Official Title: A Phase II, Safety, and Efficacy Study of Tiragolumab Plus Atezolizumab and Atezolizumab Monotherapy in Patients with Metastatic and/or Recurrent PD-L1-Positive Cervical Cancer

NCT Number: NCT04300647

Document Date: SAP Version 2: 17-June-2021

STATISTICAL ANALYSIS PLAN

TITLE:	**A PHASE II, SAFETY, AND EFFICACY STUDY OF TIRAGOLUMAB PLUS ATEZOLIZUMAB AND ATEZOLIZUMAB MONOTHERAPY IN PATIENTS WITH METASTATIC AND/OR RECURRENT PD-L1-POSITIVE CERVICAL CANCER**
PROTOCOL NUMBER:	WO42017
STUDY DRUG:	Tiragolumab and Atezolizumab
VERSION NUMBER:	2
IND NUMBER:	147026
EUDRACT NUMBER:	2019-004895-21
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted]
DATE FINAL:	See electronic date stamp below

STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
17-Jun-2021 16:05:04	Company Signatory	[redacted]

STATISTICAL ANALYSIS PLAN VERSION HISTORY

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
2	See electronic date stamp on title page	V 4, 25 March 2021
1	16 December 2020	V 2, 19 June 2020

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

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

Section	Description of Change	Rationale for Change
4.4.1, 4.1.3, 4.2, 4.3, 4.4	Change of population for efficacy analysis to only randomized patients who receive at least one dose of study treatment. Patients grouped by treatment received.	This change enables evaluation of the efficacy of tiragolumab in combination with atezolizumab and atezolizumab monotherapy in the context of currently available therapy, in line with the use of a pre-specified reference for the primary statistical test.
2.3.1	Change of primary analysis timing to enable at least 6 months of follow-up from the onset of response for the majority of patients	This change enables sufficient follow-up of the responders and to assess the durability of the response
2.2.3, 4.4.7	Addition of a potential [redacted]	This change enables evaluation of consistency with the efficacy and safety observed in the global population

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

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1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study WO42017, "A Phase II, Safety, and Efficacy Study of Tiragolumab plus Atezolizumab and Atezolizumab Monotherapy in Patients with Metastatic and/or Recurrent PD-L1–positive Cervical Cancer". The background for the study can be found in the study Protocol.

2. STUDY DESIGN

Study WO42017 is a randomized, Phase II, global, multicenter, open-label study designed to evaluate the efficacy and safety of tiragolumab plus atezolizumab and atezolizumab monotherapy in patients with metastatic and/or recurrent PD-L1–positive cervical cancer after progression or recurrence from at least one platinum-based but no more than two prior systemic therapies.

Approximately 160 patients will be randomized in this study global enrollment phase in a 3:1 ratio. Additional patients may be subsequently randomized in a [redacted]. Women with Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 who have metastatic and/or recurrent PD-L1–positive cervical cancer are eligible (refer to protocol synopsis in Appendix 1 for complete eligibility criterion).

In the doublet arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle, followed by tiragolumab at a fixed dose of 600 mg administered by IV infusion Q3W also on Day 1 of each 21-day cycle.

In the atezolizumab monotherapy arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle.

Treatment may be continued as long as patients are experiencing clinical benefit, as assessed by the investigator, in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status. Patients who meet the criteria for equivocal disease progression per RECIST v1.1 will be permitted to continue treatment (tiragolumab in combination with atezolizumab or atezolizumab alone) if they meet all of the following criteria:

- Evidence of clinical benefit, as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values indicating unequivocal progression of disease)
- No decline in ECOG Performance Status that can be attributed to disease progression

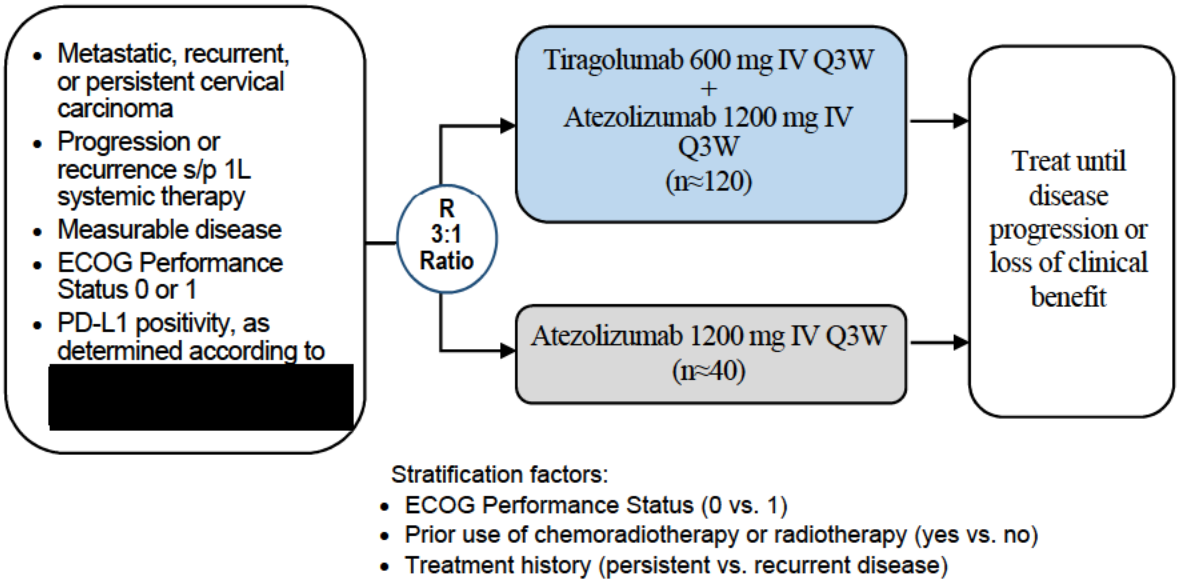
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Crossover is allowed from the atezolizumab monotherapy arm to the tiragolumab plus atezolizumab arm after unequivocal progressive disease has been recorded during atezolizumab monotherapy, at the discretion of the investigator and after consultation with the Medical Monitor.

