Official Title: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) as Adjuvant Therapy After Definitive Local Therapy in Patients With High-Risk Locally Advanced Squamous Cell Carcinoma of the Head and Neck

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STATISTICAL ANALYSIS PLAN

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) AS ADJUVANT THERAPY AFTER DEFINITIVE LOCAL THERAPY IN PATIENTS WITH HIGH-RISK LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK**
PROTOCOL NUMBER:	WO40242
STUDY DRUG:	Atezolizumab
VERSION NUMBER:	2
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EUDRACT NUMBER:	2017-003302-40
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted], Ph.D.
DATE FINAL:	See electronic date stamp below

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

Date and Time(UTC)	Reason for Signing	Name
30-Mar-2022 02:31:26	Company Signatory	[redacted]

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

A plan for a formal analysis of OS at the interim EFS analysis has been added in accordance with Type C WRO FDA feedback, dated 18 March 2020, regarding the format and content of a potential marketing application based on the results of Study WO40242. Specifically, a nominal α of 0.001% is spent on the OS analysis at the interim EFS analysis (Sections 2.3 and 2.4).

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

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1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and the statistical methods for the Study WO40242 (hereinafter IMvoke010), "A Phase III, multicenter, randomized, double-blind, placebo-controlled study of Atezolizumab (Anti–PD–L1 antibody) as adjuvant therapy after definitive local therapy in patients with high-risk locally advanced squamous cell carcinoma of the head and neck". The background for the study can be found in the study protocol. The analyses described in this SAP will supersede those specified in Protocol WO40242 for the purposes of a regulatory filing.

2. STUDY DESIGN

IMvoke010 is a global Phase III, multicenter, randomized, double-blind, placebo-controlled study of atezolizumab as adjuvant therapy after definitive local therapy (DLT) in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) who are at high risk for disease recurrence or progression following DLT. The study is designed to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of adjuvant treatment with atezolizumab compared with placebo in patients with locally advanced SCCHN who have not progressed after receiving definitive local therapy.

Male and female patients ≥18 years of age who have an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and histologically confirmed SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, and who have received definitive local therapy and are classified as being at high risk for recurrence or progression are eligible for study participation. The definition of high risk is based on the American Joint Committee on Cancer (AJCC) 8th Edition Cancer Staging Manual and includes:

- Human papillomavirus (HPV)-negative Stage IVA T4a + N0–N2 or T1–T3 + N2 SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, regardless of tobacco use history
- HPV-negative Stage IVB T1–T4a + N3 or T4b + N0–N3 SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, regardless of tobacco use history
- HPV-positive oropharyngeal carcinoma Stage III (clinical T1–T2 + N3) and ≥ 10 pack year smoking history and/or ≥ 10-year smokeless tobacco use history
- HPV-positive oropharyngeal carcinoma Stage III (clinical T3 + N3 or clinical T4 + N0–N3 or pathologic T3–T4 + N2) regardless of tobacco use history

Approximately 406 patients globally will be randomized. All eligible patients will be randomized in a 1:1 ratio to one of the following arms:

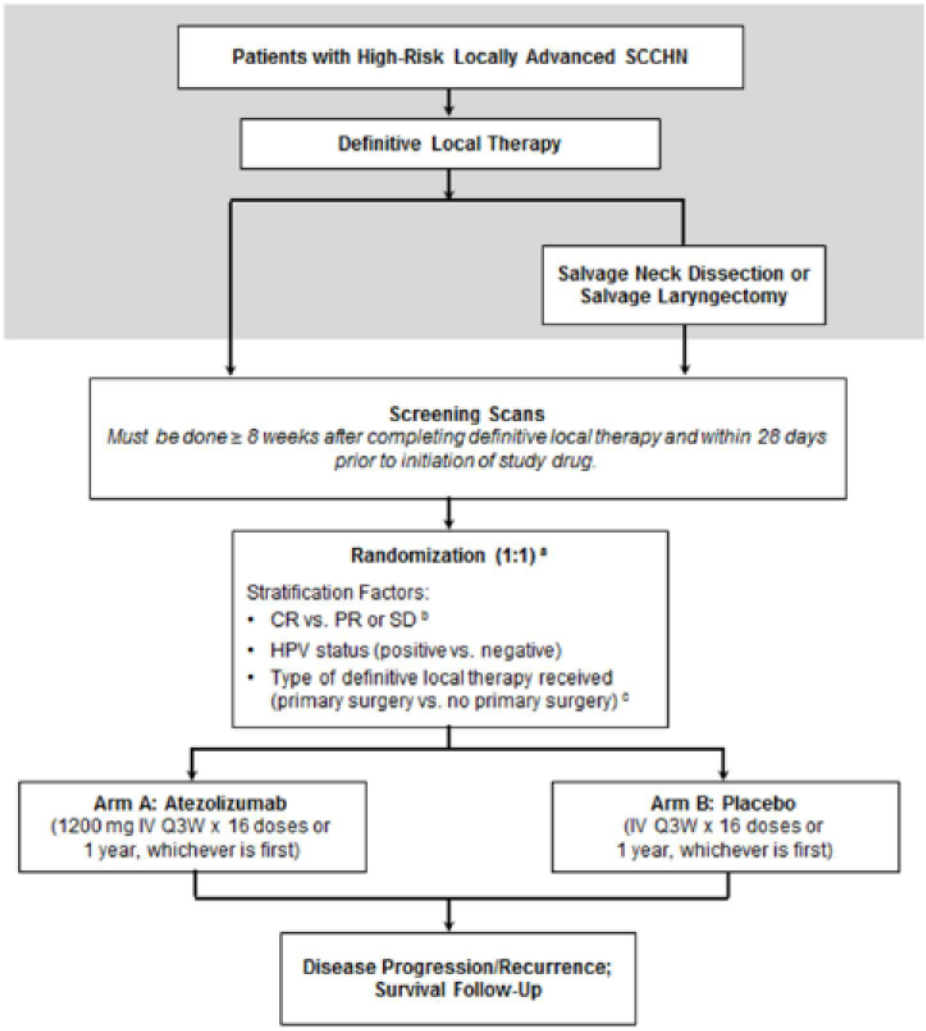
- Arm A (experimental arm): atezolizumab 1200 mg (21-day cycle for 16 cycles or until 1 year)
- Arm B (control arm): placebo (21-day cycles for 16 cycles or until 1 year)

Randomization will be stratified by the following three factors:

- Response to definitive local therapy (complete response [CR] vs. partial response [PR] or stable disease [SD])
- HPV status (positive vs. negative) - Patients with HPV-positive oropharyngeal carcinoma will be limited to 20% of study population
- Type of definitive local therapy received (primary surgery vs. no primary surgery)

Figure 1 illustrates the study design. Further details of the study design can be found in the protocol.

Figure 1 Study Schema



CR=complete response; C1D1=Cycle 1 Day 1; concurrent CRT=concurrent chemoradiation; HPV=human papillomavirus; PD=progressive disease; PR=partial response; Q3W=every 3 weeks; RT=radiation therapy; SCCHN=squamous cell carcinoma of the head and neck; SD=stable disease.

Note: Shaded box indicates off-study treatments.

[a] Patients must initiate study treatment (C1D1) within 28 days of the screening scans (post-definitive local therapy scans), and within 16 weeks after completion of definitive local therapy (if salvage neck dissection or salvage laryngectomy was not performed) or within 20 weeks after completion of definitive local therapy (if salvage neck dissection or salvage laryngectomy was performed). The date of completion of definitive local therapy is exclusive of salvage surgery.

[b] In the event scans are performed prior to conducting a salvage surgery, the response to initial definitive local therapy prior to salvage surgery should be used for stratification.

[c] Primary surgery: primary surgery followed by either postoperative RT or postoperative concurrent CRT, induction chemotherapy followed by primary surgery alone, or induction chemotherapy followed by primary surgery followed by RT or concurrent CRT.
No primary surgery: induction chemotherapy followed by RT or concurrent CRT, concurrent CRT alone, or any of the aforementioned modalities followed by salvage neck dissection or salvage laryngectomy (salvage laryngectomy is only for patients with laryngeal or hypopharyngeal cancer).

Patients will undergo scheduled tumor assessments (see Appendix 2 and Appendix 3 for details) via imaging at baseline and every 9 weeks following Cycle 1 Day 1 (every three cycles) for the first 2 years. Tumor assessments will occur every 12 weeks during Year 3, and every 16 weeks during Years 4 and 5, and annually thereafter at the investigator's discretion as clinically indicated. Tumor assessments will continue per schedule regardless of whether study drug is given, held, or discontinued (even if a new follow-up anti-cancer therapy is started) until death, disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), disease progression (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1), loss to follow-up, the end of Year 5, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patients who are randomized with evidence of residual disease at baseline (as assessed by screening scans) will be assessed for disease progression according to RECIST v1.1. For patients who are randomized with no evidence of disease at baseline (as assessed by screening scans), disease recurrence will be determined and confirmed based on unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis. All patients will undergo a physical examination every 3 weeks, and if recurrent or progressive disease is suspected on clinical grounds, tumor assessments must be performed expeditiously, even if not mandated in the schedule of activities. In cases of equivocal radiographic evidence of recurrence or progression, recurrence or progression must be confirmed by repeat tumor assessments after 9 weeks or earlier as clinically indicated.

