab (Arm A) or BSC (Arm B).

In Arm A, atezolizumab is administered intravenously on Day 1 of each 21-day cycle for a total of 16 cycles. Patients randomized to Arm B are continually followed starting on Day 1 of each 21-day cycle. To ensure the same frequency of study assessments between the treatment arms, including assessments for disease recurrence and safety, patients in Arm B are required to undergo medical contacts every 3 weeks (q3w) for assessments during the first year, which consists of formal clinic visits alternating with clinical contacts (either via telephone call or formal outpatient clinic visit) for symptom and adverse event assessment. No crossover is allowed from Arm B to Arm A.

All patients in the randomized phase undergo scheduled tumor assessments at baseline and every 4 months starting at Cycle 1, Day 1 in the first year and every 6 months in the second year by CT following randomization. Patients who have not experienced recurrence of disease undergo tumor assessments every 6 months by CT and X-ray during Years 3–5 post-randomization (starting with CT scan, alternating with X-ray), and annually thereafter by X-ray. In the absence of disease recurrence, tumor assessments should continue, regardless of whether patients start new anti-cancer therapy, until disease recurrence, withdrawal of consent, death, loss to follow-up, or study termination by the Sponsor, whichever occurs first.

Approximately 1280 patients are expected to be accrued in the enrollment phase to meet the goal of approximately 1005 patients total in the randomized phase under the assumption that a dropout rate of approximately 21% is expected during adjuvant cisplatin-based chemotherapy treatment.

The end of the study is defined as when approximately 564 OS events (the required number of deaths for the final OS analysis) have occurred in the intent-to-treat (ITT) population. Additionally, the Sponsor may decide to terminate the study at any time.

2.1 PROTOCOL SYNOPSIS

The protocol synopsis can be found in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2, Appendix 3, and Appendix 4.

2.2 OUTCOME MEASURES

The following objectives will be evaluated in patients with Stage IB–IIIA NSCLC. Unless otherwise noted, all analyses (except for Section 4.9) are based on all randomized patients in the randomized phase. The analyses in Section 4.9 will be based on all enrolled patients in the enrollment phase.

2.2.1 Primary Efficacy Outcome Measure

- DFS, defined as the time from randomization to the date of occurrence of any of the following, whichever occurs first:

  First recurrence of NSCLC, as determined by the investigator after an integrated assessment of radiographic data, biopsy sample results (if available), and clinical status

  Occurrence of new primary NSCLC, as assessed by the investigator

  Death from any cause

This efficacy outcome measure will be assessed in the PD-L1 subpopulation (defined as ≥1% tumor cell [TC] expression in tumor cell membrane detected by the Ventana PD-L1 SP263 assay; hereinafter referred to as SP263 TC≥1%) within the Stage II–IIIA population, in patients with Stage II–IIIA NSCLC, and in the ITT (Stage IB-IIIA) population.

2.2.2 Secondary Efficacy Outcome Measures

- OS, defined as the time from randomization to death from any cause, in the ITT population
- DFS rates at 3 years and 5 years in the PD-L1 subpopulation (defined as SP263 TC ≥1%) within the Stage II–IIIA population, in the Stage II–IIIA population, and in the ITT population
- DFS in the PD-L1 subpopulation (defined as SP263 TC ≥50%) among patients with Stage II–IIIA NSCLC

2.2.3 Exploratory Outcome Measures

- DFS in TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3 subpopulations defined by PD-L1 SP142 IHC in both the Stage II–IIIA and the ITT populations
- DFS in the PD-L1 subpopulations defined by 22C3 tumor proportion score (TPS) ≥1% and TPS ≥50% in both the Stage II–IIIA and the ITT populations
- DFS in the PD-L1 subpopulations defined by SP263 TC ≥1% and TC ≥50% in the ITT population
- Status of exploratory biomarkers from tumor tissue specimens and blood collected before, during, or after treatment at the first evidence of radiographic disease recurrence or new primary NSCLC; these exploratory biomarkers include, but are not limited to, immune-related biomarkers (e.g., PD-L1, CD8), NSCLC-related biomarkers, and circulating tumor biomarkers (e.g., ctDNA), as defined by IHC, qRT-PCR, NGS, or other methods. DFS in these exploratory biomarker subpopulations may be assessed.

2.2.4 Pharmacokinetic Outcome Measures

- Atezolizumab maximum serum concentration (C_{max}) observed after infusion on Day 1 of Cycle 1

- Atezolizumab minimum serum concentration (C_{min}) under steady-state conditions within a dosing interval prior to the infusion on Day 1 of Cycles 2, 3, 4, 8, and 16 and at study termination

2.2.5 Safety Outcome Measures

- Incidence, nature, and severity of adverse events, serious adverse events, and adverse events of special interest graded according to the National Cancer Institutes Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0)
- Changes from baseline in vital signs, physical findings, and targeted clinical laboratory results

2.2.6 Immunogenicity Measures

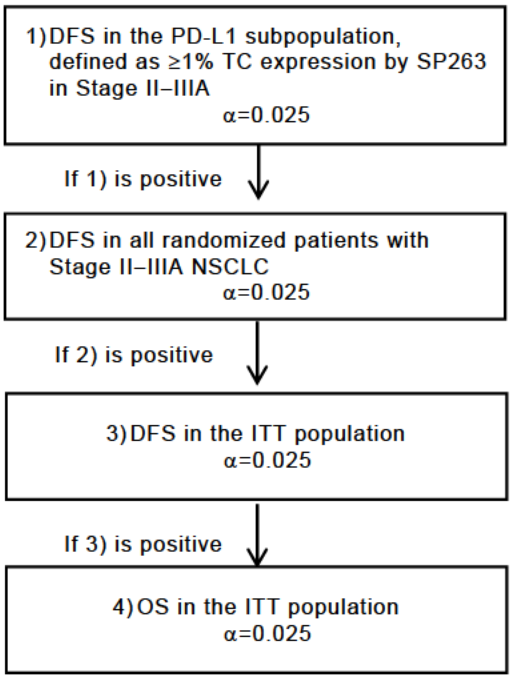
- Incidence of anti-drug antibody (ADA) response to atezolizumab and potential correlation with pharmacokinetic, safety, and efficacy parameters

2.3 DETERMINATION OF SAMPLE SIZE

Approximately 1280 patients are expected to be accrued during the enrollment phase. With an approximate 21% dropout rate during the adjuvant cisplatin-based chemotherapy, approximately 1005 patients will enter the randomization phase, including approximately 882 patients in the Stage II–IIIA population. Among the Stage II–IIIA NSCLC patients, approximately 474 patients will be in the PD-L1 subpopulation (as defined by SP263 TC≥1%).

The overall type I error rate will be controlled for the one-sided test at 0.025. The overview of the alpha control is shown in Figure 2.

Figure 2 Overview of the Alpha Control (One-Sided)



DFS=disease-free survival; ITT=intent to treat; OS=overall survival; TC=tumor cells.

Estimates of the number of events required to demonstrate efficacy with regard to DFS are based on the following assumptions:

- 1:1 randomization ratio
- One-sided significance level of 0.025 in the PD-L1 subpopulation (SP263 TC ≥1%) within the Stage II–IIIA population, the Stage II–IIIA population, and the ITT population
- For Stage II–IIIA:

  89.8% power to detect a hazard ratio (HR) of 0.65, corresponding to an improvement in median DFS from 34 months to 52 months in the PD-L1 subpopulation (SP263 TC ≥1%) within the Stage II–IIIA population

  90.7% power to detect an HR of 0.73, corresponding to an improvement in median DFS from 34 months to 46.6 months in the Stage II–IIIA population

- For ITT (i.e., Stage IB–IIIA):

  76.4% power to detect an HR of 0.78, corresponding to an improvement in median DFS from 38 months to 48.7 months in the ITT population

- One interim DFS analysis to be performed when approximately 80% of the total DFS events required for the final DFS analysis have occurred in the PD-L1 subpopulation (SP263 TC ≥1%) within the Stage II–IIIA population; the stopping

boundaries for the interim and final DFS analyses will be determined based on the Hwang-Shih-DeCani alpha spending function with the gamma parameter of −0.9 (Hwang et al. 1990)

- Dropout rate of 5% per 24 months

The estimates of the number of events required to demonstrate efficacy with regards to OS are based on the following assumptions:

- 1:1 randomization ratio
- One-sided significance level of 0.025 in the ITT population (i.e., Stage IB–IIIA)
- 77% power to detect an HR of 0.78, corresponding to an improvement in median OS from 66 months to 84.6 months in the ITT population
- Four interim OS analyses to be performed, one at the time of the DFS interim analysis, the second at the time of the final DFS analysis, and the other two when approximately 73% and 88%, respectively, of the total OS events required for the final OS analysis have occurred; the stopping boundaries for the interim and final OS analyses will be determined based on the alpha spending function with the cumulative one-sided alpha of 0.001, 0.012, 0.022, 0.024, and 0.025 in the order of analyses (DeMets and Lan 1994)
- Dropout rate of 5% per 36 months

With these assumptions, the final DFS analysis will be conducted when approximately 237 DFS events in the PD-L1 subpopulation (SP263 TC ≥1%) within the Stage II–IIIA population have been observed if the interim DFS analysis in the PD-L1 subpopulation (SP263 TC ≥1%) within the Stage II–IIIA population is not statisticially significant. Otherwise, the final DFS analysis will be conducted when approximately 459 events in the Stage II–IIIA population have been observed if the interim DFS analysis in the Stage II–IIIA population is not statisticially significant. Similarly, if the interim DFS analysis is negative in the ITT population only, the final DFS analysis will be conducted when approximately 492 events in the ITT population have been observed. This is expected to occur approximately 68 months after the first patient is randomized. More details of the minimum detectable difference in HR are specified in Table 1.

Given the sample size of 1005, the final OS analysis will be conducted when approximately 564 OS events in the Stage IB–IIIA population have occurred, which is expected at approximately 121 months after the first patient is randomized.

2.4 INTERIM AND PRIMARY ANALYSIS TIMING

2.4.1 Planned Interim Analysis for Disease-Free Survival

There will be one planned interim DFS analysis in the study. The interim DFS analysis will be conducted by an independent data coordinating center (iDCC) and reviewed by the independent Data Monitoring Committee (iDMC). Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The interim DFS analysis will be conducted when approximately 80% of the information has been observed in the PD-L1 subpopulation defined by SP263 TC ≥1% within the Stage II–IIIA population (i.e., at the date when approximately 190 DFS events occur in the PD-L1 subpopulation within the Stage II–IIIA population). This is expected to occur approximately 56 months after the first patient is randomized.