The primary study objectives are to make a preliminary assessment of efficacy of tiragolumab in combination with atezolizumab and atezolizumab monotherapy, as measured by independent review committee (IRC)-determined confirmed objective response rate (ORR), and to evaluate safety.

The study schema is provided in Figure 1.

Figure 1 Study Schema



1L=first-line; CDx=companion diagnostic; ECOG =Eastern Cooperative Oncology Group; PD-L1=programmed death–ligand 1; Q3W=every 3 weeks; R=randomization; s/p= status post.

Note: Crossover is allowed from the atezolizumab monotherapy arm to the tiragolumab plus atezolizumab arm after unequivocal progressive disease has been recorded during atezolizumab monotherapy, at the discretion of the investigator and after consultation with the Medical Monitor.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. The Protocol Synopsis includes the study objectives, inclusion and exclusion criteria, outcome measures, and statistical methods as stated in the protocol.

2.2 DETERMINATION OF SAMPLE SIZE

Approximately 160 patients are planned for enrollment in the global enrollment phase. After completion of the global enrollment, additional patients may be subsequently randomized [redacted]

2.2.1 Type I Error Control

Type I error for the study is [redacted] (one-sided).

The primary endpoint is confirmed ORR, defined as the proportion of patients with a complete response (CR) or a partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by an independent review committee (IRC) according to RECIST v1.1.

Primary statistical test is a [redacted] at a one-sided [redacted] significance level, and the ORR of the doublet arm will be compared to a historical reference of 14.6% (Chung et al. 2019). This is the only comparison with a statistical hypothesis testing.

No type I error control is applied for descriptive comparisons, including that of the atezolizumab monotherapy ORR to the historical reference.

[redacted]

2.2.2 Primary Endpoint: Confirmed ORR

The overall statistical power under several assumptions of the true underlying ORR in the tiragolumab in combination with atezolizumab arm is given in Table 1, with the following considerations taken into account:

- [redacted], historical reference of 14.6% (Chung et al. 2019)
- alpha = [redacted], one-sided
- 3:1 randomization ratio
- True underlying ORR in tiragolumab in combination with atezolizumab arm between [redacted]
- [redacted]

Table 1 Overall Statistical Power in the Comparison of ORR in the Tiragolumab in Combination with Atezolizumab Arm to a Reference Point of 14.6%

Reference ORR 14.6% [a] (MDO [b] = [redacted])	True Underlying ORR in Tiragolumab in Combination with Atezolizumab [redacted]
Power	

MDO = minimum detectable observation; ORR = overall response rate.

[a] Source: Chung et al. 2019.

[b] MDO is defined as the smallest observed ORR leading to statistical significance at final analysis.

The ORR in the atezolizumab monotherapy arm will only be compared with the historical reference and with tiragolumab in combination with atezolizumab as a descriptive comparison, with no type I error control. The probability of the observed ORR in the atezolizumab monotherapy arm being greater than a reference point at the time of final ORR analysis is also shown in Table 2.

Table 2 Probability of Observed ORR in the Atezolizumab Monotherapy Arm Greater than a Reference Point at the Final Analysis for ORR

Reference ORR 14.6% [a]	True Underlying ORR in Atezolizumab Monotherapy [redacted]
P(ORR_{AM} > ref ORR)	

ORR = overall response rate.

[a] Source: Chung et al. 2019.

[redacted]

[redacted]

2.3 INTERIM AND PRIMARY ANALYSIS TIMING

2.3.1 Primary Analysis Timing

The primary analysis of confirmed ORR will be performed once all patients have been enrolled and a minimum follow-up of approximately 6 months after the second tumor assessment, or approximately 9 months after randomization, has been achieved among the patients, who remain in follow-up for ORR assessment, whichever is earlier.

The analysis of confirmed ORR for [redacted] will be conducted after all enrolled Chinese patients [redacted] have had a minimum follow-up of approximately 6 months after the second tumor assessment, or approximately 9 months after randomization, has been achieved among the patients, who remain in follow-up for ORR assessment, whichever is earlier.

[redacted]

[redacted]

[redacted]

[redacted]

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Eligible patients will be randomized in a 3:1 ratio to receive either atezolizumab plus tiragolumab or atezolizumab monotherapy with the use of a stratified permuted-block randomization. The randomization will be stratified for the following factors:

- ECOG Performance Status (0 vs. 1)
- Prior use of chemoradiotherapy or radiotherapy (yes vs. no)
- Treatment history (persistent vs. recurrent disease)

[redacted]

3.2 INDEPENDENT REVIEW COMMITEE

An Independent Review Committee (IRC) will be used to conduct a blinded radiology review of the imaging data and will provide an independent assessment of tumor response and progression for all patients according to a separate IRC Charter. The IRC will follow the Response Evaluation Criteria in Solid Tumor, Version 1.1 (RECIST 1.1).

3.3 DATA MONITORING

The Sponsor will monitor patient safety throughout the study. In addition to the ongoing assessment of the incidence, nature, and severity of adverse events; deaths; vital signs; and laboratory abnormalities, the Sponsor will review all cumulative data at regular intervals during the study.

An Internal Monitoring Committee (IMC) composed of representatives from safety science, clinical science, and statistics, who are independent from the study team, will also be established. Representatives from other functions may be added on an ad hoc

basis depending on the nature of the findings. The primary responsibility of the IMC is to evaluate the safety, not efficacy, of treatment arms being evaluated. The IMC will share responsibility with the study team for the monitoring of patient safety.

The IMC may meet during the course of the study. The IMC may conduct an ad hoc meeting should an unexpected safety concern arise, as specified in the IMC Charter. At the time of each review of cumulative data, the IMC may make recommendations in consideration of the totality of the available data. Specific operational details such as the committee's composition, timing of meetings, and members' roles and responsibilities will be detailed in an IMC Charter.

4. STATISTICAL METHODS

The analyses described in this SAP will supersede those specified in Protocol WO42017 for the purposes of a regulatory filing.