The primary efficacy endpoint of this study is event-free survival (EFS), as assessed by the investigator according to unequivocal radiographic evidence of disease recurrence or unequivocal radiographic evidence of progression per RECIST v1.1. See Section 2.2 for details on the primary efficacy endpoint, secondary endpoints, and other endpoints such as safety, and exploratory endpoints.

There is one interim futility and efficacy analysis planned for investigator-assessed EFS in this study when approximately 146 EFS events have occurred, which is approximately 47 months after the first patient is randomized.

An external independent Data Monitoring Committee (iDMC) will evaluate safety data and interim futility and efficacy analyses for investigator-assessed EFS according to policies and procedures detailed in an iDMC Charter.

The end of this study will occur when both of the following criteria have been met:

- The last patient, last visit (LPLV) has occurred
- Approximately 191 deaths have occurred in the intent-to-treat (ITT) population

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study is expected to be approximately 111 months.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1 and includes the study objectives, inclusion and exclusion criteria, outcome measures, and statistical methods as stated in the Protocol. For additional details, see the Schedule of Assessments in Appendix 2 and Appendix 3.

2.2 ENDPOINTS

This study will evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of atezolizumab compared with placebo as adjuvant therapy after definitive local therapy in patients with high-risk locally advanced SCCHN.

2.2.1 Primary Efficacy Endpoint

The primary efficacy endpoints for this study is investigator-assessed EFS, defined as the time from randomization to the first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression (per RECIST v1.1) per assessment by investigator, or death from any cause, whichever occurs first.

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study are the following:

- OS, defined as the time from randomization to death from any cause
- Independent Review Facility (IRF)-assessed EFS, defined as the time from randomization to the first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression (per RECIST v1.1) per assessment by IRF, or death from any cause, whichever occurs first
- Investigator-assessed EFS and IRF-assessed EFS at 1, 2, 3, and 4 years
- OS at 2, 3, and 5 years
- Change from baseline in physical functioning over time while receiving treatment as assessed through use of the five-item Physical Functioning subscale (Questions 1–5) of the European Organisation for Research and Treatment of Cancer Quality-of-Life–Core 30 Questionnaire (EORTC QLQ-C30)
- Change from baseline in health-related quality of life (HRQoL) over time while receiving treatment as assessed through use of the two-item GHS/QoL subscale (Questions 29 and 30) of the EORTC QLQ-C30

2.2.3 Safety Endpoints

- The incidence and severity of adverse events, including serious adverse events and immune-mediated adverse events, with severity determined according to National

Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0

2.2.4 Pharmacokinetic Endpoints

- Serum concentration of atezolizumab at specified time points

2.2.5 Immunogenicity Endpoints

- Incidence of anti-drug antibody (ADA) response to atezolizumab

2.2.6 Exploratory Endpoints

2.2.6.1 Exploratory Immunogenicity Endpoints

- Relationship between ADA status and efficacy, safety, or pharmacokinetic endpoints.

2.2.6.2 Exploratory Biomarker Endpoints

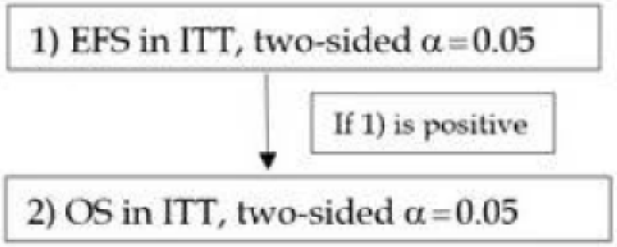
- Relationship between biomarkers (e.g., programmed death- Ligand 1 [PD-L1], ctDNA, Tumor Mutation Burden [TMB] and others) in tumor tissue and/or blood and efficacy, disease status, resistance, or other biomarker endpoints.
- Relationship between biomarkers at the time of recurrence (i.e., local recurrence, new second primary SCCHN lesion, or development of distant metastasis) or progression of disease and any immunomodulatory activity of atezolizumab (i.e., tumor-immune infiltration) in patients with confirmed recurrence or progression of disease in patients assigned to atezolizumab

2.2.6.3 Exploratory PRO Endpoints

- Change from baseline over time of treatment/disease-related symptoms as evaluated by selected items of the EORTC QLQ-C30 and Quality of Life–Head and Neck Cancer, Module 35 Questionnaire (QLQ-H&N35) questionnaires during treatment, treatment discontinuation and survival follow-up
- Time to confirmed deterioration (TTCD) in Physical Functioning, GHS/QoL, Dyspnea, Fatigue, and Appetite Loss subscales of EORTC QLQ-C30, and Pain subscale and Choking item of EORTC QLQ-H&N35, defined as time from randomization to deterioration (10-point change) on two consecutive assessments or one deterioration on one assessment followed by death within 9 weeks
- Utility EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L)

2.3 DETERMINATION OF SAMPLE SIZE

Figure 2 Type I Error Control Plan



EFS=event-free survival; OS = overall survival; ITT=intent-to-treat (population).

The overall type I error rate will be controlled for the two-sided test at 0.05. An overview of the α control is shown in Figure 2.

The sample size determination is based on the number of events required to demonstrate efficacy with regard to investigator-assessed EFS in the ITT population. The estimate of the number of events required is based on the following assumptions:

- Two-sided significance level of 0.05 for the EFS comparison in the ITT population
- 82% power to detect an HR of 0.65, corresponding to an improvement in median EFS from 40 months in the placebo arm to 61.5 months in the atezolizumab arm for the ITT population
- One interim futility and efficacy EFS analysis performed when approximately 80% of the total number of EFS events required for the final analysis are expected to have occurred
  - Crossing boundaries for the interim efficacy and final EFS analyses are determined through use of the Lan-DeMets approximation to the O'Brien-Fleming boundary.
- Dropout rate of 5% per 24 months

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

- Two-sided significance level of 0.05 for the OS comparison in the ITT population
- 80% power to detect an HR of 0.65, corresponding to an improvement in median OS from 70 months in the placebo arm to 107.7 months in the atezolizumab arm for the ITT population
- Two interim efficacy OS analyses performed at the time of the interim and the final EFS analyses, at which time approximately 93 OS events (i.e., 49% of the total number of OS events required for the final analysis) and 121 OS events (i.e., 63% of the total number of OS events required for the final analysis) are expected to have occurred; a nominal α of 0.001% is spent on the first interim OS analysis at the time

of the interim EFS analysis; and crossing boundaries for the second interim and final OS analyses are determined through use of the Lan-DeMets approximation to the Pocock boundary.

- Dropout rate of 5% per 36 months

The final EFS analysis will be conducted when approximately 183 EFS events have occurred in the ITT population (expected to occur approximately 59 months after the first patient is randomized) or 65 months after the first patient is randomized, whichever occurs earlier. This number of events would allow for a minimum detectable difference (MDD) corresponding to an HR of approximately 0.74 in the ITT population.

The final OS analysis will be conducted when approximately 191 OS events have occurred in the ITT population, which is expected to occur approximately 99 months after the first patient is randomized. This number of events corresponds to a MDD in HR of approximately 0.72 in the ITT population.

With these assumptions, approximately 406 patients in total will be randomized into this study.

2.4 ANALYSIS TIMING

There is one interim futility and efficacy analysis planned for the investigator-assessed EFS in this study when approximately 146 EFS events have occurred, which is approximately 47 months after the first patient is randomized. The final EFS analysis will be conducted when approximately 183 EFS events have occurred in the ITT population (expected to occur approximately 59 months after the first patient is randomized) or 65 months after the first patient is randomized, whichever occurs earlier.

Two interim efficacy OS analyses are planned at the time of the interim and final EFS analyses, at which time approximately 93 OS events (i.e., 49% of the total number of OS events required for the final analysis) and 121 OS events (i.e., 63% of the total number of OS events required for the final analysis) are expected to have occurred. The final OS analysis will be conducted when approximately 191 OS events have occurred in the ITT population, which is expected to occur approximately 99 months after the first patient is randomized.

An iDMC will be set up to evaluate safety data on an ongoing basis as well as to review the interim futility and efficacy analysis of investigator-assessed EFS. Any outcomes of these reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRBs/ECs. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an independent Data Coordinating Center (iDCC). A detailed plan will be included in the iDMC Charter.