The final DFS analysis will be conducted when approximately 237 DFS events in the PD-L1 subpopulation (SP263 TC ≥1%) within the Stage II–IIIA population have been observed if the interim DFS analysis in the PD-L1 subpopulation (SP263 TC ≥1%) within the Stage II–IIIA population is not statisticially significant. Otherwise, the final DFS analysis will be conducted when approximately 459 events in the Stage II–IIIA population have been observed if the interim DFS analysis in the Stage II–IIIA population is not statisticially significant. Similarly, if the interim DFS analysis is negative in the ITT population only, the final DFS analysis will be conducted when approximately 492 events in the ITT population have been observed. This is expected to occur approximately 68 months after the first patient is randomized.

To control the type I error for DFS at a one-sided alpha of 0.025, the stopping boundaries for the interim and final DFS analyses are to be computed with use of the Hwang-Shih-DeCani alpha spending function with the gamma parameter of –0.9 as shown in Table 1. Boundaries will be adjusted based on observed numbers of DFS events, and the exact timing of this analysis will depend on the occurrence of DFS events.

Table 1 Analysis Timing and Stopping Boundaries for Disease-Free Survival

			Stopping Boundary (one-sided p-value)		
Type of Analysis	Planned Information Fraction	No. of Events (SP263 TC≥1% in Stage II–IIIA/ Stage II–IIIA/ITT)	Stage II–IIIA NSCLC PD-L1 Subpopulation with SP263 TC ≥1%	Stage II–IIIA NSCLC	ITT NSCLC
DFS interim analysis	80%	190/367/394	HR ≤ 0.738 (p ≤ 0.0181)	HR ≤ 0.803 (p ≤ 0.0181)	HR ≤ 0.810 (p ≤ 0.0181)
DFS final analysis	100%	237/459/492	HR ≤ 0.758 (p ≤ 0.0167)	HR ≤ 0.820 (p ≤ 0.0167)	HR ≤ 0.825 (p ≤ 0.0167)

HR = hazard ratio; NSCLC = non–small cell lung cancer; DFS = disease-free survival.

2.4.2 Planned Interim Analyses for Overall Survival

Four interim OS efficacy analyses are planned. The first interim OS analysis will be conducted at the time of the interim DFS analysis, which is expected to occur approximately 56 months after the first patient is randomized (if DFS is positive as per Figure 2). It is projected that approximately 254 OS events in the ITT population (i.e.,

approximately 45% of the information) will have been observed at the interim DFS analysis.

The second interim OS analysis will be conducted at the time of the final DFS analysis, which is expected to occur approximately 68 months after the first patient is randomized. It is projected that approximately 333 OS events in the ITT population (i.e., approximately 59% of the information) will have been observed at the final DFS analysis.

The third interim OS analysis will be conducted at the date when approximately 73% of the information has been observed in the ITT population (i.e., at the date when approximately 412 OS events occur for the ITT population). This is expected to occur approximately 83 months after the first patient is randomized.

The fourth interim OS analysis will be conducted at the date when approximately 88% of the information has been observed in ITT population (i.e., at the date when approximately 497 OS events occur for the ITT population. This is expected to occur approximately 102 months after the first patient is randomized,.

The final OS analysis will be conducted at the date of when approximately 564 OS events have occurred in the ITT population. This is expected to occur approximately 121 months after the first patient is randomized.

The exact timing of these OS analyses will depend on the occurrence of OS events. If a significantly smaller number of OS events ($<$ 224 events) is observed at the first OS IA, a nominal one-sided type I error of 0.00005 will be assigned to test the first OS IA; all the following OS analyses will be conducted based on the pre-specified number of events in Table 2. The stopping boundaries for the interim and final OS analyses are shown in Table 2. Boundaries will be adjusted based on observed numbers of OS events. The p-value will be used to claim crossing of the boundaries.

Table 2 Stopping Boundaries for Overall Survival in ITT (Stage IB–IIIA)

Type of Analysis	Analysis Timing (Months from FPI)	Planned Information Fraction (Number of Events)	Stopping Boundary in HR (p-Value) One-Sided α=0.025
OS first interim analysis	56	45% (254)	HR $\leq$ 0.678 ($p \leq 0.0010$)
OS second interim analysis	68	59% (333)	HR $\leq$ 0.780 ($p \leq 0.0119$)
OS third interim analysis	83	73% (412)	HR $\leq$ 0.813 ($p \leq 0.0181$)
OS fourth interim analysis	102	88% (497)	HR $\leq$ 0.809 ($p \leq 0.0093$)
OS final analysis	121	100% (564)	HR $\leq$ 0.811 ($p \leq 0.0063$)

FPI = first patient in; HR = hazard ratio; NSCLC = non–small cell lung cancer; OS = overall survival.

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). Randomization to the treatment and control arms will occur in a 1:1 ratio with use of a permuted-block randomization method. Randomization will be stratified by the following factors:

- Sex (female vs. male)
- Tumor histology (squamous vs. non-squamous)
- Extent of disease (Stage IB vs. Stage II vs. Stage IIIA)
- PD-L1 tumor expression status (TC2/3 and any IC vs. TC0/1 and IC2/3 vs. TC0/1 and IC0/1 using the SP142 IHC assay)

3.2 DATA MONITORING

An external iDMC will evaluate safety data on an ongoing basis, as well as the interim DFS analysis data. All summaries and analyses by treatment arm for the iDMC's review will be prepared by an external iDCC. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the Investigational Review Boards/Ethics Committees (IRBs/ECs). A detailed plan will be included in the iDMC Charter.

4. STATISTICAL METHODS

Unless otherwise noted, the analysis methods and plans in Section 4 will focus on patients in the randomized phase only. The analysis plan for patients in the enrollment phase will be specified in Section 4.9, and the analysis results will be reported in a standalone section of the Clinical Study Report (CSR).

4.1 ANALYSIS POPULATIONS

4.1.1 Efficacy Analysis Populations

The ITT population is defined as all randomized patients with resected Stage IB (tumors ≥4 cm)–IIIA NSCLC, whether or not the patient received the assigned treatment. Patients will be grouped by their assigned treatment at randomization by the IxRS.

The Stage II–IIIA population is defined as all randomized patients with extent of disease as either Stage II or Stage III, and is a subset of the ITT population.

The PD-L1 SP263 biomarker-evaluable population in Stage II–IIIA is defined as all randomized patients from the Stage II–IIIA population who have a valid PD-L1 SP263 measurement at baseline. Similarly, the PD-L1 SP263 biomarker-evaluable population in ITT is defined as all randomized patients from the ITT population who have a valid PD-L1 SP263 measurement at baseline.

4.1.2 Safety-Evaluable Population

The safety-evaluable population is defined as all randomized patients who received at least one dose of atezolizumab and all randomized patients who were randomized to the control arm and did not receive any dose of atezolizumab but who had at least one post-baseline safety assessment (e.g., adverse events, laboratory tests, vital signs), regardless of their assigned treatment at randomization (atezolizumab/BSC).

4.1.3 Pharmacokinetic-Evaluable Population

The pharmacokinetic-evaluable population is defined as all randomized patients who received any dose of atezolizumab and who have evaluable pharmacokinetic samples.

4.1.4 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.

4.1.5 Enrolled Population

The enrolled population is defined as all eligible patients who were enrolled in the enrollment phase, regardless if they are subsequently randomized or not.

4.1.6 Enrolled Safety-Evaluable Population

The enrolled safety-evaluable population is defined as all eligible patients who were enrolled in the enrollment phase and who received at least one dose of chemotherapy

(cisplatin, vinorelbine, docetaxel, gemcitabine, or pemetrexed), regardless of whether they are subsequently randomized or not.

4.2 ANALYSIS OF STUDY CONDUCT

Study enrollment, study treatment administration, reasons for discontinuation from study treatment, and reasons for study termination will be summarized for the PD-L1 subpopulation (SP263 TC ≥1%) within the Stage II–IIIA population, the Stage II–IIIA population, and the ITT population by treatment arm (depending on the results of the primary endpoint analyses). Major protocol deviations, including major deviations of inclusion/exclusion criteria for the randomized phase, will be reported and summarized by treatment arm for the ITT population. Duration of follow-up will be summarized by treatment arm for the ITT population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic characteristics, such as age, sex, race/ethnicity, baseline disease characteristics (e.g., ECOG performance status), medical history, concomitant medications, and cisplatin-based regimen, will be summarized by treatment arm for the PD-L1 subpopulation (SP263 TC ≥1%) within the Stage II–IIIA population, the Stage II–IIIA population, and the ITT population (depending on the results of the primary endpoint analyses).

Descriptive statistics (mean, median, standard deviation, and range) 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 the patient receiving the first dose of atezolizumab on Cycle 1, Day 1 for the atezolizumab arm or prior to the Cycle 1, Day 1 date of observation for the BSC arm in the randomized phase, unless otherwise noted.

4.4 EFFICACY ANALYSIS

To manage the small strata size with the consideration of prognostic significance, stratified analyses for DFS in the PD-L1 subpopulation defined by SP263 TC ≥1% in Stage II–IIIA NSCLC and stratified analyses for DFS in Stage II–IIIA NSCLC will use the following stratification factors at randomization: stage (II vs. IIIA), sex (female vs. male), and histology (squamous vs. non-squamous). Stratified analyses for DFS in the ITT population will use the following stratification factors at randomization: stage (IB and II combined vs. IIIA), sex (female vs. male), histology (squamous vs. non-squamous), and PD-L1 tumor expression status by SP142 IHC assay ([TC2/3 and any IC, TC0/1 and IC2/3 combined] vs. TC0/1 and IC0/1).

Stratified analyses of DFS in other PD-L1 subpopulations (e.g., SP263 TC ≥50% in Stage II–IIIA NSCLC) will use the same set of stratification factors used for the stratified analyses of DFS in the PD-L1 subpopulation defined by SP263 TC ≥1% in Stage II–IIIA NSCLC.

The set of stratification factors used in the stratified analyses of DFS for a specific analysis population (e.g., the ITT population) will be applied to all other efficacy endpoints where stratified analyses are planned for the same analysis population.

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is duration of DFS as assessed by the investigator. DFS is defined as the time from the date of randomization to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC, or death due to any cause, whichever occurs first. Data for patients who are not reported as experiencing disease recurrence, a new primary NSCLC, or death will be censored at the date of the last tumor assessment. If no post-baseline data are available, DFS will be censored at the date of randomization. If recurrence of disease or new primary NSCLC prior to randomization is documented, DFS will be censored at the date of randomization.