4.1 ANALYSIS POPULATIONS

4.1.1 Treated Patients Population

The Treated Patients Population is defined as all randomized patients that have received at least any dose of study treatment. Patients will be grouped according to the actual treatment received. The Treated Patients Population will be used at primary analysis for the efficacy analysis.

4.1.2 ITT Population

The ITT population is defined as all randomized patients, irrespective of whether or not the patient received the assigned treatment. Patients will be grouped according to the treatment assigned at randomization. The ITT Population will be used for efficacy sensitivity analysis.

4.1.3 IA Treated Patients Population

The IA Treated Patients Population is defined as all patients randomized at least 5 months prior to the interim analysis CCOD that have received at least any dose of study treatment. Analysis by treatment arm performed on the IA Treated Patients Population will be grouped according to the actual treatment received. The IA Treated Patients Population will be used at interim analysis for the efficacy analysis.

4.1.4 Crossover Population

The Crossover Patients, Treated Patients Population or Safety Population is defined as all patients randomized to the atezolizumab monotherapy arm that crossed-over to the tiragolumab in combination with atezolizumab arm, and received at least any dose of tiragolumab after cross-over but not prior to cross-over.

4.1.5 Pharmacokinetic-Evaluable Population

The Pharmacokinetic-Evaluable Population is defined as all patients who received any dose of study treatment and who have at least one post-baseline PK sample available.

4.1.6 Safety Population

The safety population is defined as patients who received at least one dose of tiragolumab or atezolizumab. The Safety Population is identical to the Treated Patients Population (see Section 4.1.1) and will be used for the safety analysis.

4.2 ANALYSIS OF STUDY CONDUCT

Enrollment, major protocol deviations including major deviations of inclusion/exclusion criteria, and reasons for discontinuation from the study will be summarized by treatment arm for the ITT Population. Study treatment administration and reasons for discontinuation from study treatment will be summarized for the Safety Population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic characteristics (age, race/ethnicity, geographic region), baseline disease characteristics (histology, initial diagnosis stage, target lesions size, disease location, PD-L1 expression, number of prior lines of systemic anti-cancer therapy, prior bevacizumab use) and stratification factors (ECOG performance status, prior use of (chemo) radiotherapy, treatment history) will be summarized by treatment arm for the Treated Patients Population and for the IA Treated Patients Population at interim analysis.

Baseline values are the last available data obtained prior to the patient receiving the first dose of any component of study treatment on Cycle 1, Day 1 (or at screening, for patients who were not treated), unless otherwise noted. Descriptive statistics (mean, median, standard deviation, minimum, maximum) will be presented for continuous variables, and frequencies and percentages will be presented for categorical variables.

4.4 EFFICACY ANALYSIS

4.4.1 Primary Efficacy Endpoint

4.4.1.1 Objective Response Rate (confirmation required)

The primary efficacy endpoint is confirmed objective response rate (ORR), defined as the proportion of patients with a confirmed objective response, either complete response (CR) or partial response (PR), observed on two consecutive assessments ≥ 4 weeks apart with the use of RECIST v1.1, based on IRC assessment.

In the primary efficacy analysis, patients without any post-baseline tumor assessments will be considered non-responders. Confirmed ORR will be analyzed for the Treated Patients Population at primary analysis. Confirmed ORR will be analyzed for the IA Treated Patients Population at interim analysis.

A one-sample z-test for proportion will be used to compare the confirmed ORR of the tiragolumab in combination with atezolizumab arm to the historical reference (see Section 2.2.2). No formal treatment comparison will be performed between the two arms or between the atezolizumab monotherapy arm and the historical reference.

An estimate of the confirmed ORR and its 95% CI will be calculated for each treatment arm using the Clopper-Pearson method.

In order to characterize responders, descriptive statistics (e.g. median, range) will be provided for time from randomization to response (TTR) for patients with an objective response.

4.4.2 Secondary Efficacy Endpoint

4.4.2.1 Duration of Response

A secondary endpoint is duration of response (DOR), defined for patients with a confirmed objective response, as the time from the first documented objective response to documented disease progression with the use of RECIST v1.1, as determined by the IRC, or death from any cause, whichever occurs first.

Data for patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the date of the last tumor assessment at which they were known to be progression-free. DOR will be analyzed in a subset of patients (those who achieve an objective response) from the Treated Patients Population at primary analysis and from the IA Treated Patients Population at interim analysis.

The analysis of DOR is based on a non-randomized subset of patients (those who achieve an objective response); therefore, comparisons between treatment arms will be made for descriptive purposes only. In particular, Kaplan-Meier methodology will be used to estimate the median DOR for each treatment arm, and Kaplan-Meier curves will be produced. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median DOR for each treatment arm (Brookmeyer and Crowley 1982). The Kaplan-Meier approach will also be used to estimate 6-month DOR rate in each arm.

4.4.2.2 Disease Control Rate

A secondary endpoint is [redacted]

The methodologies described for the analysis of confirmed ORR will be used for the analysis of DCR (except the formal treatment comparison with the historical reference that will not be performed on DCR).

4.4.2.3 Best Clinical Response

A secondary endpoint is best clinical response (BCR), defined as the proportion of patients with a CR, PR, or SD, as clinically determined by the investigator.

[redacted]

The methodologies described for the analysis of confirmed ORR will be used for the analysis of BCR (except the formal treatment comparison with the historical reference that will not be performed on BCR). DOR as clinically determined by the investigator will also be provided, and the methodology will be the same as used for the analysis of the IRC DOR.

4.4.2.4 Progression-Free Survival

A secondary efficacy endpoint is progression-free survival (PFS), defined as the time from randomization to the first documented disease progression as determined by the IRC with the use of RECIST v1.1, or death from any cause, whichever occurs first.

Data for patients who are alive and have not experienced disease progression at the time of analysis will be censored at the date of the last tumor assessment at which they were known to be progression-free with radiographic evidence. Data for patients with no post-baseline tumor assessment will be censored at the date of randomization. PFS will be analyzed in the Treated Patients Population and in the IA Treated Patients Population at interim analysis

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

The Kaplan-Meier approach will also be used to estimate 6-month PFS rate in each arm.