The interim futility analysis for investigator-assessed EFS will allow potential early stopping of the trial for lack of treatment benefit. The iDMC may recommend that the

study be stopped for futility if the observed EFS hazard ratio > 0.9 of atezolizumab arm over the control arm, which provides a probability of 74% to stop the study if the true EFS hazard ratio is 1.0 (i.e., no treatment benefit based on EFS). If there is a true treatment benefit based on EFS under the target hazard ratio of 0.65, the chance of stopping for futility is 2%.

The efficacy crossing boundaries for interim efficacy and final EFS analyses will be determined through use of the Lan-DeMets approximation to the O'Brien-Fleming boundary based on the actual observed number of events. If the difference in investigator-assessed EFS is statistically significant, OS will be tested. The stopping boundaries for the second interim and final OS analyses will be determined through use of the Lan-DeMets approximation to the Pocock boundary based on the actual observed number of events. The approximate analysis timing and the stopping boundaries for the interim and final analyses for the co-primary endpoints are shown in Table 1. The exact timing of these analyses will depend on the actual accrual rate and occurrence of EFS and OS events as indicated above.

Table 1 Analysis Timing and Stopping Boundary for Interim Efficacy and Final Analysis for Investigator-Assessed Event-Free Survival and Overall Survival

Analysis	Time from FPI (months)	Investigator-Assessed EFS		OS	
		Information Fraction [a] (No. of Events)	Stopping Boundary HR (p-value [b]) α= 0.05	Information Fraction [a] (No. of Events)	Stopping Boundary HR (p-value [b]) α= 0.05
EFS IA	47	80% (146)	HR $\leq$ 0.688 ($p \leq 0.0242$)	49% (93)	HR $\leq$ 0.399 ($p \leq 0.00001$)
EFS FA and OS IA	59	100% (183)	HR $\leq$ 0.741 ($p \leq 0.0430$)	63% (121)	HR $\leq$ 0.683 ($p \leq 0.0367$)
OS FA	99	—	—	100% (191)	HR $\leq$ 0.723 ($p \leq 0.0252$)

EFS=event-free survival; FA=final analysis; FPI=first patient in; HR=hazard ratio; IA=interim analysis; No.=number; OS=overall survival.

[a] The proportion of target number of events at each look given the total target number of events.

[b] Two-sided p-value.

3. STUDY CONDUCT

3.1 RANDOMIZATION

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

- Response to definitive local therapy (CR vs. PR or SD)

- In the event scans are performed prior to conducting a salvage surgery, the response to initial definitive local therapy prior to salvage surgery should be used for stratification.

- HPV status (positive vs. negative)
  - Patients with HPV-positive oropharyngeal carcinoma will be capped at 20%.
- Type of definitive local therapy received (primary surgery vs. no primary surgery)
  - Primary surgery: patients who received a primary surgery to the primary tumor site in the head and neck as part of initial definitive local therapy regardless of whether a salvage surgery was received
  - No primary surgery: patients who did not receive a primary surgery to the primary tumor site in the head and neck as part of initial definitive local therapy, but may or may not have had a salvage surgery

3.2 INDEPENDENT REVIEW FACILITY

An Independent Review Facility (IRF) will be used to conduct a blinded centralized radiology review of the imaging data and will provide an independent assessment of tumor response data for all patients according to an IRF charter. EFS assessment by IRF will be used for the secondary efficacy endpoints (Section 4.4).

3.3 DATA MONITORING

An iDMC will be set up to evaluate safety data on an ongoing basis as well as to review the futility and efficacy analysis for investigator-assessed EFS. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities, as well as a detailed monitoring plan. All summaries and analyses by treatment arm for the iDMC's review will be prepared by an external independent data coordinating center (iDCC). Following the data review, the iDMC will provide a recommendation as to whether the study may continue, whether amendment(s) to the protocol should be implemented, whether the interim analysis boundary is crossed, or whether the study should be stopped. The final decision will rest with the Sponsor. Any outcomes of these 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. STATISICAL METHODS FOR THE GLOBAL POPULATION

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

The ITT population is defined as all randomized patients, regardless of whether they received any of the assigned treatment.

4.1.2 Pharmacokinetic-Evaluable Population

The pharmacokinetic (PK)-evaluable population is defined as all patients who have received at least one dose of atezolizumab and provided at least one PK sample that was evaluable.

4.1.3 Anti-Drug-Antibody-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.

4.1.4 Safety-Evaluable Population

The safety-evaluable population is defined as all randomized patients who received any amount of the study treatment. For the safety analyses, patients will be grouped according to whether any amount of atezolizumab was received, including when atezolizumab was received in error. Specifically, for patients who were randomized to the control arm, if atezolizumab was received in error, patients will be grouped to the atezolizumab arm for the safety analyses.

4.2 ANALYSIS OF STUDY CONDUCT

Study enrollment, study drug administration, reasons for study drug discontinuation, and reasons for study termination will be summarized for all patients in the ITT population by treatment arm. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized for ITT population by treatment arm. 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, the three stratification factors (response to definitive local therapy, type of definitive local therapy and HPV status), and baseline disease characteristics (e.g., ECOG performance status, tobacco use, disease stage, primary tumor site) will be summarized by treatment arm for the ITT population.

Baseline values are the last available data obtained prior to the patient receiving the first dose of study treatment, unless otherwise noted. Summary of descriptive statistics (i.e., mean, standard deviation, median, and range) will be presented for continuous variables and frequencies (percentages) and/or proportions will be presented for categorical variables.

4.4 EFFICACY ANALYSIS

Efficacy analyses will be performed on the ITT population. Patients will be grouped according to the treatment assigned at randomization by IxRS.

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is EFS, as assessed by the investigator according to unequivocal radiographic evidence of disease recurrence or unequivocal radiographic evidence progression per RECIST v1.1.

EFS is defined as the time from randomization to the first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression (per RECIST v1.1) or death from any cause, whichever occurs first. Patients who have not experienced disease recurrence or progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of randomization.

The timing of the final investigator-assessed EFS and OS analyses is described in Section 2.4. Interim analyses are planned for both investigator-assessed EFS and OS endpoints; the details are described in Section 2.4.

To control the overall type I error rate for the two-sided test at 0.05, comparisons between treatment arms with respect to investigator-assessed EFS and OS will be conducted hierarchically (see Section 2.3).

The primary analysis of the study will test the equality of EFS distributions in two arms:

H_0: $S_{EFS\_A}(t) = S_{EFS\_B}(t)$ versus H_1: $S_{EFS\_A}(t) \neq S_{EFS\_B}(t)$

EFS will be compared between treatment arms with the use of the stratified log rank test. The HR for EFS for the comparison will be estimated using a stratified Cox regression model. If the estimate of the HR is < 1 and the two-sided p-value corresponding to the stratified log-rank test is less than the specified α level, then the null hypothesis will be rejected and it will be concluded that atezolizumab prolongs the duration of EFS relative to control treatment. The 95% CI for the HR will be provided. The stratification factors will be those used during randomization, as recorded in the IxRS.

Results from an unstratified analysis will also be presented.

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

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 Overall Survival

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 when they were last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization. The methodologies outlined

for the investigator-assessed EFS (see Section 4.4.1) will be used for the analyses of OS.

4.4.2.2 Event-Free Survival Assessed by IRF

The methodologies outlined for the investigator-assessed EFS (see Section 4.4.1) will be used for the analyses of IRF-assessed EFS.

4.4.2.3 Investigator-Assessed and IRF-Assessed Event-Free Survival at Landmark Timepoints

Investigator-assessed and IRF-assessed EFS at 1, 2, 3, and 4 years are defined as the probabilities that patients do not have EFS events 1, 2, 3 and 4 years after randomization, respectively. The EFS rates in the ITT population will be estimated using Kaplan Meier methodology for each treatment arm, along with 95% CIs calculated using the standard error derived from the Greenwood formula. The 95% CI for the difference in EFS rates between the two treatment arms will be estimated using the normal approximation method.

4.4.2.4 Overall Survival at Landmark Timepoints

OS at 2, 3, and 5 years is defined as the probabilities that patients do not have an OS events 2, 3 and 5 years after randomization. The OS rates in the ITT population will be analyzed using the same methods as outlined in Section 4.4.2.3.

4.4.2.5 Patient-Reported Outcomes

The secondary PRO endpoints are the change in scores from baseline over time in the Physical Function and Global Health Status subscales of the EORTC QLQ-C30 questionnaire. These assessments collect data about symptoms commonly associated with cancer treatments, and disease and treatment impact on patients' functioning.