To control the overall level of significance at a one-sided error of 0.025, comparisons with respect to DFS between the treatment and control arm for the PD-L1 subpopulation defined by SP263 TC $\geq$1% within the Stage II–IIIA population, Stage II–IIIA population, and the ITT population will be conducted hierarchically as described in Figure 2. Treatment comparisons will be based on the stratified log-rank test.

The null and alternative hypotheses regarding DFS in each population can be phrased in terms of the DFS survival functions $S_A(t)$ in the atezolizumab arm (Arm A) and $S_B(t)$ in the control arm (Arm B), respectively:

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

The HR will be estimated with use of a stratified Cox regression model, including a two-sided 95% CI. The stratification factors used for the analysis are described in Section 4.4. The results for unstratified analysis will also be presented. Kaplan-Meier methodology will be used to estimate the median DFS for each treatment arm and the Kaplan-Meier curve will be constructed to provide a visual description of the difference between the treatment and control arms. Brookmeyer-Crowley methodology will be used to construct the two-sided 95% CI for the median DFS for each treatment arm (Brookmeyer and Crowley 1982).

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 OS Analysis

OS is defined as the time from the date of randomization to death due to any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization.

The methodology (as described in Section 4.4.1) used for DFS will be applied to OS in the ITT population. An overview of the OS testing schema is shown in Figure 2.

4.4.2.2 Disease-Free Survival 3-Year and 5-Year Landmark Analyses

The DFS rate at 3 years and at 5 years will be analyzed for the PD-L1 subpopulation (SP263 TC ≥1%) in Stage II–IIIA NSCLC, the Stage II–IIIA population, and the ITT population (depending on the results of the primary endpoint analyses). These DFS rates will be estimated by the Kaplan-Meier methodology for each treatment arm, with two-sided 95% CIs calculated using Greenwood's formula.

4.4.2.3 DFS Analysis in Additional PD-L1 Subpopulation Defined by the Anti–PD-L1 (SP263) IHC Assay

DFS in the PD-L1 subpopulation, defined by SP263 TC ≥50% in Stage II–IIIA NSCLC will be analyzed by using the same methodology in Section 4.4.1.

4.4.3 Exploratory Analyses

Unless otherwise indicated, the exploratory analyses, sensitivity analyses, and subgroup analyses will be performed in the PD-L1 subpopulation defined by SP263 TC ≥1% within the Stage II–IIIA patients, the Stage II–IIIA patients, and/or the ITT population (depending on the results of the primary endpoint analyses).

4.4.3.1 DFS and OS Rates at Landmark Timepoints

In addition to the DFS 3-year and 5-year survival rates as secondary endpoints, the DFS and OS rate at various other timepoints (every 1 year from randomization) will be estimated with use of Kaplan-Meier methodology for each treatment arm, along with two-sided 95% CIs calculated with use of Greenwood's formula for exploratory purposes.

4.4.3.2 DFS Analyses in Other PD-L1 Subpopulations

DFS in other PD-L1 subpopulations will be analyzed by using the same methodology in Section 4.4.1. These PD-L1 subpopulations include TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3 defined by SP142 in both the Stage II–IIIA and the ITT populations; the PD-L1 subpopulations defined by 22C3 TPS ≥1% and TPS ≥50% in both the Stage II–IIIA and the ITT populations; and the PD-L1 subpopulations defined by SP263 TC ≥1% and TC ≥50% in the ITT population.

4.4.3.3 OS Analyses in Other Subpopulations

OS in other subpopulations will be analyzed by using the same methodology in Section 4.4.1. These subpopulations will include the PD-L1 subpopulation (defined by SP263 TC ≥1% in Stage II–IIIA NSCLC), the Stage II–IIIA population, and the PD-L1 subpopulations defined by SP263 TC ≥1% and TC ≥50% in the ITT population.

4.4.3.4 Exploratory Analyses of Biomarkers

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with disease status and/or study drug response, including

efficacy and/or adverse events. The biomarkers include but are not limited to ctDNA, PD-L1, and CD8, as defined by IHC, qRT-PCR, or other methods.

Details of these analyses will be described in Biomarker Analysis Plan(s) (BAP[s]). These exploratory analyses will not be included in the CSR for this study.

4.4.4 Sensitivity Analyses

4.4.4.1 Loss to Follow-Up on DFS

The impact of loss to follow-up on DFS will be assessed depending on the number of patients who are lost to follow-up. If >5% of patients are lost to follow-up for DFS in either treatment arm, a sensitivity analysis ("worse-case" analysis) will be performed in which patients who are lost to follow-up will be considered to have recurrent disease at the date of the last tumor assessment.

4.4.4.2 Missed Visits for DFS

To evaluate the impact of missed visits, sensitivity analyses with a different censoring rule will be performed for the primary endpoint of DFS. Data for patients with a DFS event who missed two or more scheduled assessments immediately prior to the DFS event will be censored at the last date with adequate radiologic assessment prior to the missed visits.

4.4.5 Subgroup Analyses

The consistency of DFS and OS results in subgroups defined by demographic, baseline disease characteristics, and stratification factors will be examined. Summaries of DFS, including the unstratified HR estimated from a Cox proportional hazards model and Kaplan-Meier estimates of median DFS and median OS, will be produced separately for each level of the subgroup and displayed in a forest plot (Lewis and Clarke 2001). Kaplan-Meier plots of DFS and OS will also be produced for selected subgroups.

The subgroups to be considered include but are not limited to the following:

- Demographics (e.g., age at randomization, sex, race, ethnicity)
- Baseline disease characteristics (e.g., tumor histology, extent of disease [stage], ECOG performance status, regional lymph node positive, smoking history, chemotherapy regimen before randomization, EGFR mutation status, ALK mutation status, EGFR/ALK mutation status)
- PD-L1 expression level by SP263 (e.g., TC ≥50%, TC<1%)
- PD-L1 expression level by SP142 (e.g., TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3, TC0 and IC0)

4.5 PHARMACOKINETIC ANALYSES

Atezolizumab serum concentration data (C_{min} and C_{max}) 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

Unless otherwise specified, safety analyses described below will be conducted for the safety-evaluable population.

4.6.1 Exposure of Study Medication

Study drug exposure will be summarized to include treatment duration, number of doses, and dose intensity using descriptive statistics for the atezolizumab arm only.

4.6.2 Adverse Events

Verbatim description of adverse events will be mapped to the medical dictionary for regulatory activities (MedDRA) thesaurus terms and graded according to NCI CTCAE v4.0. Treatment-emergent adverse events (defined as events occurring on or after the first dose of atezolizumab, or, for patients in the BSC arm, after the date of randomization) will be summarized by mapped term, appropriate thesaurus level, NCI CTCAE grade, and treatment arm. In addition, common adverse events (defined as adverse events that occur in at least 10% of patients), serious adverse events, severe adverse events (Grades 3, 4, or 5), adverse events of special interest, immune-mediated adverse events, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity.

Summaries of treatment-related serious adverse events, treatment-related adverse events of special interest, and all listings of adverse events will include all events that occur during or after the first study drug treatment. Safety summaries of all other adverse events will include treatment-emergent adverse events up to the clinical cutoff date.

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

4.6.3 Laboratory Data

Laboratory data will be classified according to NCI CTCAE v4.0. Laboratory data with values outside the normal ranges will be summarized. In addition, selected laboratory data will be summarized by treatment arm and grade.

4.6.4 Vital Signs

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

4.7 ANTI-DRUG ANTIBODY

Serum levels and incidence of ADAs against atezolizumab will be summarized. The analyses of demographics and baseline characteristics, pharmacokinetics, key efficacy, and safety by ADA status may be conducted to explore the potential impact of immunogenicity. ADA results will be summarized and listed by patient for patients in the ADA-evaluable population only.

4.8 MISSING DATA

Please refer to Sections 4.4.1 and 4.4.2 for methods of handling missing data for the primary and secondary efficacy endpoints.

4.9 ENROLLED POPULATION

Study enrollment, demographics and baseline characteristics, major protocol deviations (including major deviations of inclusion/exclusion criteria for enrollment phase), study treatment administration, reasons for discontinuation from study treatment, and reasons for study termination during enrollment phase will be summarized for the enrolled population.

Study drug exposure of chemotherapy during enrollment phase will be summarized to include treatment duration, number of doses, and dose intensity using descriptive statistics for the enrolled safety-evaluable population.

Adverse events, serious adverse events, and death (cause of death) during enrollment phase will be summarized for the enrolledsafety-evaluable population. Listings of adverse events will be included.

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Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, OPEN–LABEL, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (ANTI–PD–L1 ANTIBODY) COMPARED WITH BEST SUPPORTIVE CARE FOLLOWING ADJUVANT CISPLATIN-BASED CHEMOTHERAPY IN PATIENTS WITH COMPLETELY RESECTED STAGE IB–IIIA NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29527
VERSION NUMBER:	8
EUDRACT NUMBER:	2014–003205–15
IND NUMBER:	117296
NCT NUMBER:	NCT02486718
TEST PRODUCT:	Atezolizumab (MPDL3280A; RO5541267)
PHASE:	III
INDICATION:	Non–small cell lung cancer
SPONSOR:	F. Hoffmann–La Roche Ltd

Objectives

The following efficacy objectives will be evaluated in patients with Stage IB–IIIA non–small cell lung cancer (NSCLC).

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective of the study is as follows:

- To evaluate the efficacy of atezolizumab monotherapy treatment compared with best supportive care (BSC) as measured by disease-free survival (DFS) as assessed by the investigator in the PD-L1 *subpopulation* (defined *as ≥1% tumor-cell (TC) expression* by the *SP263* immunohistochemistry [IHC] assay) within the Stage II–IIIA population; in all randomized *patients with* Stage II–IIIA *NSCLC*; and in the intent-to-treat (ITT) population

Secondary Efficacy Objectives

The secondary efficacy objectives of the study are to evaluate the efficacy of atezolizumab monotherapy treatment compared with BSC on the basis of the following outcome measures:

- Overall survival (OS) in the ITT population
- 3-year and 5-year DFS rates in the PD-L1 *subpopulation* (defined *as ≥1% TC expression* by the *SP263* IHC assay) within the Stage II–IIIA population, in all randomized patients with Stage II–IIIA NSCLC, and in the ITT population
- DFS *in* the PD-L1 *subpopulation* (defined *as ≥50% TC expression* by the SP263 IHC assay) in *patients with* Stage II–IIIA *NSCLC*

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab treatment after up to four cycles of cisplatin-based chemotherapy in the adjuvant setting
- To evaluate the incidence and titers of anti-therapeutic antibodies (ATAs) against atezolizumab in the adjuvant setting and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is as follows:

- To characterize the pharmacokinetics of atezolizumab treatment in the adjuvant setting

Exploratory Objectives

The exploratory objectives for this study are as follows:

- *To evaluate DFS in TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3 subpopulations defined by PD-L1 SP142 IHC in both the Stage II–IIIA and the ITT populations*
- *To evaluate DFS in the PD-L1 subpopulations defined by 22C3 TPS ≥1% and TPS ≥50% in both the Stage II–IIIA and the ITT populations*
- *To evaluate DFS in the PD-L1 subpopulations defined by SP263 TC ≥1% and TC ≥50% in the ITT population*
- To evaluate the relationship between tumor and blood-based biomarkers (including but not limited to PD-L1, PD-1, somatic mutations, and others), as defined by immunohistochemistry (IHC) or quantitative reverse transcriptase–polymerase chain reaction, next generation sequencing, and/or other methods and measures of efficacy
- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to atezolizumab in the adjuvant treatment setting
- To evaluate biomarkers at the time of apparent recurrence of primary disease (i.e., NSCLC primary disease recurrence, occurrence of new primary NSCLCs) and to distinguish any immunomodulatory activity of atezolizumab (i.e., tumor-immune infiltration) in patients with confirmed recurrence of disease in patients assigned to atezolizumab

Study Design

Description of Study

This study is a Phase III, global, multicenter, open-label, randomized, study (IMpower010) comparing the efficacy and safety of atezolizumab versus BSC in patients with Stage IB–Stage IIIA NSCLC following resection and adjuvant chemotherapy, as assessed by DFS per the investigator and OS. The study consists of two phases: an enrollment phase and randomized phase.