4.4.2.5 Overall Survival

A secondary efficacy endpoint is overall survival (OS). OS is defined as the time from randomization to death from any cause.

Data for patients who are not reported as having died at the time of analysis will be censored at the date last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization. OS will be analyzed for the Treated Patients Population and in the IA Treated Patients Population at interim analysis.

Kaplan-Meier methodology will be used to construct survival curves for each treatment arm and to estimate median OS for each treatment arm. The Brookmeyer-Crowley

methodology will be used to construct the 95% CI for the median OS for each treatment arm (Brookmeyer and Crowley 1982).

The Kaplan-Meier approach will also be used to estimate 6-month OS rate in each arm, along with 95% CI calculated using Greenwood's formula. 12-month OS rate in each arm will also be provided as appropriate.

Duration of survival follow-up will be summarized for all patients in the analysis using descriptive statistics (median, range). Duration of survival follow-up is defined as the survival time for all patients in the analysis (whether a patient is alive or has died).

4.4.3 Exploratory Efficacy Endpoints

4.4.3.1 Disease Control Rate [redacted]

Disease control rate is defined as the proportion of patients with either confirmed objective response (CR or PR observed on [redacted]. The methodologies described for the analysis of confirmed ORR will be used for the analysis of DCR [redacted] (except the formal treatment comparison with the historical reference that will not be performed on DCR [redacted]).

4.4.3.2 Investigator-assessed Objective Response Rate (confirmation required)

Investigator-assessed ORR, is defined as the proportion of patients with a confirmed objective response, either CR or PR, observed on two consecutive assessments ≥ 4 weeks apart with the use of RECIST v1.1, based on the investigator assessment. The methodologies described for the analysis of confirmed ORR will be used for the analysis of investigator-assessed ORR (except the formal treatment comparison with the historical reference that will not be performed on investigator-assessed ORR).

4.4.3.3 Assessment of Tumor Burden

Changes over time in the sum of longest diameters (SLD) for target lesions identified by the IRC will be plotted for each patient by visit for each treatment arm.

4.4.3.4 Best change from baseline in tumor burden (% SLD)

A summary of the best percent change from baseline, defined as the smallest percent change observed post-baseline, in the sum of longest diameters (SLD) for target lesions, according to the IRC, will be presented by treatment arm.

A waterfall plot or vertical bar chart of observed best percent change from baseline ordered from highest (i.e., largest increase) to lowest (i.e., largest decrease) by patient will be presented for each treatment arm.

[redacted]

4.4.4 Crossover Analyses

4.4.4.1 Confirmed Objective Response Rate after Crossover

Confirmed ORR after crossover is defined as the proportion of patients with a confirmed objective response during the post crossover period, either complete response (CR) or partial response (PR), observed on two consecutive assessments ≥ 4 weeks apart with the use of RECIST v1.1, based on IRC assessment.

The tumor assessment just preceding crossover will serve as a re-baseline scan against which all subsequent scans will be compared. Confirmed ORR after crossover will be analyzed for the Crossover Patients, Treated Patients Population.

The methodologies described for the analysis of confirmed ORR will be used for the analysis of confirmed ORR after crossover (except the formal treatment comparison with the historical reference that will not be performed on confirmed ORR after crossover).

Duration of response will also be provided and the methodology will be the same as used for the analysis of the IRC DOR.

4.4.4.2 Analysis of Overall Survival Accounting for Crossover

The impact of subsequent crossover for patients in the atezolizumab arm on OS will be assessed depending on the number of patients who crossover to atezolizumab plus tiragolumab. If more than 10% of patients in the atezolizumab arm crossover, the following analyses may be performed:

- OS will be discounted according to a range of possible effects on OS of subsequent crossover (e.g. 10%, 20%, 30%, 40%, 50%).
- Additional sensitivity analyses may be conducted if deemed necessary.

4.4.5 Sensitivity Analyses

Sensitivity analyses will also be performed for the primary endpoint of confirmed ORR to check the robustness of the primary results.

Confirmed ORR will be estimated for each treatment arm among all treated patients without major exclusion/inclusion criterion protocol deviation (also excluding patients without measurable disease at study entry, according to the IRC) and that are PD-L1

positive per [redacted] according to glass reads only of the [redacted]. Confirmed ORR will also be estimated among the ITT Population.

Furthermore, at interim analysis, confirmed ORR will be analyzed for the IA Treated Patients Population (see Section 4.4.1.1). [redacted]

4.4.6 Subgroup Analyses

The consistency of confirmed ORR results in subgroups defined by demographics (age, race/ethnicity, geographic regions), baseline disease characteristics (histology, prior bevacizumab use, maximal extent of disease, PD-L1 expression level) and stratification factors (ECOG performance status, prior use of (chemo) radiotherapy, treatment history) will be examined. Summaries of confirmed ORR by subgroup will be provided.

Kaplan-Meier plots of PFS and OS will also be produced for selected subgroups.

[redacted]

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

PK samples of tiragolumab and atezolizumab will be collected in this study.

Tiragolumab and atezolizumab serum concentration data (minimum serum concentration and maximum serum concentration) will be tabulated and summarized.

Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Additional PK analyses will be conducted, as appropriate, based on the availability of data. These additional analyses may not be included in the CSR for this study.

4.6 SAFETY ANALYSES

Unless specified otherwise, safety analyses described below will be conducted for the Safety Population (see Section 4.1.3).

Patients will be grouped into two categories:

- atezolizumab monotherapy
    - Patients that received at least one dose of atezolizumab and never received any dose of tiragolumab.
    - Information from patients originally randomized to atezolizumab monotherapy; that received at least one dose of atezolizumab prior to crossover and received a dose of tiragolumab after crossover; safety information up until the first dose of tiragolumab treatment will be included.
- tiragolumab in combination with atezolizumab
    - Patients originally randomized to tiragolumab in combination with atezolizumab that received at least one dose of tiragolumab.
    - Patients randomized to atezolizumab monotherapy that received a dose of tiragolumab (due to a medication error) prior to an eventual crossover.