The Physical Function (items 1-5 in QLQ-C30) and GHS/QoL (items 29 and 30 in QLQ-C30) scales will be scored according to the EORTC scoring manual, 3rd edition (Fayers et al. 2001). A high score for the Physical Function subscale represents a high/healthy level of functioning and a high score for the GHS/QoL subscale represents a high HRQoL. Both scales will be linearly transformed so that each score will range from 0 to 100. Patients perceive a ≥10-point change in the EORTC subscale score as clinically significant (Osoba et al. 1998). Therefore, a change score from baseline of at least 10 points per scale will be used to define clinically meaningful improvement and deterioration. All the analyses of Physical Functioning and Global Health Status will be performed for the ITT population.

Visit Score Summary and Change from Baseline

Visit summary and change from baseline analyses will be provided for the Physical Function and Global Health Status subscale of the EORTC QLQ-C30 at each assessment timepoint during the study through the completion of treatment and

follow-up assessments. Summary statistics for the standardized scores (number of patients, mean, standard deviation, median, minimum and maximum score), and score change(s) from baseline to each timepoint will be presented by treatment arm.

Completion Rate

Completion rates will be summarized by listing the number and proportion of patients among those expected to complete the EORTC QLQ-C30 questionnaire at each timepoint in the ITT population.

4.4.3 Sensitivity Analyses

The sensitivity analyses will use statistical methodologies analogous to those used in the primary analysis of investigator-assessed EFS as specified in Section 4.4.1.

4.4.3.1 Impact of Missing Tumor Assessments on Investigator-assessed EFS

The potential impact of missing scheduled tumor assessments on the primary analysis of investigator-assessed EFS will be assessed depending on the number of patients who missed consecutive assessments scheduled immediately prior to the date of the EFS event. The following two sensitivity analyses may be performed:

- If a patient missed two or more assessments scheduled immediately prior to the date of the EFS event (disease recurrence, disease progression, or death), the patient will be censored at the last tumor assessment prior to the missed visits;
- If a patient missed two or more assessments scheduled immediately prior to the date of the EFS event, the patient will be counted as having the EFS event on the date of the first of these missing assessments.

Statistical methodologies analogous to those used in the primary analysis of EFS as specified in Section 4.4.1 will be used for this sensitivity analysis.

4.4.3.2 Impact of Non-Protocol-Specified Anti-Cancer Therapy on Investigator-assessed EFS and OS

The impact of non−protocol-specified anti-cancer therapy on EFS may be assessed, depending on the number of patients who receive non−protocol-specified anti-cancer therapy before an EFS event. If >5% of patients received non−protocol-specified anti-cancer therapy before an EFS event in any treatment arm, a sensitivity analysis will be performed in which data from patients who receive non−protocol-specified anti-cancer therapy before an EFS event will be censored at the last tumor assessment date before receipt of non−protocol-specified anti-cancer therapy.

The impact of non−protocol-specified anti-cancer therapy on OS may be assessed, depending on the number of patients who receive non−protocol-specified anti-cancer therapy before an OS event. If >10% of patients received non−protocol-specified anti-cancer therapy before an OS event in any treatment arm, a sensitivity analysis will be performed using a discount method. The discount method uses a 'discounted'

survival time for both treatment arms, after switching for patients who switch treatments based on a user-specified assumption for the effect on OS. The duration from initiation of non-protocol-specified anti-cancer therapy to death or censoring date will be discounted in accordance with a range of possible effects on OS of subsequent non-protocol-specified anti-cancer therapy (e.g., 20%, 30%, 50%, etc.).

4.4.3.3 Impact of Treatment Discontinuation due to Adverse Events on Investigator-assessed EFS

A sensitivity analysis will be performed to assess the impact of treatment discontinuation due to adverse events on the investigator-assessed EFS analysis if >5% patients discontinue study treatment due to adverse events prior to an EFS event. In this analysis, the EFS for any patients who discontinue study treatment due to adverse events prior to an EFS event will be censored at the time of the last tumor assessment prior to treatment discontinuation.

4.4.3.4 Impact of Loss to Follow-Up on EFS

The impact of loss to follow-up on EFS 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 EFS in either treatment arm, a sensitivity analysis will be performed in which patients who are lost to follow-up will be considered to have recurrent disease/disease progression at the date of the last tumor assessment.

4.4.3.5 Impact of Loss to Follow-Up on OS

The impact of loss to follow-up on OS 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 OS in either treatment arm, a sensitivity analysis will be performed in which patients who are lost to follow-up will be considered having died at the last date they were known to be alive.

4.4.4 Subgroup Analyses

The duration of investigator-assessed EFS and OS may be examined in subgroups to assess the consistency of the study results. These subgroups are defined by the following:

- Demographics (e.g., age, sex, and race, ethnicity, region)
- Baseline prognostic characteristics (e.g., ECOG performance status, tobacco use history)
- Baseline disease characteristics (e.g., response to definitive local therapy [CR vs. PR/SD], HPV status [positive vs. negative] and primary surgery status (primary surgery vs. no primary surgery); AJCC Staging at Initial Diagnosis, Site of primary tumor)

Summaries of EFS and OS, including unstratified HRs estimated from Cox proportional hazards models will be displayed in a forest plot (Lewis and Clarke 2001). Kaplan-Meier

estimates of median EFS and OS will be produced separately for each level of the subgroups for the comparisons between two treatment arms.

4.5 PHARMACOKINETIC ANALYSES

PK analyses will be performed on the pharmacokinetic-evaluable population.

Atezolizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized. Summary of descriptive statistics (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean coefficient of variation) will be tabulated by cycle, as appropriate and as data allow. Individual and mean serum atezolizumab concentrations will be plotted. Atezolizumab concentration data may be subjected to population analyses to derive PK parameters such as CL, volume of distribution, and area under the curve, as warranted by the data. Potential correlations of relevant PK parameters with dose, safety, efficacy, or biomarker outcomes may be explored. Additional PK analyses may be conducted, as appropriate, and based on the availability of data. These additional PK analyses may not be included in the Clinical Study Report (CSR).

4.6 IMMUNOGENICITY ANALYSES

Summary of the numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be presented. Summary of baseline prevalence will be based on all patients with at least one evaluable baseline ADA assessment; analysis of post-baseline incidence will be based on ADA-evaluable population. Patients will be grouped according to treatment received to determine post-baseline incidence.

Patients are considered to be ADA positive post baseline if:

- They are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or
- If they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response).

Similarly, patients are considered to be ADA negative post baseline if:

- They are ADA negative or have missing data at baseline and all post-baseline samples are negative, or
- If they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected)

The relationship between ADA status and demographics and baseline characteristics, pharmacokinetics, safety and key efficacy endpoints may be conducted to explore the potential impact of immunogenicity.

4.7 SAFETY ANALYSES

Safety analyses will be performed on the safety-evaluable population.

4.7.1 Exposure of Study Medication

Study drug exposure statuses, which include treatment duration, number of doses, and dose intensity will be summarized for each treatment arm with descriptive statistics.

4.7.2 Adverse Events

Verbatim description of adverse event terms will be mapped to the medical dictionary for regulatory activities (MedDRA) thesaurus terms, and adverse event severity will be graded in accordance to NCI CTCAE v4.0. All treatment-emergent adverse events (events occurring on or after the first study drug treatment up to the data cutoff date) will be summarized by mapped term, appropriate thesaurus level, NCI CTCAE grade and treatment arm. In addition, common adverse events serious adverse events, severe adverse events (Grade $\geq$ 3), adverse events of special interest, immune-mediated adverse events and adverse events leading to study drug discontinuation or interruption will be summarized. Multiple occurrences of the same event will be counted once at the maximum severity.

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

4.7.3 Laboratory Data

Selected laboratory data will be classified in accordance with NCI CTCAE v4.0 and shift tables from baseline value to worst value during the study post-baseline will be presented.

4.7.4 Vital Signs

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

4.8 EXPLORATORY ANALYSES

4.8.1 Exploratory Patient Reported Outcomes Analyses

Patient-reported data regarding treatment/disease-related symptoms as evaluated by selected items of the EORTC QLQ-C30 (Dyspnea, Appetite Loss, Fatigue, Social Functioning) and QLQ-H&N35 (Pain, Pain Killers, Dry Mouth, Sticky Saliva, Choking, Senses Problems and Speech Problems) will be collected.

Symptom scores of primary interest from EORTC QLQ-C30 are Dyspnea, Appetite Loss, and Fatigue. Scores of primary interest from the EORTC QLQ-H&N35 are Pain (items 31-34) and Choking (item 38). All symptom scales will be scored according to the EORTC scoring manual, 3rd edition (Fayers et al. 2001). The Choking item was selected from the Swallowing subscale of EORTC QLQ-H&N35 questionnaire, and it will

be scored following the procedure applied for the single item scales of the EORTC scoring manual.

Similar to Physical Function and Global Health Status subscales, all symptom scales and single-item measures will be linearly transformed so that each score will range from 0 to 100. A high score item represents a high level of symptomatology/ problems. A change score from baseline of at least 10 points is perceived by patients as clinically meaningful (Osoba et al. 1998), and will be used to define clinically meaningful improvement and deterioration.