In the enrollment phase, patients who have recently undergone complete resection of their NSCLC will be screened, and eligible patients will be enrolled to receive one of four regimens of cisplatin-based chemotherapy (cisplatin plus vinorelbine, docetaxel, gemcitabine, or pemetrexed; based on investigator choice). The randomized phase will start after patients have completed their cisplatin-based chemotherapy and are still considered eligible to proceed with randomization.

Male and female patients age ≥ 18 years with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who have a complete surgical resection of histologically or cytologically confirmed Stage IB (tumors ≥ 4 cm)–IIIA NSCLC are potentially eligible. At screening, tumor specimens from each potentially eligible patient will be tested for PD-L1 expression by a central laboratory with use of an IHC assay, but patients will be enrolled in the study regardless of the PD-L1 status. Patients who fulfill the eligibility criteria will receive adjuvant cisplatin-based chemotherapy in the enrollment phase of the study. Patients will

receive up to four cycles of cisplatin-based chemotherapy unless unacceptable toxicity, disease relapse, or patient's decision to discontinue occur.

Patients who experience disease recurrence of their primary disease at any time up to completion of chemotherapy will not be eligible for the randomized phase of the study. Additionally, patients must fulfill the eligibility criteria of the randomized phase prior to randomization.

Eligible patients will go on to be randomized in a 1:1 ratio to receive either atezolizumab (Arm A) or BSC (Arm B).

In Arm A, atezolizumab will be administered intravenously on Day 1 of each 21-day cycle for a total of 16 cycles. Patients randomized to Arm B will be continually followed starting on Day 1 of each 21-day cycle. To ensure the same frequency of study assessments between the treatment arms, including assessments for disease recurrence and safety, patients in Arm B will be required to undergo medical contacts every 3 weeks for assessments during the first year, which will consist of formal clinic visits alternating with clinical contacts (either via telephone call or formal outpatient clinic visit) for symptom and adverse event assessment. No crossover will be allowed from Arm B to Arm A.

All patients in the randomized phase will undergo scheduled tumor assessments at baseline and every 4 months starting at Cycle 1, Day 1 in the first year and every 6 months in the second year by computed tomography (CT) following randomization. Patients who have not experienced recurrence of disease will undergo tumor assessments every 6 months by CT and X-ray during Years 3–5 post-randomization (starting with CT scan, alternating with X-ray), and annually thereafter by X-ray. In the absence of disease recurrence, tumor assessments should continue regardless of whether patients start new anti-cancer therapy, until disease recurrence, withdrawal of consent, death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. Patients from both treatment arms will undergo a mandatory tumor biopsy sample collection, unless not clinically feasible as assessed by investigators, at the first evidence of radiographic disease recurrence. These data will 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 will be analyzed to evaluate the association between changes in tumor tissue and clinical outcome as well as to understand further the potential mechanisms of resistance and recurrence to atezolizumab compared with such mechanisms after treatment with chemotherapy alone. This exploratory biomarker evaluation will not be used for any treatment-related decisions. Tumor assessments will be performed by the investigator.

Safety assessments will include the incidence, nature, and severity of adverse events; serious adverse events; adverse events of special interest; and laboratory abnormalities, graded per National Cancer Institutes Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v4.0). Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry.

Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of ATAs to atezolizumab. Patient samples, including archival and fresh tumor tissues, as well as serum and plasma and whole blood, will be collected for future exploratory biomarker assessments.

All patients in the randomized phase will undergo safety, tolerability, and exploratory assessments on Day 1 of each 21-day cycle until recurrence of disease during the first 48 weeks, and patients who have experienced recurrence of disease will undergo these assessments within 30 days after the last dose of atezolizumab is administered

Number of Patients

Approximately 1280 patients are expected to be accrued in the enrollment phase to meet the goal of approximately $1005\ patients$ total in the randomized phase, under the assumption that a dropout rate of approximately 21% is expected during adjuvant cisplatin–based chemotherapy treatment.

Target Population

Inclusion Criteria

Inclusion Criteria for Enrollment Phase

Patients must meet all of the following criteria to be eligible to enter the enrollment phase and receive cisplatin-based chemotherapy regimen in this study:

- A representative formalin-fixed paraffin-embedded (FFPE) tumor specimen in paraffin block (preferred) or 15 (or more) unstained, freshly cut, serial sections (on slides) from an FFPE resected tumor specimen is required for participation in this study. This specimen must be accompanied by the associated pathology report.
- Signed Informed Consent Form
- Age $\geq$ 18 years
- ECOG performance status of 0 or 1
- Histological or cytological diagnosis of Stage IB (tumors $\geq$ 4 cm)–IIIA (T2–3 N0, T1–3 N1, T1-3 N2, T4 N0-1) NSCLC (per the Union Internationale Contre le Cancer/American Joint Committee on Cancer [UICC/AJCC] staging system, 7th edition)
- Patients must have had complete resection of NSCLC 4–12 weeks ($\geq$ 28 days and $\leq$ 84 days) prior to enrollment and must be adequately recovered from surgery

  Accepted types of resection include any of the following: lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy.

  Resection by segmentectomy or wedge resection is not allowed.
- If mediastinoscopy was not performed preoperatively, it is expected that, at a minimum, mediastinal lymph node systematic sampling will have occurred, though complete mediastinal lymph node dissection (MLND) is preferred. Systematic sampling is defined as removal of at least one representative lymph node at specified levels. MLND entails resection of all lymph nodes at those same levels. For a right thoracotomy, sampling or MLND is required at levels 4 and 7 and for a left thoracotomy, levels 5 and/or 6 and 7. **Exceptions will be granted for the following situations:**

  If there is clear documentation in the operative report or in a separately submitted addendum by the surgeon of exploration of the required lymph node areas, the patient will be considered eligible if no lymph nodes are found in those areas.

  If patients have documented N2 disease in one level (per the UICC/AJCC staging system, 7th edition), not all levels need to be sampled.

  If the preoperative staging imaging results (contrast CT and PET scans) do not suggest evidence of disease in the mediastinum, the patient will be considered eligible if N2 nodal sampling is not performed per surgeon's decision.
- Eligible to receive a cisplatin-based chemotherapy regimen
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to enrollment:
  - ANC $\geq$ 1500 cells/μL
  - Platelet count $\geq$ 100,000 cells/μL
  - Prothrombin time/INR $\leq$ 1.5, or, if patient is receiving therapeutic anticoagulation, prothrombin time/INR $<$ 3.0
  - aPTT $\leq$ institutional upper limit of normal (ULN) OR, if patient is receiving therapeutic anticoagulation, aPTT must be $<$ 1.5 $\times$ ULN
  - Total bilirubin $\leq$ 1.25 $\times$ ULN

    Patients with known Gilbert disease who have serum bilirubin $\leq$ 3 $\times$ ULN may be enrolled.

- SGOT (AST) $\leq 2.5 \times$ ULN
- SGPT (ALT) $\leq 2.5 \times$ ULN
- Calculated creatinine clearance (CRCL) $\geq$ 60 mL/min, with use of the institutional guidelines or standard Cockcroft and Gault formula (1976)

- For women of childbearing potential and men with partners of childbearing potential, agreement (by patient and/or partner) to use a highly effective form(s) of contraception during study treatment that results in a low failure rate of $< 1\%$ per year when used consistently and correctly. Women and men should continue contraceptive use for 6 months after the last dose of cisplatin-based chemotherapy (cisplatin plus vinorelbine, docetaxel, gemcitabine, or pemetrexed). Women treated with atezolizumab should continue contraception use for 5 months after the last dose. Women must refrain from donating eggs during this same period.

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

Inclusion Criteria for Randomized Phase

Patients must meet all of the following criteria to be eligible to be randomized to receive either atezolizumab or BSC after completion of the enrollment phase and up to four cycles of cisplatin-based chemotherapy:

- Adequate hematologic and end-organ function defined by the following laboratory results obtained within 14 days prior to randomization:
  - ANC $\geq$ 1500 cells/μL (without granulocyte colony-stimulating factor support)
  - Lymphocyte count $\geq$ 500 cells/μL
  - Platelet count $\geq$ 100,000 cells/μL
  - Hemoglobin ≥ 9.0 g/dL

    Patients may be transfused to meet this criterion.
  - INR or aPTT $\leq 1.5 \times$ ULN

    This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.
  - AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ ULN
  - Serum bilirubin $\leq 1.25 \times$ ULN

    Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled.
  - Calculated CRCL ≥ 30 mL/min

    The CRCL is calculated by institutional guidelines or by the method of Cockcroft and Gault formula (1976)

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

Exclusion Criteria

Exclusion Criteria for Enrollment Phase

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

- Illness or condition that may interfere with a patient's capacity to understand, follow, and/or comply with study procedures
- Pregnant and lactating women
- Treatment with prior systemic chemotherapy, with the following exceptions:

  Chemotherapy for early stage of malignancy with curative intent, provided that the last dose received was more than 5 years prior to enrollment, may be allowed upon approval by the Medical Monitor.