Information after the start of tiragolumab, for patients randomized to atezolizumab that received a dose of tiragolumab after crossover, will be reported in separate safety analysis. Only selected safety analysis will be performed on this Crossover Patients, Safety Population.

4.6.1 Exposure to Study Medication

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

4.6.2 Adverse Events

Verbatim description of adverse events will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. Adverse events will be graded by the investigator according to the NCI CTCAE v5.0. Treatment-emergent adverse events will be summarized by mapped term, appropriate thesaurus level, NCI CTCAE grade and treatment arm. Multiple occurrences of the same event will be counted once at the maximum grade. All reported AEs, SAEs, Grade 5 AEs, treatment-related AEs (as assessed by the investigator), severe AEs (Grade ≥ 3), immune-mediated AEs (imAEs), imAEs requiring the use of systemic corticosteroids, AEs leading to study drug discontinuation, and AEs leading to interruption or reduction will be summarized.

Listings of AEs will include all treatment-emergent AEs.

[redacted]

Deaths and cause of death will be summarized by treatment arm overall, as well as, during the study treatment period, and those reported during the follow-up period after treatment discontinuation.

4.6.3 Laboratory Data

Laboratory data will be summarized by treatment arm. Laboratory data will be graded according to NCI CTCAE v5.0 and will be summarized descriptively with shift tables from baseline to worst value post-baseline.

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

4.6.4 Vital Signs

Changes from baseline in selected vital signs will be summarized by treatment arm. ECOG performance status will also be summarized over time.

4.6.5 Anti-Drug Antibody

Incidence of anti-drug antibodies (ADAs) against atezolizumab and tiragolumab will be summarized.

The immunogenicity analyses will include patients with any ADA assessments, with patients grouped according to treatment received.

Patients will be classified as treatment-emergent ADA-positive if they were ADA negative at baseline or missing data but developed an ADA response following study drug administration (treatment-induced ADA response) or if they were ADA-positive at baseline and the titre of one or more post-baseline samples was [redacted] greater ([redacted]) than the titre of the baseline sample (treatment-enhanced ADA response).

Patients will be classified as post-baseline ADA negative if they were ADA negative or missing data at baseline and all post-baseline samples were negative or if they were ADA-positive at baseline but did not have any post-baseline samples with a titre that was [redacted] greater than the titre of the baseline sample (treatment unaffected).

The number and proportion of treatment-emergent ADA-positive patients and ADA negative patients during both the treatment and follow-up periods will be summarized by treatment arm.

[redacted]

4.7 MISSING DATA

Sections 4.4.1.1, 4.4.2.4, and 4.4.2.5 describe methods for handling missing data for the primary and secondary efficacy endpoints.

5. REFERENCES

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Appendix 1 Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, SAFETY, AND EFFICACY STUDY OF TIRAGOLUMAB PLUS ATEZOLIZUMAB AND ATEZOLIZUMAB MONOTHERAPY IN PATIENTS WITH METASTATIC AND/OR RECURRENT PD-L1–POSITIVE CERVICAL CANCER**
PROTOCOL NUMBER:	WO42017
VERSION NUMBER:	4
EUDRACT NUMBER:	2019-004895-21
IND NUMBER:	147026
NCT NUMBER:	NCT04300647
TEST PRODUCTS:	Atezolizumab (RO5541267) Tiragolumab (RO7092284)
PHASE:	Phase II
INDICATION:	Cervical cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This Phase II study will evaluate the efficacy and safety of tiragolumab in combination with atezolizumab and atezolizumab monotherapy in patients with metastatic and/or recurrent programmed death-ligand 1 (PD-L1)-positive (tumor cells and tumor associated immune cells [redacted]) cervical carcinoma. Specific objectives and corresponding endpoints for the study are outlined in the following sections.

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of tiragolumab in combination with atezolizumab and of atezolizumab monotherapy on the basis of the following endpoint:

- Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or a partial response (PR) on two consecutive occasions $\geq$4 weeks apart, as determined by an independent review committee (IRC) according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of tiragolumab in combination with atezolizumab and of atezolizumab on the basis of the following endpoints:

- Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by the IRC according to RECIST v1.1
- Disease control rate (DCR), defined as the proportion of patients with a CR, PR, or stable disease (SD), as determined by an IRC according to RECIST v1.1
- Best clinical response rate (BCR), defined as the proportion of patients with a CR, PR, or SD, and the DOR as clinically determined by the investigator

- Progression-free survival (PFS) after randomization, defined as the time from randomization to the first occurrence of disease progression, as determined by the IRC according to RECIST v1.1, or death from any cause, whichever occurs first
- PFS rate at 6 months, defined as the proportion of patients who have not experienced disease progression, as determined by the IRC according to RECIST v1.1, or death from any cause at 6 months post-randomization
- Overall survival (OS) after randomization, defined as the time from randomization to death from any cause
- OS rate at 6 months and 12 months, defined as the proportion of patients who have not experienced death from any cause at 6 months and 12 months post-randomization, respectively

Safety Objective

The safety objective for this study is to evaluate the safety and tolerability of tiragolumab in combination with atezolizumab and of atezolizumab monotherapy on the basis of the following endpoint:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0)

[redacted]

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the pharmacokinetics of tiragolumab and atezolizumab on the basis of the following endpoints:

- Serum concentrations of tiragolumab at specified timepoints
- Serum concentrations of atezolizumab at specified timepoints

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to tiragolumab and atezolizumab on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs to tiragolumab and to atezolizumab during the study

[redacted]

[redacted]

Study Design

Description of Study

Overview of Study Design

This Phase II, global, open-label, randomized study is designed to evaluate the efficacy and safety of tiragolumab in combination with atezolizumab and of atezolizumab monotherapy in patients with metastatic and/or recurrent PD-L1–positive cervical cancer after progression or recurrence from at least one platinum-based but no more than two prior systemic therapies.

Approximately 160 patients will be enrolled in the global enrollment phase of this study. Women with Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 who have metastatic and/or recurrent PD-L1–positive cervical cancer are eligible.