For all QLQ-C30 and QLQ-H&N35 exploratory items/scales completed by patients, visit summary statistics of the standardized scores and score change(s) from baseline to each study timepoint will be produced by treatment arm. Summary statistics include the number of patients, mean, standard deviation, median, minimum and maximum scores.

The number and proportion of patients who improved, deteriorated or remained stable in relation to their baseline score will be summarized by treatment arm. The summaries will be provided for the Physical Function, Global Health Status, Dyspnea, Appetite Loss, and Fatigue subscales of the EORTC QLQ-C30, and Pain and Choking scale/item of the EORTC QLQ-H&N35 at each assessment timepoint during the study through the completion of treatment, and during follow-up assessments (for Physical Functioning and Global Health Status only).

Time to confirmed deterioration (TTCD) analysis will be performed for Physical Functioning and GHS/QoL scales, and for patient-reported symptoms of Dyspnea (item 8), Appetite Loss (item 13) and Fatigue (items 10, 12, 18) as measured by the EORTC QLQ-C30. Likewise, TTCD analyses will be conducted for Pain subscale (items 31-34) and Choking item (item 38) of the EORTC QLQ-H&N35. TTCD for selected symptoms of EORTC QLQ-C30 and EORTC QLQ-H&35 is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration. Confirmed clinical deterioration is defined as a clinically meaningful increase from baseline in a symptom score that must be held for at least two consecutive assessments or an initial clinically meaningful increase above baseline followed by death within 9 weeks from the last assessment. If no baseline or post-baseline assessment is performed, patients will be censored at the randomization date. Patients who did not reach an event of confirmed deterioration before the last PRO assessment is completed will be censored at the date of last PRO assessment.

Time to confirmed deterioration in patient-reported symptoms will be analyzed using statistical methodologies analogous to those used in the primary analysis of Investigator-assessed EFS as specified in Section 4.4.1. Completion rates will be summarized by listing the number and proportion of patients among those expected to complete the EORTC QLQ-C30 and QLQ-H&N35 assessments at each timepoint in the ITT population.

EQ-5D-5L Health Status Data

The EQ-5D-5L data will be collected to assess health status and to generate HRQoL and utility scores for use in economic models for reimbursement.

For the EQ-5D-5L health-state profiles, descriptive statistics that summarize the proportions of patients who reported having "no", "slight", "moderate", "severe" or "extreme" problems at each timepoint will be reported. Frequencies and percentages of missing data will also be reported at each timepoint. Patients without post-baseline assessments will be excluded from this analysis. A single summary index from the EQ-5D-5L health status will be used in this study for economic modeling. This analysis will not be included in the CSR for this study.

4.8.2 Exploratory Biomarker Analyses

Exploratory biomarker analyses will be performed in an effort to understand the association of biomarkers with disease status and/or study drug response, including efficacy and/or adverse events. The biomarkers include but are not limited to PD-L1, ctDNA, and TMB as defined by IHC, qRT-PCR, or other methods.

These analyses will not be included in the CSR.

4.9 MISSING DATA

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

5. REFERENCES

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

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Appendix 1 Protocol Synopsis

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) AS ADJUVANT THERAPY AFTER DEFINITIVE LOCAL THERAPY IN PATIENTS WITH HIGH-RISK LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK**
PROTOCOL NUMBER:	WO40242
VERSION NUMBER:	10
EUDRACT NUMBER:	2017-003302-40
IND NUMBER:	135963
NCT NUMBER	03452137
TEST PRODUCT:	Atezolizumab (RO5541267)
PHASE:	Phase III
INDICATION:	Locally advanced squamous cell carcinoma of the head and neck (SCCHN)
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of atezolizumab compared with placebo as adjuvant therapy after definitive local therapy in patients with high-risk locally advanced squamous cell carcinoma of the head and neck (SCCHN). Specific objectives and corresponding endpoints for the study are outlined *in the following table.*

Objectives and Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of atezolizumab compared with placebo	• Investigator-assessed EFS, defined as the time from randomization to the first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression (per RECIST v1.1) per assessment by investigator, or death from any cause, whichever occurs first
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of atezolizumab compared with placebo	• *OS after randomization, defined as the time from randomization to death from any cause* • IRF-assessed EFS, defined as the time from randomization to the first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression (per RECIST v1.1) per assessment by IRF, or death from any cause, whichever occurs first • IRF-assessed EFS and investigator-assessed EFS at 1, 2, *3, and 4 years* • OS at 2, 3 and *5 years*
• To evaluate clinical benefit in atezolizumab compared with placebo in terms of impact on QoL and physical functioning	• Change from baseline in physical functioning over time while receiving treatment as assessed through use of the five-item Physical Functioning subscale (Questions 1–5) of the EORTC QLQ-C30 • Change from baseline in QoL over time while receiving treatment, as assessed through use of the two-item GHS/QoL subscale (Questions 29 and 30) of the EORTC QLQ-C30
Safety Objective	**Corresponding Endpoint**
• To evaluate the safety and tolerability of atezolizumab	• Incidence and severity of adverse events, including serious adverse events and immune-mediated adverse events, with severity determined according to NCI CTCAE v4.0
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the pharmacokinetics of atezolizumab	• Serum concentrations of atezolizumab at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the incidence and titers of ADAs against atezolizumab	• Incidence of ADA response to atezolizumab

Objectives and Endpoints (cont.)

Exploratory Immunogenicity Objective	Corresponding Endpoint
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or pharmacokinetic endpoints
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate and identify biomarkers in tumor tissue and blood that are associated with response to atezolizumab (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to atezolizumab (i.e., mechanism of action biomarkers), are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of atezolizumab activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers (e.g., PD-L1, ctDNA, TMB, *TEFF* gene expression, and others) in tumor tissue and/or blood and efficacy, disease status, resistance, or other biomarker endpoints • Relationship between biomarkers at the time of apparent recurrence (i.e., local recurrence, new second primary SCCHN lesion, or development of distant metastasis) or progression of disease and any immunomodulatory activity of atezolizumab (i.e., tumor-immune infiltration) in patients with confirmed recurrence or progression of disease in patients assigned to atezolizumab
Exploratory PRO Objectives	**Corresponding Endpoints**
• To evaluate health status utility scores of patients treated with atezolizumab • To evaluate evolution of treatment/disease-related symptoms over time from the patients' perspective	• Utility scores based on EQ-5D-5L (including VAS) • Change over time of treatment/disease-related symptoms, as evaluated by selected items of the EORTC QLQ-C30 and QLQ-H&N35 Questionnaires during treatment, treatment discontinuation and survival follow-up • Other PRO endpoints (e.g., time-to-*confirmed* symptom deterioration, proportion of patients with clinical deterioration) to document treatment and disease burden

ADA = anti-drug antibody; ctDNA = circulating tumor DNA; EFS = event-free survival; EORTC = European Organisation for the Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; GHS = global health status; IRF = Independent Review Facility; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PRO = patient-reported outcome; QLQ-C30 = Quality of Life–Core 30 Questionnaire; QLQ-H&N35 = Quality of Life–Head and Neck, Module 35 Questionnaire; QoL = quality of life; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SCCHN = squamous cell carcinoma of the head and neck; TMB = tumor mutation burden; VAS = Visual Analog Scale.

Study Design

DESCRIPTION OF STUDY

Study WO40242 is a global Phase III, multicenter, randomized, double-blind, placebo-controlled study of atezolizumab as adjuvant therapy after definitive local therapy in patients with locally advanced SCCHN who are at high risk for disease recurrence or progression following definitive local therapy. The study is designed to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of adjuvant treatment with atezolizumab compared with placebo in patients with locally advanced SCCHN who have not progressed after receiving definitive local therapy.