  Low-dose chemotherapy for non-malignant conditions may be allowed upon approval by the Medical Monitor.
- Hormonal cancer therapy or radiation therapy as prior cancer treatment within 5 years before enrollment

  Prior surgery, biologic therapy, hormonal therapy, or radiation therapy for a malignancy over 5 years prior to enrollment that is now considered cured is acceptable.
- Treatment with any other investigational agent with therapeutic intent within 28 days prior to enrollment
- A hearing loss (measured by audiometry) of 25 dB at two contiguous frequencies (audiometry will only be required for patients who have suspected or definitive hearing loss)
- Known sensitivity to any component of the chemotherapy regimen the patient will be assigned to, or to mannitol
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti–PD-1, and anti–PD-L1 therapeutic antibodies

  Patients who have had prior anti–CTLA-4 treatment may be enrolled, provided the following requirements are met:

  Last dose of anti–CTLA-4 at least 6 weeks prior to randomization

  No history of severe immune-mediated adverse effects from anti–CTLA-4 (NCI CTCAE Grades 3 and 4)
- Malignancies other than NSCLC within 5 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death (e.g., expected 5-year OS > 90%) treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.

Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen are eligible for this study.

Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., no psoriatic arthritis) are permitted provided that they meet the following conditions:

Rash must cover less than 10% of body surface area

Disease is well controlled at baseline and only requiring low potency topical steroids

No acute exacerbations of underlying condition within the last 12 months requiring treatment with either PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors or high potency or oral steroids.

- Positive test for HIV

  All patients will be tested for HIV prior to the inclusion into the study, and patients who are HIV-positive will be excluded from the clinical study.

- Patients with active hepatitis B (chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as the presence of hepatitis B core (HBc) antibody and absence of HBsAg) are eligible only if they are negative for HBV DNA. HBV DNA must be obtained in these patients prior to enrollment.

  Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

- Active tuberculosis
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within the previous 3 months, unstable arrhythmias, or unstable angina

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, 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.

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

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

- Prior allogeneic bone marrow transplantation or solid organ transplant
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- Known tumor PD-L1 expression status as determined by an IHC assay from other clinical studies (e.g., patients whose PD-L1 expression status was determined during screening for entry into a study with anti–PD-1 or anti–PD-L1 antibodies but were not eligible are excluded)

<u>Specific Exclusions for Pemetrexed Treatment</u>

- Patients with squamous cell histology

Exclusion Criteria for Randomized Phase

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

- Signs or symptoms of infection within 14 days prior to randomization (severe infection within 28 days prior to randomization), including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received therapeutic oral or IV antibiotics within 14 days prior to randomization

  Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.
- Major surgical procedure within 28 days prior to randomization or anticipation of need for a major surgical procedure during the course of the study
- Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation that such a live attenuated vaccine will be required during the study
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or interleukin-2) within 4 weeks or 5 drug-elimination half-lives of the drug, whichever is longer, prior to randomization

  Prior treatment with cancer vaccines is allowed
- Treatment with systemic corticosteroids or other immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 14 days prior to randomization

  Patients who have received acute, low-dose (≤10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be randomized in the study.

  The use of corticosteroids (≤10 mg oral prednisone or equivalent) for chronic obstructive pulmonary disease; mineralocorticoids (e.g., fludrocortisone), for patients with orthostatic hypotension or low dose supplemental corticosteroids for adrenocortical insufficiency is allowed

Length of Study

The DFS final analysis will be conducted when approximately *237* DFS events in the *PD-L1 subpopulation (defined by SP263 TC≥1%) within the* Stage II–IIIA population have been observed. This is expected to occur approximately *68 months* after the first patient is randomized. *This number of events corresponds* to a minimum detectable difference in HR of approximately 0.*758 in the PD-L1 subpopulation within the Stage II–IIIA population.*

Given the sample size of *1005*, *the final OS analysis will be conducted when* approximately *564* OS events in the all randomized Stage IB–IIIA population *have occurred*, which is expected at approximately *121 months* after the first patient is randomized.

End of Study

The end of the study is defined as when approximately *564* OS events *(the required number of deaths for the final OS analysis)* have occurred in the ITT population. Additionally, the Sponsor may decide to terminate the study at any time.

Outcome Measures

Efficacy Outcome Measures

Primary Efficacy Outcome Measure

The primary efficacy outcome measure for this study is as follows:

- DFS, defined as the time from randomization to the date of occurrence of any of the following, whichever occurs first:
  - First recurrence of NSCLC, as determined by the investigator after an integrated assessment of radiographic data, biopsy sample results (if available), and clinical status
  - Occurrence of new primary NSCLC, as assessed by the investigator
  - Death from any cause

This efficacy outcome measure will be assessed in *the* PD-L1 *subpopulation* (defined *as ≥1% TC expression* by the *SP263* IHC assay) within the Stage II-IIIA population, in all randomized patients *with* Stage II-IIIA NSCLC, and in the ITT population.

Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- OS, defined as the time from randomization to death from any cause, in the ITT population
- DFS rates at 3 years and 5 years in the PD-L1 *subpopulation* (defined *as ≥1% TC expression* by the *SP263* IHC assay)*, in the* Stage II–IIIA *population (i.e., all randomized patients with Stage II–IIIA NSCLC)* and *in* the ITT *population*
- DFS in the PD-L1 *subpopulation,* defined *as TC ≥50% by the SP263 IHC assay within patients with* Stage II–IIIA *NSCLC*

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events, serious adverse events, and adverse events of special interest graded according to the NCI CTCAE v4.0
- Changes from baseline in vital signs, physical findings, and targeted clinical laboratory results
- Incidence of ATA response to atezolizumab and potential correlation with PK, safety, and efficacy parameters

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Atezolizumab maximum serum concentration (C_{max}) observed after infusion on Day 1 of Cycle 1
- Atezolizumab minimum serum concentration under steady-state conditions within a dosing interval (C_{min}) prior to the infusion on Day 1 of Cycles 2, 3, 4, 8, and 16 and at study termination

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- *DFS in TC3 or IC3, TC2/3 or IC2/3, TC1/2/3 or IC1/2/3 subpopulations defined by PD-L1 SP142 IHC in both the Stage II-IIIA and the ITT populations*
- *DFS in the PD-L1 subpopulations defined by 22C3 TPS≥1% and TPS≥50% in both the Stage II-IIIA and the ITT populations*
- *DFS in the PD-L1 subpopulations defined by SP263 TC ≥1% and TC ≥50% in the ITT population*
- Status of PD-L1–, immune-, and NSCLC-related and other exploratory biomarkers in tumor tissues, and blood collected before, during, or after treatment with atezolizumab or at first evidence of radiographic disease recurrence or confirmation of new primary NSCLC

- Exploratory biomarkers in biopsy specimens and blood collected at the first evidence of radiographic disease recurrence or confirmation of new primary NSCLC

Investigational Medicinal Product

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

Statistical Methods

Efficacy analyses will be performed on *randomized patients within* one or more populations, *including PD-L1 subpopulations of patients with Stage II-IIIA NSCLC, all randomized patients with Stage II-IIIA NSCLC,* and *the ITT population,* with patients grouped according to the treatment assigned at randomization, regardless of whether they received any assigned study treatment.

Safety analyses will be performed on all randomized patients who received any amount of study treatment, with patients allocated by whether any amount of atezolizumab treatment was received.

Primary Analysis

The primary efficacy endpoint is duration of DFS as assessed by the investigator. DFS is defined as the time from the date of randomization to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC or death due to any cause, whichever occurs first. Data for patients who are not reported as experiencing disease recurrence, a new primary NSCLC, or death will be censored at the date of the last tumor assessment. If no post-baseline data are available, DFS will be censored at the date of randomization plus 1 day.

To control the overall level of significance at a one-sided error of 0.025, comparisons with respect to DFS between the treatment and control arm *for the PD-L1 subpopulation defined by SP263 TC≥1% within the Stage II–IIIA population, the randomized Stage II–IIIA population,* and the ITT population, will be conducted hierarchically.

The null and alternative hypotheses regarding DFS in each population can be phrased in terms of the DFS survival functions $S_A(t)$ in the atezolizumab arm (Arm A) and $S_B(t)$ in the control arm (Arm B), respectively:

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

The HR will be estimated with use of a stratified Cox regression model, including two-sided 95% CIs. The *stratification factors used for the analysis are described in the protocol.* The unstratified HR will also be presented. Kaplan-Meier methodology will be used to estimate the median DFS for each treatment arm and the Kaplan-Meier curve will be constructed to provide a visual description of the difference between the treatment and control arms. Brookmeyer-Crowley methodology will be used to construct the *two-sided* 95% CI for the median DFS for each treatment arm.

Determination of Sample Size

Approximately 1280 patients are expected to be accrued *during the enrollment phase. With an approximate 21%* dropout rate during adjuvant cisplatin-based chemotherapy, approximately *1005 patients* will enter the randomization phase, including *approximately 882 patients* in the Stage II-IIIA population, and within Stage II-IIIA NSCLC patients, approximately *474 patients* in the *PD-L1 subpopulation (≥1% TC expression) defined by the SP263 IHC assay.*

Emerging data from atezolizumab first-line NSCLC Phase III Study GO29431 (IMpower110) have observed clinical benefit with atezolizumab monotherapy in PD-L1 TC-defined subgroups. The TC-based assay SP263 appeared to capture a broader patient population with similar efficacy as compared to SP142. These findings are consistent with results observed in other PD-L1/PD-1 studies. With these data external to Study GO29431 and evolving biomarker landscape, the primary analysis of DFS in the PD-L1 subgroups (TC2/3 or IC2/3, TC1/2/3 or IC1/2/3) defined by SP142 will be replaced with DFS in the PD-L1 subgroup (≥1% TC expression) defined by SP263.