Additional patients may be subsequently randomized in [redacted]

After providing informed consent, patients will undergo screening procedures as outlined in the schedule of activities. Patients who do not meet the criteria for participation in this study (screen failure) may qualify for an additional two re-screening opportunities (for a total of three screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are rescreened within 60 days after previously signing the consent form. The investigator will record reasons for screen failure in the screening log.

During screening, tumor specimens from each potentially eligible patient will be prospectively tested for PD-L1 expression, as assessed by a central laboratory, using the [redacted]. Only patients who are PD-L1–positive with [redacted] will be enrolled.

Eligible patients will be randomized in a 3:1 ratio to receive either tiragolumab in combination with atezolizumab or atezolizumab alone.

Eligible patients will be stratified by ECOG Performance Status (0 versus 1), prior use of chemoradiotherapy or radiotherapy (yes versus no), and treatment history (persistent versus recurrent disease).

In the doublet arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion every 3 weeks (Q3W) on Day 1 of each 21-day cycle, followed by tiragolumab at a fixed dose of 600 mg administered by IV infusion Q3W also on Day 1 of each 21-day cycle.

In the atezolizumab monotherapy arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle.

Treatment may be continued as long as patients are experiencing clinical benefit, as assessed by the investigator, in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status. Patients who meet the criteria for equivocal disease progression per RECIST v1.1 will be permitted to continue treatment (tiragolumab in combination with atezolizumab or atezolizumab alone) if they meet all of the criteria specified.

During the study, serum samples will be collected to monitor tiragolumab in combination with atezolizumab and atezolizumab pharmacokinetics and to detect the presence of antibodies to tiragolumab and atezolizumab. Patient samples, including archival and fresh tumor tissue, serum, plasma, and blood samples, will also be collected for [redacted]

Patients will undergo tumor assessments at baseline and every 6 weeks (±7 days) for 48 weeks following Day 1 of Cycle 1 regardless of treatment delays. After the completion of the Week 48 tumor assessment, tumor assessments will be required every 9 weeks (±7 days) regardless of treatment delays until unequivocal radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after disease progression per RECIST v1.1), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Patients who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments at the frequency described above until study

treatment is discontinued. Patients who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. In the absence of radiographic disease progression per RECIST v1.1, tumor assessments should continue regardless of whether a patient starts a new anti-cancer therapy.

Response will be assessed according to RECIST v1.1. Objective response will be determined at a single timepoint by the IRC according to RECIST v1.1.

Crossover is allowed from the atezolizumab monotherapy arm to the tiragolumab plus atezolizumab arm after unequivocal progressive disease has been recorded during atezolizumab monotherapy, at the discretion of the investigator and after consultation with the Medical Monitor. For patients who crossover from atezolizumab monotherapy to tiragolumab plus atezolizumab, the tumor assessment just preceding crossover will serve as a rebaseline scan against which all subsequent scans will be compared.

After initiation of study treatment, all adverse events will be reported according to the adverse event reporting period. After this period, all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigators become aware of any serious adverse events or adverse events of special interest that are believed to be related to prior treatment with study drug(s). These events should be reported using the Adverse Event electronic Case Report Form (eCRF). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or protocol-related procedures until a final outcome can be reported.

After study treatment discontinuation, survival follow-up information will be collected by means of telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted 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 study, study staff may use a public information source (e.g., county records) when permissible to obtain information about survival status only.

Treatment after Disease Progression

During the study, patients who meet criteria for disease progression per RECIST v1.1 and show evidence of clinical benefit may continue study treatment at the investigator's discretion provided that the patients meet all of the following criteria:

- Evidence of clinical benefit, as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values indicating unequivocal progression of disease)
- No decline in ECOG Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Safety Monitoring

The Sponsor will monitor patient safety throughout the study. In addition to the ongoing assessment of the incidence, nature, and severity of adverse events; deaths; vital signs; and laboratory abnormalities, the Sponsor will review all cumulative data at regular intervals during the study.

Internal Monitoring Committee

An Internal Monitoring Committee (IMC) composed of representatives from safety science, clinical science, and statistics, who are independent from the study team, will be established. Representatives from other functions may be added on an ad hoc basis depending on the nature of the findings. The primary responsibility of the IMC is to evaluate the safety, not

efficacy, of treatment arms being evaluated. The IMC will share responsibility with the study team for the monitoring of patient safety.

The IMC may meet during the course of the study. The IMC may conduct an ad hoc meeting should an unexpected safety concern arise, as specified in the IMC Charter. At the time of each review of cumulative data, the IMC may make recommendations in consideration of the totality of the available data. Specific operational details such as the committee's composition, timing of meetings, and members' roles and responsibilities will be detailed in an IMC Charter.

Number of Patients

Approximately 160 patients with metastatic and/or recurrent PD-L1–positive cervical cancer will be enrolled in the global enrollment phase. A total of approximately [redacted]

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Life expectancy ≥ 12 weeks
- Ability to comply with the study protocol
- ECOG Performance Status of 0 or 1
- Histologically confirmed recurrent or persistent squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix (neuroendocrine, clear cell, and sarcoma histologies are not allowed) after progression on or after 1–2 lines of prior systemic chemotherapy in the metastatic/recurrent setting that is not amenable to curative treatment with systemic chemotherapy, surgery, and/or radiotherapy

  At least one prior line of platinum-based systemic chemotherapy.