Male and female patients 18 years of age who have an Eastern Cooperative Oncology Group *(ECOG) Performance Status of* 0 or 1 and histologically confirmed SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, and who have received definitive local therapy and are classified as being at high risk for recurrence or progression are eligible for study participation (see *the following table* for eligibility requirements). The definition of high risk is based on the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (8th edition) and includes:

- Human *papilloma virus* (HPV)-negative Stage IVA T4a + N0–N2 or T1–T3 + N2 SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, regardless of tobacco use history
- HPV-negative Stage IVB T1–T4a + N3 or T4b + N0–N3 SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, regardless of tobacco use history
- HPV-positive oropharyngeal carcinoma Stage III (clinical T1–T2 + N3) and ≥ 10 packs/year smoking history and/or ≥ 10-year smokeless tobacco use history
- HPV-positive oropharyngeal carcinoma Stage III (clinical T3 + N3 or clinical T4 + N0–N3 or pathologic T3–T4 + N2), regardless of tobacco use history

Primary Site, HPV Status, AJCC Stage, 8th Edition, and Tobacco Use Requirements for Eligibility

Primary Site	HPV Status	Stage	T Status	N Status	M Status	Tobacco Use History
Oral cavity, oropharynx, larynx, or hypopharynx	Negative	IVA	T4a	N0, N1, N2a, N2b, or N2c	M0	NA
			T1, T2, or T3	N2a, N2b, or N2c	M0	NA
Oral cavity, oropharynx, larynx, or hypopharynx	Negative	IVB	T1, T2, T3, or T4a	N3a or N3b	M0	NA
			T4b	N0, N1, N2a, N2b, N2c, N3a, or N3b	M0	NA
Oropharynx	Positive	III	cT1 or cT2	cN3	M0	≥ 10 packs/yr smoking and/or ≥ 10-yr smokeless tobacco
			cT3	cN3	M0	NA
			cT4	cN0, cN1, cN2, or cN3	M0	NA
			pT3 or pT4	pN2	M0	NA

AJCC = American Joint Committee on Cancer; c = clinical staging; HPV = human papillomavirus; M = distant metastasis; N = regional lymph node; NA = not applicable; p = pathological staging; T = primary tumor.

For patients whose planned definitive local therapy begins with induction chemotherapy or concurrent chemoradiotherapy *(CRT)*, radiographic staging to assess eligibility should be done before definitive local therapy. For patients whose planned definitive local therapy begins with primary surgery, pathologic staging based on primary surgery should be done to assess eligibility. In addition, the primary tumor (T) and regional lymph node (N) must be synchronous. Metachronous presentation is considered recurrence in this study, which is not permitted.

Definitive local therapy is defined as any of the following combined modality approaches:

- Primary surgery followed by either postoperative *radiotherapy* (RT) or postoperative concurrent CRT

- Induction chemotherapy followed by primary surgery alone (e.g., laryngectomy)
- Induction chemotherapy followed by primary surgery followed by postoperative RT or postoperative concurrent CRT
- Induction chemotherapy followed by RT or concurrent CRT
- Concurrent CRT

Salvage neck dissection is permitted for neck disease after completion of RT or concurrent CRT. Salvage laryngectomy is permitted only for patients with laryngeal or hypopharyngeal cancer after completion of RT or concurrent CRT. Salvage surgery is not considered part of initial definitive local therapy for this study.

Patients with oropharyngeal or oral cavity cancer who have persistent disease at the primary site post-concurrent CRT or post-RT are not eligible, regardless of whether or not salvage resection of the primary tumor has been received.

Agents used in definitive local therapy must include *Food and Drug Administration* (FDA-) approved or European Medicines Agency (EMA)-approved platinum agent as part of an induction regimen or an FDA-approved or EMA-approved platinum agent or anti-EGFR agent as part of concurrent therapy with *RT*.

Surgery alone or RT alone is not considered a definitive local therapy and is an exclusion criterion. Patients who have received neoadjuvant treatment or any systemic anti-cancer therapy without definitive local therapy (either surgery and/or radiation) for locally advanced head and neck cancer are not eligible. In addition, use of any systemic therapy after permitted definitive local therapies (e.g., after surgery, radiation, or concurrent CRT) is not permitted.

Patients who experience disease progression or recurrence during or following definitive local therapy are not eligible. Patients must have had a complete response (CR), partial response (PR), or stable disease (SD) as assessed in comparison to scans done prior to definitive local therapy. Both response in the head and neck region (performed via magnetic resonance imaging [MRI] with contrast or computed tomography [CT] with contrast) and absence of metastasis outside of the head and neck region (performed via CT with contrast of the chest and abdomen) must be documented on scans performed ≥ 8 weeks (56 days) after completing definitive local therapy, and within 28 days prior to initiation of study drug (patients who receive salvage surgery must have screening scans after salvage surgery).

Patients who have an equivocal response after definitive local therapy at their post-definitive local therapy scans (done at screening) should receive further evaluation (e.g., positron emission tomography [PET] scans) per local standard as well as a biopsy if indicated. Investigators may use the PET scan and/or biopsy results, if performed, to inform their assessment of the screening CT and/or MRI scans. If the assessment is still equivocal, that patient is not eligible.

Patients must initiate study treatment within 28 days of the screening scans and within 16 weeks after completion of definitive local therapy (if salvage neck dissection or salvage laryngectomy was not performed) or within 20 weeks after completion of definitive local therapy (if salvage neck dissection or salvage laryngectomy was performed) (*see* the *following* table). The date of completion of definitive local therapy is exclusive of salvage surgery.

Timing for Post-Definitive Local Therapy Screening Scans and Initiation of Study Treatment

Salvage Surgery	Time from Completing Definitive Local Therapy to Screening Scan [a]	Time from Completing Definitive Local Therapy to Initiation of Study Treatment
No	8–16 weeks	≤ 16 weeks
Yes	8–20 weeks	≤ 20 weeks

[a] Screening scans must be done within 4 weeks (28 days) of initiation of study treatment. Screening scans for patients who receive salvage surgery must be done after salvage surgery.

Approximately 406 patients globally will be randomized. All patients will be randomized to one of the following arms in a 1:1 ratio:

- Arm A (experimental arm): atezolizumab 1200 mg every 3 weeks (Q3W)
- Arm B (control arm): placebo Q3W

Randomization will be stratified by the following factors:

- Response to definitive local therapy (CR vs. PR or SD)

  In the event scans are performed prior to conducting a salvage surgery, the response to initial definitive local therapy prior to salvage surgery should be used for stratification.
- HPV status (positive vs. negative)

  Patients with HPV-positive oropharyngeal carcinoma will be capped at 20%.
- Type of definitive local therapy received (primary surgery vs. no primary surgery)
  - Primary surgery: Patients who received a primary surgery to the primary tumor site in the head and neck as part of initial definitive local therapy, regardless of whether a salvage surgery was received.
  - No primary surgery: Patients who did not receive a primary surgery to the primary tumor site in the head and neck as part of initial definitive local therapy but may or may not have had a salvage surgery.

For patients to be eligible, a representative pretreatment tumor specimen for exploratory biomarker research must be available and confirmed before the randomization. The tissue sample must be submitted within 4 weeks after randomization.

Patients in both treatment arms will receive 16 cycles or up to 1 year (whichever occurs first) of treatment with either atezolizumab (fixed dose of 1200 mg) or placebo. Treatment will be administered by IV infusion on Day 1 of each 21-day cycle. Treatment will be discontinued in the event of disease recurrence (i.e., local recurrence, new second primary SCCHN lesion, or development of distant metastasis), disease progression, unacceptable toxicity, consent withdrawal, or study termination by the Sponsor.

The primary endpoint of this study will be investigator-assessed event-free survival (EFS). Patients will undergo scheduled tumor assessments by means of imaging at baseline and every 9 weeks following Day 1, Cycle 1 (every three cycles) for the first 2 years. Tumor assessments will occur every 12 weeks during Year 3, every 16 weeks during Years 4 and 5, and annually thereafter at the discretion of the investigator if clinically indicated. Tumor assessments will continue per schedule, regardless of whether study drug is given, held, or discontinued (even if a new follow-up anti-cancer therapy is started) until death, disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), disease progression (per Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1]), loss to follow-up, the end of Year 5, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patients who are randomized with evidence of residual disease at baseline (as assessed by screening scans) will be assessed for disease progression according to RECIST v1.1. For patients who are randomized with no evidence of disease at baseline (as assessed by screening scans), disease recurrence will be determined and confirmed based on unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis. All patients will undergo a physical examination Q3W, and if recurrent or progressive disease is suspected based on clinical grounds, tumor assessments must be performed expeditiously, even if not mandated in the schedule of activities. In cases of equivocal radiographic evidence of recurrence or progression, recurrence or progression must be confirmed by repeat tumor assessments after 9 weeks or earlier as clinically indicated.

To capture disease and treatment burden, patients will complete selected items from the validated and reliable European Organisation for the Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire and the Quality of Life–Head and Neck, Module 35 Questionnaire. In addition, the EuroQol Dimension, 5-Level Questionnaire, including the health status Visual Analog Scale will be collected for health economic modeling purposes.

Safety assessments will include the incidence, nature, and severity of adverse events, changes in vital signs, and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

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

After study treatment discontinuation, survival status, subsequent anti-cancer therapies (including targeted therapies and immunotherapies), and patient-reported outcomes will be collected for all patients until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

An external independent Data Monitoring Committee (iDMC) will evaluate safety data and interim *futility and* efficacy analyses *for investigator-assessed EFS* according to policies and procedures detailed in an iDMC Charter.

NUMBER OF PATIENTS

Approximately *406* patients with high-risk locally advanced SCCHN will be enrolled across all sites during the enrollment phase of the study.