The overall type I error rate will be controlled for the one-sided test at 0.025:

The estimates of the number of events required to demonstrate efficacy with regard to DFS are based on the following assumptions:

- *1:1 randomization ratio*
- One-sided significance level of 0.025 in the *PD-L1 subpopulation defined as patients with SP263 TC ≥1% Stage II-IIIA NSCLC,* the randomized Stage II–IIIA population*, and the ITT population*
- For Stage II–IIIA:

  *89.*8% power to detect an HR of 0.*65*, corresponding to an improvement in median DFS from *34 months to 52 months in the PD-L1 subpopulation defined by SP263 TC ≥1% within the Stage II–IIIA population*

  90.7% power to detect an HR of 0.73, corresponding to an improvement in median DFS from 34 months to 46.6 months in the all-randomized Stage II–IIIA population
- For Stage IB–IIIA:

  76.4% power to detect an HR of 0.*78*, corresponding to an improvement in median DFS from *38* months to *48.7* months in the ITT population
- One DFS interim analysis to be performed when approximately *80*% of the total DFS events in the primary efficacy analysis populations required for the primary analysis have occurred. The *stopping boundaries for DFS interim and final analyses* will be determined based on the *Hwang-Shih-DeCani alpha spending function with the gamma parameter of –0.9*.
- Dropout rate of 5% per 24 months

The estimates of the number of events required to demonstrate efficacy with regard to OS are based on the following assumptions:

- *1:1 randomization ratio*
- One-sided significance level of 0.025 in the *ITT population (i.e., Stage IB-IIIA)*
- *77*% power to detect an HR of 0.78, corresponding to an improvement in median OS from 66 months to *84.6* months in the ITT population
- Four interim OS analyses to be performed, one at the time of the DFS interim analysis, the second one at the time of DFS final analysis, and the other two when approximately *73% and 88%* of the total OS events required for the final analysis have occurred, respectively. *The stopping boundaries for OS interim and final analyses will be determined based on the alpha spending function with the cumulative one-sided alpha of 0.001, 0.012, 0.022, 0.024, and 0.025 in the order of analyses*.
- Dropout rate of 5% per 36 months

With these assumptions, the DFS final analysis will be conducted when approximately *237* DFS events in the *PD-L1 subpopulation (defined by SP263 TC≥1%) within the* Stage II–IIIA population have been observed. This is expected to occur approximately *68 months* after the first patient is randomized. *This number* of events *corresponds* to a minimum detectable difference in HR of approximately 0.*758 in the PD-L1 subpopulation within the Stage II–IIIA population.*

Given the sample size of *1005*, *the final OS analysis will be conducted when* approximately *564* OS events in the all randomized Stage IB–IIIA population *have occurred*, which is expected at approximately *121 months* after the first patient is randomized.

Interim Analyses

An external independent Data Monitoring Committee (iDMC) will evaluate safety data on an ongoing basis and *will* also *review* the interim *analysis of* DFS data. All summaries and analyses by treatment arm for the iDMC's review will be prepared by an external independent data coordinating center (iDCC). Members of the iDMC will be external to the Sponsor and will

follow a charter that outlines their roles and responsibilities. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRBs/ECs. A detailed plan will be included in the iDMC Charter.

There will be one planned interim analysis for DFS in the study. To ensure the study continues to meet the highest standards of integrity, the interim analysis of DFS will be conducted by an iDCC and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

This DFS interim analysis will be conducted when approximately *80%* of the information has been observed in the *PD-L1 subpopulation defined by SP263 TC ≥1% within the* Stage II–IIIA *population* (i.e., at the *date* when approximately *190* DFS events occur in the *PD-L1 subpopulation within the* Stage II–IIIA population). This is expected to occur approximately *56 months* after the first patient is randomized; however, the exact timing of this analysis will depend on the actual number and the timing of DFS events.

The final DFS analysis will be conducted at the *date* when approximately *237* DFS events occur in the *PD-L1* subpopulation *within* the Stage II–IIA population. This is expected to occur approximately *68* months after the first patient is randomized; however, the exact timing of this analysis will depend on the actual number and timing of DFS events.

Four interim efficacy analyses of OS are planned. The first OS interim analysis will be conducted at the time of the DFS interim analysis (if DFS is positive). It is projected that approximately *254* OS events in the ITT population *(i.e., approximately 45% of the information)* will have been observed at the DFS interim analysis, but the exact timing of this analysis *may* depend on the actual number and timing of DFS events.

The second interim OS analysis will be conducted at the time of the final DFS analysis. It is projected that approximately *333* OS events in *the ITT population (i.e., approximately 59% of the information)* will have been observed at the final DFS analysis, but the exact timing of this analysis *may* depend on the actual number and timing of DFS events.

The third interim OS analysis will be conducted at the date when approximately *73%* of the information has been observed in the ITT population (i.e., at the date when approximately *412* OS events occur for *the ITT population*). This is expected to occur approximately 83 months after the first patient is randomized.

The fourth interim OS analysis will be conducted at the date when approximately *88%* of the information has been observed in ITT population (i.e., at the date when approximately *497* OS events occur for *the ITT population*. This is expected to occur approximately 102 months after the first patient is randomized, but the exact timing of this analysis *may* depend on the actual number and timing of OS events.

The final OS analysis will be conducted at the date of when approximately *564* OS events have occurred in *the ITT population*. This is expected to occur approximately *121 months* after the first patient is randomized, but the exact timing of this analysis *may* depend on the actual number and timing of OS events.

Appendix 2
Schedule of Assessments for Enrollment Phase (Cisplatin-Based Chemotherapy Administration)

Study Procedure	Screening	Day 1 of Cycles 1–4 (±3 days) [a]	Day 8 of Cycles 1–4 (±1 day)	Chemotherapy Discontinuation (<30 days after last treatment) [b]
Informed consent [c]	x [c]			
Biomarker samples [d]	x	x		
Demographic information	x			
Medical history	x			
Concurrent medications	x	x		
Serum pregnancy test (women of childbearing potential ONLY) [e]	x [c]			
Physical examination and ECOG performance status	x [c]	x		
Weight, blood pressure	x [c]	x		x
Height	x [c]			
12-lead ECG [f]	x [c]			
Serum chemistries [g]	x [c]	x [h]		x
HIV, HBV, HCV serology [i]	x			
CBC [j]	x [c]	x [h]	x	x
INR, aPTT [k]	x [c]			
Chest X-ray	x [c]			

Appendix 2 Schedule of Assessments for Enrollment Phase (Cisplatin-Based Chemotherapy Administration) (cont.)

Study Procedure	Screening	Day 1 of Cycles 1–4 (±3 days) [a]	Day 8 of Cycles 1–4 (±1 day)	Chemotherapy Discontinuation (<30 days after last treatment) [b]
Tumor assessment [l]	x [c]			x
Archival/screening FFPE tumor tissue specimen or 15 unstained slides [m]	x			
Pathology report [n]	x [m]			
Toxicity assessment for chemotherapy-related serious adverse events [o]		x		x
Adverse events		x	x	x

CRCL = creatinine clearance; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin embedded; HBV = hepatitis B virus; HCV = hepatitis C virus; IV = intravenous; MRI = magnetic resonance imaging; PD-L1 = programmed death–ligand 1; RCR = Roche Clinical Repository.

[a] Patients will receive their first dose of chemotherapy the day of enrollment, if possible. If this is not possible, the first dose should occur no later than 5 days after enrollment. Screening assessments performed ≤96 hours before Cycle 1, Day 1 are not required to be repeated for Cycle 1, Day 1. In addition, ECOG performance status, limited physical examination, and local laboratory tests may be performed ≤96 hours before Day 1 of each cycle as specified in Section 4.6.2.

[b] This visit could be used as the screening visit for randomized phase if it is within the screening window. The visit at which the decision is made to discontinue treatment (e.g., after completion of four cycles or when disease recurrence or unacceptable toxicity is determined or confirmed) may be considered as the treatment discontinuation visit.

[c] Written informed consent is required for performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry (except where otherwise specified) may be used for screening assessments, rather than repeating such tests. Screening evaluations that should be completed no earlier than 14 days prior to enrollment include: CBC with differential and platelet count, serum chemistries, physical examination, height, weight, medical history, concurrent medications, ECG, INR, aPTT, pathology report, serum pregnancy test, and toxicity assessment for chemotherapy-related serious adverse events. Chest X-ray and tumor assessment should be completed no earlier than 28 days prior to enrollment. Screening blood pressure must be done within 28 days of enrollment and must be <150/90 mmHg. Complete and limited physical examinations are defined in Section 4.5.3.

Appendix 2 Schedule of Assessments for Enrollment Phase (Cisplatin-Based Chemotherapy Administration) (cont.)

[d] Plasma and serum for biomarkers will be collected only from enrolled patients prior to pre-dose on Day 1 of Cycle 1 cisplatin-based chemotherapy administration. Whole blood will be collected at screening.

[e] 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.

[f] ECG should be obtained within 14 days before enrollment if clinically indicated or if pre-operative test results showed abnormalities. If pre-operative ECG was normal and there is no indication of a change in cardiac condition a repeat ECG within 14 days is not mandatory. Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[g] To include, at a minimum, sodium, potassium, chloride, BUN or urea, creatinine, AST (SGOT) and/or ALT (SGPT), total bilirubin, alkaline phosphatase.

[h] Tests should be obtained within 24 hours prior to day of treatment with results known prior to day of treatment. Laboratory samples that are drawn within 48 hours prior to treatment that are normal will be acceptable. CBC for Day 8 is only required for chemotherapy regimens with Day 8 administration.

[i] See Section 4.5.6 for serology tests. All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical study. HBV DNA must be collected on or before Cycle 1, Day 1 in patients who have negative serology for hepatitis B surface antigen and positive serology for hepatitis B core antibody. HCV RNA must be collected on or before Cycle 1, Day 1 in patients who test positive for anti-HCV.

[j] To include ANC, platelet count, hemoglobin.

[k] More frequent testing is indicated if there is any suspicion of elevated values (i.e., patient is on low dose anticoagulation for a venous access device).

[l] CT scans (with oral and/or IV contrast unless contraindicated) of the chest and abdomen and a CT and/or MRI scan of the brain to rule out CNS metastasis, especially if patient has Stage IIIA disease. Bone scans and CT scans of the neck should also be performed if clinically indicated.

[m] A representative FFPE tumor specimen in paraffin block (preferred) or of 15 (or more) unstained, freshly cut, serial sections (on slides) from an FFPE resected tumor specimen is required for participation in this study. This specimen must be accompanied by the associated pathology report. Retrieval of archival tumor sample can occur outside the 28-day screening period.

[n] Copies of the pathology report must be submitted.

[o] For patients who experience an ongoing study agent-related serious adverse event upon active treatment completion, or at discontinuation from the study, should be contacted by the investigator or his/her designee until the event is resolved or determined to be irreversible

Appendix 3
Schedule of Assessments for Randomized Phase (Atezolizumab or Best Supportive Care)

Study Procedure	Both Arms	Arm A (Atezolizumab)		Arm B (Best Supportive Care)			Both Arms
	Screening for Randomization	All Cycles	Discontinuation [a]	Cycles 1, 3, 5, 7, 9, 11, 13, and 15	Cycles 2, 4, 6, 8, 10, 12, 14, and 16	Discontinuation [a]	
	Days -28 to -1	Day 1 (±3 days)[b]	≤30 Days after Last Dose	Day 1 (±3 Days for Cycles ≥3)	Day 1 (±3 Days)	≤30 Days after 1 Year of Observation	Follow-Up
Review of eligibility criteria	x						
Pregnancy test (women of childbearing potential ONLY) [c]	x [c]	x [d]	x [d]				
ECOG performance status	x	x	x	x			
Complete physical examination [e]	x		x			x	
Limited physical examination [e]		x		x			
Weight	x	x	x	x		x	
Vital signs [f]	x	x	x	x		x	
12-lead ECG	x	x [g]	x [g]				
Hematology [h]	x	x [h]	x	x [h]		x	
Serum chemistry [i]	x	x [i]	x	x [i]		x	
Coagulation panel (aPTT, INR)	x		x				
Urinalysis [j]	x	x [k]		x [k]			

Appendix 3 Schedule of Assessments for Randomized Phase (Atezolizumab or Best Supportive Care) (cont.)