  Radiosensitizing cisplatin given with radiotherapy is not considered a line of systemic chemotherapy.
- Measurable disease, defined as:
  - At least one lesion that can be accurately and reliably measured in at least one dimension using computed tomography (CT) or magnetic resonance imaging (MRI) scan. Positron emission tomography (PET-CT) may be used if the CT portion is of diagnostic quality.
  - Tumors within a previously irradiated field cannot serve as a “target lesion”; however, they may serve as a “non-target lesion.”
- Formalin-fixed, paraffin-embedded (FFPE) cervical cancer tissue specimen (archival or tissue obtained from biopsy at screening) that is PD-L1 positive, as determined by the [redacted], with positivity defined as [redacted] as determined by a central laboratory
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to randomization:
  - [redacted]

- [redacted]
  - [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
- [redacted]
- Recovery from the effects of surgery, radiotherapy, or chemoradiotherapy

  At least 6 weeks must have elapsed from the last administration of chemoradiotherapy, and at least 3 weeks must have elapsed from the last administration of radiotherapy alone.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period, for 90 days after the final dose of tiragolumab, and for 5 months after the final dose of atezolizumab.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

<u>Exclusion Criteria</u>

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

- FFPE cervical cancer tissue specimens (archival or tissue obtained from biopsy at screening) that is PD-L1 negative, as determined by the [redacted], with negativity defined as [redacted], as determined by a central laboratory

- Pregnant or breastfeeding, or intending to become pregnant during study treatment, within 90 days after the final dose of tiragolumab, or within 5 months after the final dose of atezolizumab

  Women of childbearing potential must have a negative pregnancy test result within 14 days prior to Cycle 1, Day 1.
- Treatment with investigational therapy with therapeutic intent within 28 days prior to randomization
- Planned surgery during the study
- Current treatment with anti-viral therapy for [redacted]
- Substance abuse within 12 months prior to screening, in the investigator's judgment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Bilateral hydronephrosis that cannot be alleviated by ureteral stents or percutaneous drainage
- History of other malignancy within 5 years prior to screening, except for those with an expected negligible risk for metastases or death (e.g., 5-year OS > 90%) after curative treatment

  Examples include appropriately treated basal or squamous cell skin carcinoma, Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) Stage I Grade 1 uterine cancer or ductal carcinoma in situ of the breast.
- Active or untreated CNS or brain metastases
- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for ≥ 1 week prior to randomization
- Leptomeningeal disease
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, total serum calcium > 12 mg/dL, or corrected serum calcium greater than ULN)
- Known, clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease, or current alcohol abuse
- Active or history of autoimmune disease or immune deficiency, [redacted]
- [redacted]

[redacted]

- Active tuberculosis
- Severe infection per investigator judgment at the time of randomization, including, but not limited to, use of systemic antibiotics, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that, in the opinion of the investigator, could impact patient safety
- Significant cardiovascular disease, such as cardiac disease New York Heart Association Class II or greater, myocardial infarction, or cerebrovascular accident within 3 months prior to randomization, unstable arrhythmias, or unstable angina

  Patients with known coronary artery disease, congestive heart failure not meeting the above criterion or with a 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.
- Major surgical procedure other than for diagnosis within 28 days prior to randomization or anticipation of need for a major surgical procedure during the study
- 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 renders the patient at high risk for treatment complications
- Illnesses or conditions that interfere with the patient's capacity to understand, follow, and/or comply with study procedures
- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation that such a live attenuated vaccine will be required during the study
- Patients must not receive live, attenuated influenza vaccines (e.g., FluMist®) within 4 weeks prior to randomization, during treatment, for 90 days following the last dose of tiragolumab, and for 5 months following the last dose of atezolizumab.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti–CTLA-4, anti-TIGIT, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2 [IL-2]) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to randomization
- Treatment with systemic immunosuppressive medications (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 1 week prior to randomization or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
  - [redacted]
  - [redacted]
- History of severe allergic anaphylactic reactions to chimeric, fully humanized, or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the tiragolumab or atezolizumab formulations

End of Study

The end of this study is defined as the date when the "last patient last visit" occurs (i.e., when the last patient has recorded her last visit). The end of the study is expected to occur approximately [redacted] months after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time. If the Sponsor decided to terminate the study, patients who are still receiving study treatment or undergoing survival follow-up may be enrolled in an extension study.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 36 months.

Investigational Medicinal Products

Test Products (Investigational Drugs)

Atezolizumab

In the atezolizumab monotherapy arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle.

Treatment may be continued as long as patients are experiencing clinical benefit, as assessed by the investigator, in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

Tiragolumab and Atezolizumab

In the doublet arm, patients will receive atezolizumab at a fixed dose of 1200 mg administered by IV infusion Q3W on Day 1 of each 21-day cycle, followed by tiragolumab at a fixed dose of 600 mg administered by IV infusion Q3W also on Day 1 of each 21-day cycle. The tiragolumab and atezolizumab doses are fixed and are not dependent on body weight.

Administration of tiragolumab and atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Statistical Methods

Primary Analysis

The primary efficacy objective for this study is to evaluate the efficacy of tiragolumab in combination with atezolizumab and of atezolizumab monotherapy on the basis of the following endpoint:

- ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions $\geq$4 weeks apart, as determined by the IRC according to RECIST v1.1

The primary efficacy analysis population will consist of all randomized patients who receive at least one dose of study treatment, with patients grouped according to treatment received.

The primary efficacy analysis will take place once all patients have been enrolled and a minimum follow-up of approximately 6 months after the second tumor assessment, or approximately 9 months after randomization, has been achieved among those patients, who remain in follow-up for ORR assessment, whichever is earlier.

In the primary analysis, patients whose ORR assessment was missing will be counted as not achieving a response. A one-sample z-test for proportion will be used for comparing the ORR of the tiragolumab in combination with atezolizumab arm to the historical reference. An estimate of the ORR and its 95% CI will be calculated for each treatment arm.

Determination of Sample Size

A total of 160 patients will be enrolled in this study and randomized in a 3:1 ratio (tiragolumab in combination with atezolizumab and atezolizumab monotherapy). The overall statistical power for several assumptions of the true underlying ORR in tiragolumab in combination with atezolizumab arm takes the following considerations into account:

- Primary statistical test is a [redacted] at a one-sided [redacted] significance level, and the doublet arm will be compared to a historical reference of 14.6%.

- [redacted].

No type-I error control is applied for descriptive comparisons, including that of the atezolizumab monotherapy ORR to the historical reference.