TARGET POPULATION

INCLUSION CRITERIA

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at the time of signing the Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically or cytologically confirmed SCCHN (HPV-positive Stage III oropharyngeal carcinoma or HPV-negative Stage IVA or IVB involving the oral cavity, oropharynx, larynx, or hypopharynx based on AJCC Cancer Staging Manual, 8th edition

  The primary tumor and cervical nodes must be present synchronously and eligible patients must meet one of the following criteria:

  - HPV-negative Stage IVA T4a + N0–N2 or T1–T3 + N2 SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, regardless of tobacco use history
  - HPV-negative Stage IVB T1–T4a + N3 or T4b + N0–N3 SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx, regardless of tobacco use history
  - HPV-positive oropharyngeal carcinoma Stage III (clinical T1–T2 + N3) and ≥ 10 packs/year smoking history and/or ≥ 10-year smokeless tobacco use history
  - HPV-positive oropharyngeal carcinoma Stage III (clinical T3 + N3 or clinical T4 + N0–N3 or pathologic T3–T4 + N2), regardless of tobacco use history
- HPV status, as determined locally by p16 *immunohistochemistry*, in situ hybridization, or by polymerase chain reaction–based assay
- Completed definitive local therapy (as defined below):
  - Primary surgery followed by either postoperative RT or postoperative concurrent CRT
  - Induction chemotherapy followed by primary surgery alone (e.g., laryngectomy)
  - Induction chemotherapy followed by primary surgery followed by postoperative RT or postoperative concurrent CRT
  - Induction chemotherapy followed by RT or concurrent CRT
  - Concurrent CRT

  Note: Salvage neck dissection is permitted for neck disease after completion of RT or concurrent CRT. Salvage laryngectomy is permitted only for patients with laryngeal or hypopharyngeal cancer after completion of RT or concurrent CRT.

Note: Agents used in definitive local therapy must include an FDA-approved or EMA-approved platinum agent as part of an induction regimen or an FDA-approved or EMA-approved platinum agent or anti-EGFR agent as part of concurrent therapy with *RT*.

- Absence of metastatic disease, as confirmed by negative CT with contrast of chest and abdomen within 28 days prior to initiation of study drug (for patients with a contraindication to CT with contrast, see the protocol)

  Note: Patients with a contraindication to both CT with contrast and MRI may be eligible after Medical Monitor approval has been obtained.
- Recovered from acute toxicities associated with definitive treatment to Grade 1 or lower, except fatigue, xerostomia, dysgeusia, alopecia, and toxicities related to prior treatment requiring management with a feeding tube.
- Patients with feeding tubes are eligible
- Availability of a representative pretreatment tumor specimen for exploratory biomarker research (see the protocol for information on tumor specimens) must be confirmed

  The tissue sample must be submitted within 4 weeks after randomization.
- ECOG *Performance Status* of 0 or 1
- Life expectancy $\geq$ 12 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support
  - Lymphocyte count $\geq 0.3 \times 10^9$/L (300/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin $\geq$ 90 g/L (9 g/dL)
  - Patients may be transfused to meet this criterion.
  - AST, ALT, and ALP $\leq 2.5 \times$ ULN
  - Serum bilirubin $\leq 1.5 \times$ ULN with the following exception:
  - Patients with known Gilbert disease: serum bilirubin level $\leq 3 \times$ ULN
  - Creatinine *clearance* $\geq$ 20 mL/min (calculated per institutional guidelines or by Cockcroft-Gault or *Modification of Diet in Renal Disease* formula)
  - Serum albumin $\geq$ 25 g/L (2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN
- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- Negative HIV test at screening
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

  The HBV DNA test will be performed only for patients who have a positive total HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<$1% per year during the treatment period and for 5 months after the last dose of study treatment. Women must refrain from donating eggs during this same period.

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 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, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Confirmed response of CR, PR, or SD to definitive local therapy (as compared to scans done prior to definitive local therapy) documented by CT with contrast or MRI with contrast of head and neck region done ≥ 8 weeks after completion of definitive local therapy and within 28 days prior to initiation of study drug

  If salvage neck dissection or salvage laryngectomy is not performed, patients must initiate study treatment (i.e., *Day 1 of Cycle 1*) within 16 weeks after completion of definitive local therapy.

  If salvage neck dissection or salvage laryngectomy is performed, patients must initiate study treatment within 20 weeks after completion of definitive local therapy.

  For patients who may require a salvage surgery for residual disease, the evaluation for salvage surgery must be completed and decision on whether a salvage surgery is needed must be made prior to randomization.

  Note: Patients with a contraindication to both CT with contrast and MRI may be eligible after Medical Monitor approval has been obtained (see protocol for scanning requirements).

EXCLUSION CRITERIA

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

- Patients who have received surgery alone or *RT* alone as definitive local therapy
- HPV-negative patients who have a TX tumor or NX nodal stage
- HPV-positive oropharyngeal carcinoma patients who have a clinical T0 tumor or NX nodal stage, or pathological NX, N0, or N1 nodal stage
- Patients with oropharyngeal or oral cavity cancer who have persistent disease at the primary site post-concurrent CRT or post-RT, regardless of whether or not salvage resection of the primary tumor has been received
- Squamous cell carcinoma of the nasopharynx or paranasal sinuses or non-squamous histology
- Evidence of disease progression or metastatic disease during or following definitive local therapy documented in the post-definitive local therapy screening scans
- Uncontrolled or symptomatic hypercalcemia
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see the protocol for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

- Rash must cover < 10% of body surface area.
- Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
- No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

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

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Active tuberculosis
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina
- Major surgical procedure, other than for diagnosis or salvage neck dissection or salvage laryngectomy, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- History of malignancy, including prior SCCHN primary tumors (other than current SCCHN) within 5 years prior to screening
- Patients who have malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death <5% at 5 years) are eligible provided they meet all of the following criteria:
  - Malignancy treated with expected curative intent, such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
  - No evidence of recurrence or metastasis by follow-up imaging and any disease-specific tumor markers
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) may be eligible for the study
- Prior allogeneic stem cell or solid organ transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the last dose of atezolizumab
- Current treatment with anti-viral therapy for HBV
- Prior neoadjuvant (i.e., induction) treatment or any systemic anti-cancer therapy without definitive local therapy (either surgery and/or radiation) for locally advanced head and neck cancer
- Treatment with investigational therapy within 28 days or 5 half-lives, whichever is longer, prior to initiation of study treatment

- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

  Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) may be eligible for the study after Medical Monitor approval has been obtained.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

  Patients who are receiving low-dose (equivalent to ≤ 10 mg prednisone a day) corticosteroids for radiation induced mucositis, or mucosal edema are eligible for the study.
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment or within 5 months after the last dose of study treatment

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.
- Patients who have received a non-FDA or non-EMA approved anti-EGFR agent or any other non-FDA or non-EMA approved agent as part of definitive local therapy unless the unapproved agent was given in addition to an approved platinum agent as part of an induction regimen or in addition to an approved platinum or anti-EGFR agent as part of concurrent therapy with *RT*
- Any systemic therapy after permitted definitive local therapies (defined in the protocol) (e.g., after surgery, radiation, or concurrent CRT)

  For patients who receive concurrent CRT as definitive local therapy, any systemic therapy administered >7 days after the last date of radiation is not permitted.

END OF STUDY

The end of this study *will occur* when *both* of the following criteria *have been met:*

- *The last patient, last visit has occurred.*
- *Approximately 191 deaths have occurred in the intent-to-treat (ITT) population.*

In addition, the Sponsor may decide to terminate the study at any time.

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 *111* months.

INVESTIGATIONAL MEDICINAL PRODUCTS

TEST PRODUCT (INVESTIGATIONAL DRUG)

The atezolizumab Drug Product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

COMPARATOR

The placebo will be identical in appearance to atezolizumab and will comprise the same excipients but without atezolizumab Drug Product. It should be handled, stored, and used in the same manner as atezolizumab. Placebo will be supplied by the Sponsor.

DOSAGE, ADMINISTRATION, AND COMPLIANCE

Atezolizumab (fixed dose of 1200 mg) or placebo will be administered by IV infusion on Day 1 of each 21-day cycle for 16 cycles (or up until 1 year, whichever occurs first), or until disease recurrence, disease progression, unacceptable toxicity, consent withdrawal, or study termination by the Sponsor, whichever occurs first.

Administration of 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. For anaphylaxis precautions, see the protocol. Atezolizumab infusions will be administered per the instructions outlined in the protocol.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration. Guidelines for medical management of infusion-related reactions (IRRs) are provided in the protocol. No dose modification for atezolizumab is allowed.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary efficacy endpoint is EFS, as assessed by the investigator, according to unequivocal radiographic evidence of disease recurrence or unequivocal radiographic evidence progression per RECIST v1.1.