Study Procedure	Both Arms	Arm A (Atezolizumab)		Arm B (Best Supportive Care)			Both Arms
	Screening for Randomization	All Cycles	Discontinuation [a]	Cycles 1, 3, 5, 7, 9, 11, 13, and 15	Cycles 2, 4, 6, 8, 10, 12, 14, and 16	Discontinuation [a]	
	Days –28 to –1	Day 1 (±3 days)[b]	≤30 Days after Last Dose	Day 1 (±3 Days for Cycles ≥3)	Day 1 (±3 Days)	≤30 Days after 1 Year of Observation	Follow-Up
TSH, free T3, free T4	x	x (every four cycles)	x				
Serum sample for ATA assessment (atezolizumab patients only) [l]		x	x				
Serum sample for PK sampling (atezolizumab patients only) [l]		x	x				
Blood samples for biomarkers [m]		x [m]	x	x [m]		x	x
Study drug infusion [n]		x					
Fresh biopsy specimen (mandatory for both arms) [o]	At the time of radiographic confirmation of disease recurrence or new primary NSCLC [o]						

Appendix 3 Schedule of Assessments for Randomized Phase (Atezolizumab or Best Supportive Care) (cont.)

Tumor assessments [p]	x	All patients in the randomized phase will undergo scheduled tumor assessments at baseline and every 4 months starting at Cycle 1, Day 1 in the first year and every 6 months in the second year by CT following randomization. Patients who have not experienced recurrence of disease will undergo tumor assessments every 6 months during Years 3–5 by CT and X-ray post-randomization (starting with CT scan, alternating with X-ray), and annually thereafter by X-ray until disease recurrence, death, loss to follow-up, consent withdrawal, or study termination by the Sponsor, whichever occurs first.					
	Both Arms	Arm A (Atezolizumab)		Arm B (Best Supportive Care)			Both Arms
Study Procedure	Screening for Randomization	All Cycles	Discontinuation [a]	Cycles 1, 3, 5, 7, 9, 11, 13, and 15	Cycles 2, 4, 6, 8, 10, 12, 14, and 16	Discontinuation [a]	Follow-Up
	Days –28 to –1	Day 1 (±3 days)[b]	≤30 Days after Last Dose	Day 1 (±3 Days for Cycles ≥3)	Day 1 (±3 Days)	≤30 Days after 1 Year of Observation	
Concomitant medications [q]	x	x	x	x	x	x	
Adverse events [r]	x	x	x	x	x	x	
Medical contact [s]					x		
Survival and anti-cancer therapy follow-up [t]							x

1.
2.

ATA = anti-therapeutic antibody; BSC = best supportive care; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; NSCLC = non–small cell lung cancer; PD-L1 = programmed death–ligand 1; PK = pharmacokinetic; RCR = Roche Clinical Repository; TSH = thyroid-stimulating hormone.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] Patients will be asked to return to the clinic not more than 30 days after the decision to discontinue treatment for a treatment or observation discontinuation visit.

Appendix 3 Schedule of Assessments for Randomized Phase (Atezolizumab or Best Supportive Care) (cont.)

[b] Cycle 1, Day 1 must be performed within 5 days after the patient is randomized. Screening assessments performed ≤96 hours before Cycle 1, Day 1 are not required to be repeated for Cycle 1, Day 1. In addition, ECOG performance status, limited physical examination, and local laboratory tests may be performed ≤96 hours before Day 1 of each cycle as specified in Section 4.6.2.

[c] 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.

[d] If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

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

[f] Vital signs include heart rate, respiratory rate, blood pressures, and temperature and will be performed as standard of care for patients randomized to the BSC arm. For patients randomized to the atezolizumab treatment arm, vital signs should be recorded as described in Table 10.

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

[h] Blood samples collected to monitor safety will be collected in patients randomized to both arms. Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. Refer to Section 4.5.6 for a list of laboratory test results obtained within 14 days prior to the first dose of atezolizumab treatment.

[i] Serum chemistry includes glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate *or total carbon dioxide (if considered standard of care for the site),* calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin. Refer to Section 4.5.6 for a list of laboratory results obtained within 14 days prior to first dose of atezolizumab treatment.

[j] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood).

[k] Perform if clinically indicated.

[l] For patients assigned to atezolizumab treatment arm only. See Appendix 3 for details of the ATA and PK collection schedule. Blood samples should be processed to obtain serum. A post-treatment ATA and PK sample should be collected 120 days (± 30 days) after the last dose of atezolizumab received during the treatment period unless the patient withdraws consent or the study closes.

[m] See Appendix 3 for details of the biomarker sampling schedule.

[n] Patients randomized to atezolizumab arm will receive their first dose of study drug the day of randomization if possible. If this is not possible, the first dose should occur no later than 5 days after randomization. The initial dose of atezolizumab treatment will be delivered over 60 (±15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. Atezolizumab treatment may be continued for a maximum of 16 cycles in the absence of meeting discontinuation criteria specified in Section 4.3.4.2.

Appendix 3 Schedule of Assessments for Randomized Phase (Atezolizumab or Best Supportive Care) (cont.)

[o] A mandatory biopsy is required, if clinically feasible, within 40 days of disease recurrence or prior to the start of the next anti-cancer therapy, whichever is sooner (see Section 4.5.8.1).

[p] Results must be reviewed by the investigator before dosing at the next cycle (in atezolizumab treatment arm only). Tumor assessments should continue regardless of whether patients start new anti-cancer therapy in the absence of disease recurrence unless they withdraw consent. If there is a recurrence, it is also strongly encouraged that patients be fully restaged, including a CT scan of the chest and abdomen, imaging (preferably MRI, but CT is acceptable) of the brain, and a radionuclide bone scan or positron emission tomography (PET) scan. Additional scans may be necessary as per investigator judgment if recurrence of primary lung cancer is suspected on treatment.

[q] 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.

[r] Once randomized into the study, during both the enrollment phase (cisplatin-based chemotherapy) and randomization phase (atezolizumab or BSC), all serious adverse events and adverse events of special interest will be recorded during the study and for 90 days after the last dose of study treatment (last study assessment for patients in Arm B) or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events will be recorded during the study and for 30 days after the last dose of study treatment (last study assessment for patients randomized to Arm B) or until the initiation of another anti-cancer therapy, whichever occurs first.

[s] This medical contact can be either via telephone call or formal clinic visit. *If the contact is via a formal clinic visit, additional assessments may be done as clinically indicated per local standard of care and at the discretion of the investigator.*

[t] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by Roche. All patients (irrespective of which arm they are randomized to) will be followed for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If *the patient withdraws from the atezolizumab study, the* study staff may use a public information source (e.g., county records) to obtain information about survival status only. This also applies to patients randomized to BSC arm. Patients assigned to either study arm who complete either the initial treatment or the initial observation period (16 cycles) will discontinue atezolizumab treatment or BSC and will continue follow-up tumor assessments (per the tumor assessment schedule above–see *footnote p*). No patients are allowed to cross over.

Appendix 4
Anti-Drug Antibody, Biomarker, and Pharmacokinetic Sampling Schedule

Enrollment Phase Sampling		
Study Visit	Time	Sample (All Enrolled Patients)
Screening	NA	Biomarker [a]
Cycle 1, Day 1	Pre-dose with cisplatin-based chemotherapy	Biomarker [b]

Randomized Phase (Post-Randomization) Sampling			
		Sample	
Study Visit	Time	Patients Randomized to BSC Arm	Patients Randomized to Atezolizumab Arm
	Pre-dose	Biomarker [b]	ATA Atezolizumab pharmacokinetics Biomarker [b]
Cycle 1, Day 1	30 min (±10 min) after end of atezolizumab infusion		Atezolizumab pharmacokinetics
Cycles 2, 3, 4, and 5, Day 1	Pre-dose	Biomarker (Cycle 3, Day 1, and Cycle 5, Day 1) [b]	ATA (Cycles 2, 3, and 4) Atezolizumab pharmacokinetics (Cycles 2, 3, and 4) Biomarker (Cycles 2, 3, and 5) [b]
Cycles 7 and 15, Day 1	Pre-dose	Biomarker [b]	
Cycles 8 and 16, Day 1	Pre-dose		ATA Atezolizumab pharmacokinetics Biomarker [b]
At the time of first radiographic confirmation of disease recurrence or confirmation of a new primary NSCLC	At visit		Biomarker [b]

Appendix 4
Anti-Drug Antibody, Biomarker, and Pharmacokinetic Sampling Schedule (cont.)

Randomized Phase (Post-Randomization) Sampling			
		Sample	
Study Visit	Time	Patients Randomized to BSC Arm	Patients Randomized to Atezolizumab Arm
At time of fresh biopsy (e.g., at the time of first radiographic confirmation of disease recurrence or confirmation of a new primary NSCLC)		Biomarker [b]	Biomarker [b]
Treatment discontinuation visit	At visit	Biomarker [b]	ATA Atezolizumab pharmacokinetics Biomarker [b]
Follow-up (after completion of 16 cycles of atezolizumab or BSC)	At tumor assessment visit	Biomarker [b]	Biomarker [b]
120 days (±30 days) after last dose of atezolizumab in treatment stage	At visit		ATA Atezolizumab pharmacokinetics Biomarker [b]
Any time point during the study (RCR consent required)		Optional RCR whole blood (DNA extraction) [c]	Optional RCR whole blood (DNA extraction) [c]

ATA = anti–therapeutic antibody; NA = not applicable; NSCLC = non–small cell lung cancer; RCR = Roche Clinical Repository.

[a] Whole blood for biomarkers.

[b] Plasma and serum. Note: Except for Day 1 of Cycle 1 in the enrollment phase and Day 1 of Cycle 1 in the randomization phase, all other study visits and assessments during the treatment period should be performed within ± 3 days of the scheduled date. Study assessments may be delayed or moved forward 3 days to accommodate holidays, vacations, and unforeseen delays. For biomarker samples, if the visit schedule can accommodate the ± 3 day collection window, one set of samples can be noted as satisfying two visits (e.g., treatment discontinuation and the time of fresh biopsy collection).