[redacted]

Appendix 2 Schedule of Activities

Assessment/Procedure (Window)	Screening	All Treatment Cycles [a]	Treatment Discontinuation	Long-Term Survival Follow-Up
	Days –28 to –1 [b]	Every 21 days (±3 Days) [c]	≤ 30 Days after Final Dose	Approximately Every 3 Months after Disease Progression or Loss of Clinical Benefit [d]
Informed consent	x			
Archival or fresh tumor tissue specimen for PD-L1 testing (20 FFPE slides required; blocks preferred) [e, f]	x			
Demographics (age, sex, and self-reported ethnicity/race)	x			
Medical and cervical cancer history, and baseline conditions	x			
Vital signs [g]	x	x	x	
Weight	x	x	x	
Height	x			
Complete physical examination [h]	x			
Limited physical examination [h]		x		
ECOG Performance Status	x	x	x	
ECG [i]	x			
Hematology [j]	x	x	x	
Chemistry [k]	x	x	x	
Coagulation test (PT [or INR] and aPTT [or PTT])	x		x	

Assessment/Procedure (Window)	Screening Days –28 to –1[b]	All Treatment Cycles[a] Every 21 days (±3 Days)[c]	Treatment Discontinuation ≤ 30 Days after Final Dose	Long-Term Survival Follow-Up Approximately Every 3 Months after Disease Progression or Loss of Clinical Benefit[d]
Pregnancy test[l]	x[l]	x	x	
TSH, free T3, and free T4[m]	x	x	x	
[redacted]				
Urinalysis[o]	x			
Arm A: atezolizumab plus tiragolumab administration[p]		x		
Arm B: atezolizumab administration[p]		x		
Tumor response assessment[q]	x	x[r]		x[s]
[redacted]				
Concomitant medications[t]	x	x	x	
Adverse events[u]		x	x	x[u]
Survival and anti-cancer follow-up[v]				x

ADA=anti-drug antibody; CT=computed tomography; [redacted] ECOG=Eastern Cooperative Oncology Group; eCRF=electronic Case Report Form; FFPE=formalin-fixed, paraffin-embedded; [redacted]; MRI=magnetic resonance imaging; NA=not applicable; PCR=polymerase chain reaction; PD-L1=programmed death–ligand 1; PK=pharmacokinetic; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone.

[a] Assessments should be performed before study drug infusion unless otherwise noted.

[b] Adequate hematologic and end-organ function, defined by laboratory test results, must be obtained within 14 days prior to randomization.

[c] Cycle 1 must be performed within 5 days after the patient is randomized. Screening assessments performed ≤ 4 days prior to Cycle 1, Day 1 are not required to be repeated for the Cycle 1, Day 1 infusion.

[d] This visit can also be conducted by telephone; therefore, clinic visit examinations may not occur. Approximately every 3 months is defined as every 84 days ±7 days.

[e] [redacted]

[f] Biomarker samples should not be collected for patients enrolling from [redacted]. Samples collected should match the number of slides allowed per [redacted]

[g] Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Vital signs should be recorded as described in Section 4.5.4 of the protocol.

[h] Complete physical examination must include pelvic examination. Limited physical examination will be a symptom-directed physical examination, as clinically indicated; see Section 4.5.3 of the protocol for details.

[i] ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

[j] Hematology consists of WBC count, hemoglobin, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes).

[k] Chemistry panel (serum or plasma) includes sodium, potassium, glucose, BUN or urea, creatinine, albumin, total calcium, total and direct bilirubin, ALP, ALT, AST, and LDH.

[l] Pregnancy test should be performed for women of childbearing-potential only. Pregnancy test (serum or urine) must be performed ≤14 days prior to Cycle 1, Day 1. A positive urine pregnancy test must be confirmed by a quantitative serum pregnancy test and an ultrasound confirming intrauterine pregnancy.

[m] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycles 1, 5, 9, and 13, and every fourth cycle thereafter. The thyroid-function test in Cycle 1 does not need to be performed if the previous test was performed within the screening window.

[n] [redacted]

[o] Urinalysis is required at screening and can be by dipstick (glucose, protein, ketones, blood, leukocyte esterase, nitrites, WBC, bacteria, and epithelial cells).

[p] The initial cycle of atezolizumab plus tiragolumab or atezolizumab monotherapy should be administered over [redacted] minutes for each agent. Subsequent infusions of each agent should be infused over [redacted] minutes if the previous infusion was tolerated without an infusion-related reaction, or [redacted] minutes if patient experienced an infusion-related reaction with the previous infusion (see Section 4.3.2 of the protocol). For the tiragolumab and atezolizumab doublet, the tiragolumab must be administered after the atezolizumab.

[q] At screening and subsequent visits, CT scans (with oral and/or IV contrast, unless contraindicated) or MRI scans of the chest-abdomen-pelvis will be performed. A CT (with contrast) or MRI scan of the brain must be done at screening to evaluate CNS metastases in symptomatic patients, as clinically indicated. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Refer to Section 4.5.6 of the protocol.

[r] Perform every 6 weeks (±7 days) for 48 weeks following Day 1 of Cycle 1, regardless of treatment delays. After completing the Week 48 tumor assessment, tumor assessments will be required every 9 weeks (±7 days) regardless of treatment delays, until unequivocal radiographic disease progression per RECIST v1.1 (or loss of clinical benefit for patients who continue study treatment after RECIST v1.1–defined disease progression), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

[s] If a patient discontinues study treatment for any reason other than radiographic RECIST v1.1–defined disease progression (e.g., toxicity, symptomatic deterioration), tumor assessments will continue at the same frequency as would have been followed if the patient had remained on study treatment (i.e., every 6 weeks [±7 days]) for 48 weeks following Day 1 of Cycle 1, and then every 9 weeks [±7 days] thereafter) until unequivocal radiographic disease progression per RECIST v1.1, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs, first, even if the patient starts another anti-cancer therapy after discontinuing study treatment. See Section 4.6.1 of the protocol for details.

[t] From 7 days prior to initiation of study drug until the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

[u] [redacted] Adverse events of special interest will be reported until 90 days after the final dose of study treatment, regardless of initiation of new anti-cancer therapy. After this period, all deaths should continue to be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that is believed to be related to prior exposure to study treatment (see Section 5.6 of the protocol). These events should be reported on the Adverse Event eCRF.

[v] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits every 3 months until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first. All patients will be periodically contacted 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 study, study staff may use a public information source (e.g., county records) to obtain information about survival status only.