[c] The optional RCR whole blood sample (for DNA extraction) requires an additional informed consent and the sample can be collected at any time during the course of the study.

Appendix 5
Modification Plan

MODIFICATION PLAN

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) COMPARED WITH BEST SUPPORTIVE CARE FOLLOWING ADJUVANT CISPLATIN-BASED CHEMOTHERAPY IN PATIENTS WITH COMPLETELY RESECTED STAGE IB–IIIA NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	GO29527
STUDY DRUG:	TECENTRIQ® (atezolizumab)
VERSION NUMBER:	1
IND NUMBER:	117296
EUDRACT NUMBER:	2014-003205-15
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted] Ph.D.

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1. BACKGROUND

Study GO29527 (hereinafter IMpower010) is a Phase III, global, multicenter, open-label, randomized trial comparing the efficacy and safety of atezolizumab versus best supportive care (BSC) in patients with Stage IB–Stage IIIA non–small cell lung cancer (NSCLC) following resection and adjuvant chemotherapy, as assessed by disease-free survival (DFS) per the investigator and overall survival (OS).

Given the strong efficacy, particularly in patients with tumors with high programmed death–ligand 1 (PD-L1) staining (tumor cell [TC]3 or tumor-infiltrating immune cell [IC]3), observed in the single-arm Phase Ia Study PCD4989g, and the significant improvement in OS in the intent-to-treat (ITT) population observed in the randomized Phase II POPLAR, the Sponsor, F. Hoffmann-La Roche Ltd, has initiated an extensive clinical development program with atezolizumab in the front-line NSCLC setting that includes the following studies:

- Phase III Study GO29436 (IMpower150): randomized open-label study of atezolizumab in combination with carboplatin + paclitaxel or with carboplatin + paclitaxel + bevacizumab versus carboplatin + paclitaxel + bevacizumab in chemotherapy-naive patients with Stage IV non-squamous NSCLC stratified by PD-L1 expression status
- Phase III Study GO29437 (IMpower131): randomized open-label study of atezolizumab in combination with carboplatin + paclitaxel or with carboplatin + nab-paclitaxel versus carboplatin + nab-paclitaxel in chemotherapy-naive patients with Stage IV squamous NSCLC stratified by PD-L1 expression status
- Phase III Study GO29537 (IMpower130): randomized open-label study of atezolizumab in combination with carboplatin + nab-paclitaxel versus carboplatin + nab-paclitaxel in chemotherapy-naive patients with Stage IV non-squamous NSCLC stratified by PD-L1 expression status
- Phase III Study GO29438 (IMpower132): randomized open-label study of atezolizumab in combination with carboplatin or cisplatin + pemetrexed versus carboplatin or cisplatin + pemetrexed in chemotherapy-naive patients with Stage IV non-squamous NSCLC
- Phase III Study GO29431 (IMpower110): randomized open-label study of atezolizumab versus carboplatin or cisplatin + pemetrexed or carboplatin or cisplatin + gemcitabine for PD-L1–selected, chemotherapy-naive patients with Stage IV non-squamous and squamous NSCLC

Table 1 summarizes the study design for these studies. All these studies have completed their respective primary analyses.

Table 1 Clinical Development Plan for Atezolizumab in NSCLC (First-Line)

Study (Status)	Study Design	Populations
GO29436 (IMpower150)	• Three arms, Phase III • Patient population (1202 patients randomized): First-line Stage IV NSCLC non-squamous histology • Control arm: carboplatin + paclitaxel + bevacizumab • Experimental arms: atezolizumab + carboplatin + paclitaxel + bevacizumab; atezolizumab + carboplatin + paclitaxel • Co-primary efficacy endpoints: investigator-assessed PFS per RECIST and OS	All-comer
GO29437 (IMpower131)	• Three arms, Phase III • Patient population (1021 patients randomized): First-line Stage IV NSCLC squamous histology • Control arm: carboplatin + nab-paclitaxel • Experimental arms: atezolizumab + carboplatin + nab-paclitaxel; atezolizumab + carboplatin + paclitaxel • Co-primary efficacy endpoints: investigator-assessed PFS per RECIST and OS	All-comer
GO29537 (IMpower130)	• Two arms, Phase III • Patient population (724 patients randomized): first-line Stage IV NSCLC non-squamous histology • Control arm: carboplatin + nab-paclitaxel • Experimental arm: atezolizumab + carboplatin + nab-paclitaxel • Co-primary efficacy endpoints: investigator-assessed PFS per RECIST and OS	All comer

Table 1 Clinical Development Plan for Atezolizumab in NSCLC (First-Line) (cont.)

Study (Status)	Study Design	Populations
GO29438 (IMpower132)	• Two arms, Phase III • Patient population (578 patients randomized): first-line Stage IV NSCLC non-squamous histology • Control arm: carboplatin or cisplatin + pemetrexed • Experimental arms: • atezolizumab + carboplatin or cisplatin + pemetrexed • Co-primary efficacy endpoints: investigator-assessed PFS per RECIST and OS	All-comer
GO29431 (IMpower110)	• Two arms, Phase III • Patient population (572 patients randomized): first-line Stage IV NSCLC non-squamous and squamous histology • Control arm: carboplatin or cisplatin + pemetrexed or carboplatin or cisplatin + gemcitabine • Experimental arm: atezolizumab • Primary efficacy endpoint: OS	PD-L1–selected population

IC = tumor-infiltrating immune cell; NSCLC = non–small cell lung cancer; OS = overall survival; PD-L1 = programmed death–ligand 1; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; TC = tumor cell.

On the basis of results observed from the ongoing Phase III studies as presented in Table 1, the Sponsor may be able to improve the design of the ongoing IMpower010. The possible modifications to IMpower010 are discussed in Section 2. These modifications include the PD-L1–selected and ITT populations for the primary endpoint of DFS and secondary endpoint of OS to be tested in a different order, and/or with a different alpha control method, and/or different analysis timing than what is specified in Section 6 of the current Protocol GO29527 (Version 8).

The proposed modifications to IMpower010 as outlined in this Modification Plan will be based on data generated outside of the study, with the exception of cumulative population-level PD-L1 expression prevalence data in the combined treatment arms based on ongoing study monitoring. No modifications will be based on any interim analysis of IMpower010. As such, this study is not considered an adaptive design

clinical study as defined in the U.S. Food and Drug Administration's February 2010 draft guidance "Adaptive Design Clinical Trials for Drugs and Biologics" and in the European Medicines Agency's October 2007 "Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design." Any modification derived from data entirely outside of IMpower010 will not result in statistical bias (e.g., the type I error will not be inflated).

1.1 PRIMARY AND SECONDARY EFFICACY ENDPOINTS IN IMPOWER010

The primary endpoint of IMpower010 is DFS as assessed by investigator and the secondary endpoint of this study is OS. Refer to the Section 4.4.1 and 4.4.2.1 of Statistical Analysis Plan for IMpower010 for the definitions and analysis methodologies for the DFS and OS, respectively.

DFS and OS analyses will be performed for the PD-L1 subpopulation (defined by SP263 TC ≥1%) within the Stage II–IIIA population, the Stage II–IIIA population, and the ITT population, where appropriate.

The interim and final analyses timing of DFS and the interim and final analyses timing of OS are discussed in Sections 2.4.1 and Section 2.4.2 of the study Statistical Analysis Plan, respectively.

To control for the type I error rate in the evaluation of both DFS and OS, the DFS and OS analysis testing schema are shown in Figure 2 in the study Statistical Analysis Plan.

1.2 MEASURES TO MINIMIZE BIAS

Because IMpower010 is a randomized, open-label study, the Sponsor will take steps to ensure that modifications to this study are not based on any assessment of the IMpower010 data, except for the ongoing monitoring of the PD-L1 prevalence rate within the study. The Sponsor will remain blinded to the randomization code from the interactive web/voice response system (IxRS). In the management of serious adverse events, the patient treatment information from the RAVE database can be known to the Medical Monitor, the safety scientist, and the safety operations group as outlined in the Sponsor's internal standard operating procedures.

Modifications to IMpower010 will be made prior to the planned interim DFS analysis in the study. The Sponsor will remain blinded to the IMpower010 results and treatment assignment information (including treatment assignment at randomization, patient-level PD-L1 status with a link to patient ID) until the planned DFS interim analysis if the iDMC makes a recommendation to unblind the study or until the planned DFS final analysis if the iDMC does not recommend to unblind the study at the interim analyss. A limited number of individuals on the Sponsor study team will have access to patient-level data. However, these individuals with access to patient-level data will be prohibited from

conducting any population-level data summaries by treatment arms and will not have access to treatment assignment information before the Sponsor is unblinded.

Queries to the site in order to clean the efficacy and safety data will be made by the study team according to the Sponsor's standard operating procedures.

The proposed modifications to IMpower010 as outlined in this Modification Plan will be based on data generated outside of the study and based on study-level data summaries of PD-L1 prevalence (combined treatment arms). The summary of study-level PD-L1 prevalence will be conducted by a Sponsor study team member who can only access the masked PD-L1 dataset (patient-level PD-L1 status without a link to patient ID) and will not have access to patients' efficacy and safety data in the clinical database. Emerging data external to IMpower010 may inform the need for changes in this study.

2. POTENTIAL MODIFICATION SCENARIO

Table 2 presents the modifications that may be made to IMpower010.

Table 2 Potential Modification Scenarios in IMpower010

Observed Results from External Data	Potential Modifications to DFS Final Analysis in IMpower010
Treatment effects in adjuvant studies with other agents are stronger than assumed	Decrease study follow-up time for DFS/OS interim and/or final analysis
Delayed treatment effects are observed in adjuvant studies with other agents, or their DFS IA/FA results are negative	Increase study follow-up time for DFS interim and/or final analysis

DFS = disease-free survival; OS = overall survival; IA = interim analysis; FA=final analysis.

3. CONCLUSION

Modifications to IMpower010 as outlined in this Modification Plan will be based solely on data generated outside of this study, except for the ongoing monitoring of the PD-L1 prevalence rate in the combined treatment arms within the study, which will be conducted by a Sponsor study team member who can only access the masked PD-L1 dataset (patient-level PD-L1 status without a link to patient ID) and who has no access to the study clinical database. No modifications will be based on any interim analysis of IMpower010. As such, this study is not considered an adaptive design clinical study as defined by the U.S. Food and Drug Administration and the European Medicines Agency. In addition, emerging data external to IMpower010 may inform the need for changes that are currently not captured in this Modification Plan.

4. REFERENCES

European Medicines Agency, Committee for Medicinal Products for Human Use. Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design: 18 October 2007.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry: Adaptive design clinical trials for drugs and biologics: February 2010.