EFS is defined as the time from randomization to the first documented disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), or disease progression (per RECIST v1.1) or death from any cause, whichever occurs first. Patients who have not experienced disease recurrence or progression or died at the time of analysis will be censored at the time of the last tumor assessment. Patients with no postbaseline tumor assessment will be censored at the date of randomization.

To control the overall type I error rate for the two-sided test at 0.05, *comparisons between treatment arms with respect to investigator-assessed EFS and overall survival (OS) will be conducted hierarchically.*

The primary analysis of the study will test the equality of EFS distributions in two arms:

$$H_0: S_{EFS\_A}(t) = S_{EFS\_B}(t) \text{ versus } H_1: S_{EFS\_A}(t) \neq S_{EFS\_B}(t)$$

EFS will be compared between treatment arms with the use of the stratified log-rank test. The hazard ratio (HR) for EFS for the comparison will be estimated using a stratified Cox regression model. If the estimate of the HR is <1 and the two-sided p-value corresponding to the stratified log-rank test is less than the specified α level, then the null hypothesis will be rejected and it will be concluded that atezolizumab prolongs the duration of EFS relative to control treatment. The 95% CI for the HR will be provided. The stratification factors will be those used during randomization, as recorded in the *interactive voice or web-based response system.*

Results from an unstratified analysis may also be presented.

Kaplan-Meier methodology will be used to estimate the median EFS for each treatment arm. Brookmeyer-Crowley methodology will be used to construct the 95% *confidence interval* (CI) *for ITT* of the median EFS for each treatment arm.

DETERMINATION OF SAMPLE SIZE

The overall type I error rate will be controlled for the two-sided test at 0.05.

The sample size determination is based on the number of events required to demonstrate efficacy with regard to investigator-assessed EFS in the ITT population. The estimate of the number of events required is based on the following assumptions:

- *Two-sided significance level of 0.05 for the EFS comparison in the ITT population*
- *82%* power to detect an HR of 0.65, corresponding to an improvement in median EFS from *40* months in the placebo arm to *61.5* months in the atezolizumab arm for the ITT population

- *One interim futility and efficacy EFS analysis performed when approximately 80% of the total number of EFS events required for the final analysis is expected to have occurred*

  Crossing boundaries for the interim efficacy and final EFS analyses will be determined through use of the Lan-DeMets approximation to the O'Brien-Fleming boundary.
- *Dropout rate of 5% per 24 months*

The estimate of the number of events required to demonstrate efficacy with regard to OS *is based on the following assumptions*:

- *Two-sided significance level of 0.05 for the* OS *comparison* in the *ITT population*
- *80*% power to detect an HR of 0.65, corresponding to an improvement in median OS from *70* months in the placebo arm to *107.7* months in the atezolizumab arm for the ITT population
- *One interim efficacy OS analysis performed at the time of the final EFS analysis, at which time approximately 121 OS events (i.e., 63% of the total number of OS events required for the final analysis) are expected to have occurred*

  Crossing boundaries for the interim and final OS analyses will be determined through use of the Lan-DeMets approximation to the Pocock boundary.
- *Dropout rate of 5% per 36 months*

The final EFS analysis will be conducted when approximately *183* EFS events have occurred in the ITT population (expected to occur approximately *59* months after the first patient is randomized*) or 65 months after the first patient is randomized, whichever occurs earlier*. This number of events would allow for a minimum detectable difference (MDD) corresponding to an HR of approximately 0.*74* in the ITT population.

The final OS analysis will be conducted when approximately *191* OS events have occurred in the ITT population, which is expected to occur approximately *99* months after the first patient is randomized. This number of events corresponds to a MDD in HR of approximately 0.*72* in the ITT population.

With these assumptions, approximately *406* patients in total will be randomized into this study.

INTERIM ANALYSES

Planned Interim Analyses

There is one interim *futility and efficacy* analysis planned for *investigator*-assessed EFS in this study when approximately 146 EFS events have occurred, which is approximately 47 months after the first patient is randomized. *One* interim *efficacy* analysis is planned for OS at the time of the *final* analysis *of* investigator-assessed EFS. Approximately *121* OS events are expected to have occurred at *the time of the* analysis.

An iDMC will be set up to evaluate safety data on an ongoing basis as well as to review the interim *futility and efficacy* analysis *of investigator-assessed EFS*. Any outcomes of these reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the *Institutional Review Boards/Ethics Committees*. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an independent Data Coordinating Center. A detailed plan will be included in the iDMC Charter.

The interim futility analysis of investigator-assessed EFS will allow potential early stopping of the trial for lack of treatment benefit. The iDMC may recommend that the study be stopped for futility if the observed EFS HR >0.9 of atezolizumab arm over the control arm, which provides a probability of 74% to stop the study if the true EFS HR is 1.0 (i.e., no treatment benefit based on EFS). If there is a true treatment benefit based on EFS under the target HR of 0.65, the chance of stopping for futility is 2%. The efficacy crossing boundaries for interim efficacy and final EFS analyses will be determined through use of the Lan-DeMets approximation to the O'Brien-Fleming boundary based on the actual observed number of events. If the difference in investigator-assessed EFS is statistically significant, OS will be tested. The stopping boundaries for the interim and final OS analyses will be determined through use of the Lan-DeMets approximation to the Pocock boundary based on the actual observed number of events.

Appendix 2 Schedule of Assessments

Assessment	Arm A (Atezolizumab) and Arm B (Placebo)			
	Screening [a]	All Cycles	Post-Treatment Follow-Up	
	Days –28 to –1	Day 1 (±3 Days for Cycles ≥2)	Discontinuation [b] ≤30 Days after Last Dose	Follow-Up
Signed Informed Consent Form(s)	x [c]			
Pretreatment tumor tissue specimen for biomarker testing [d]	x			
Demographic data	x			
Medical history (including drugs of abuse) and baseline conditions	x			
SCCHN cancer history/tobacco use history/alcohol use history	x			
HPV status	x [e]			
Patient-reported outcomes [f]		x [g]	x	x [h]
Vital signs [i]	x	x	x	
Weight	x	x	x	
Height	x			
Complete physical examination [j]	x		x	
Limited physical examination [k]		x [o]		
ECOG Performance Status	x	x [o]	x	
12-Lead ECG [l]	x	As clinically indicated		
Hematology [m]	x [n]	x [o]	x	
Serum chemistry [p]	x [n]	x [o]	x	

Assessment	Arm A (Atezolizumab) and Arm B (Placebo)			
	Screening [a]	All Cycles	Post-Treatment Follow-Up	
	Days −28 to −1	Day 1 (±3 Days for Cycles ≥2)	Discontinuation [b] ≤30 Days after Last Dose	Follow-Up
Pregnancy test [q]	x [n]	x [q,o]	x	
Coagulation panel (aPTT, INR)	x [n]		x	
TSH, free T3, free T4 [r]	x	x [o, r]	x	
Viral serology [s]	x			
Urinalysis [t]	x	x [u]	x	
Serum sample for ADA assessment		See Appendix 3 .		
Serum sample for PK sampling		See Appendix 3 .		
Blood samples for biomarkers		See Appendix 3 .		
Blood sample for RBR (optional) [v, w]		x [w]		
Tumor biopsy (optional) [x]		At the time of initial radiographic confirmation of disease recurrence or progression (preferred) and/or any time during treatment or survival follow-up (at investigator's discretion) [x]		
Concomitant medications [aa]	x	x	x	
Adverse events [bb]	x	x	x	
Study drug administration [cc]		x		
Survival follow-up and anti-cancer treatment				x [dd]

ADA = anti-drug antibody; C = cycle; C1D1 = Cycle 1, Day 1; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC = European Organisation for the Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HPV = human papillomavirus; IHC = immunohistochemistry; MRI = magnetic resonance imaging; PK = pharmacokinetic; PRO = patient-reported outcome; QLQ-C30 = Quality of Life–Core 30 Questionnaire; QLQ-H&N35 = Quality of Life–Head and Neck, Module 35 Questionnaire; *QoL = quality of life;* RBR = Research Biosample Repository; *RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1*; SCCHN = squamous cell carcinoma of the head and neck; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; VAS = Visual Analog Scale.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1, Day 1 may be used (except where otherwise specified); such tests do not need to be repeated for screening.

[b] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which response assessment shows recurrent or progressive disease may be used as the treatment discontinuation visit.

[c] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before, but no more than 56 days prior to initiation of study treatment.

[d] A pretreatment tumor tissue (archival or freshly obtained) sample must be submitted within 4 weeks after randomization. This specimen must be accompanied by the associated pathology report. It is strongly encouraged that representative tumor specimens in paraffin blocks (preferred) or a minimum of 15 serial, freshly cut, unstained slides be submitted. If resection specimen is not available, patients can submit tumor specimens from a core needle biopsy collected prior to study randomization. If patient is not a surgical candidate or tissue is not available from resection or biopsy, any representative tissue sample can be submitted. See Section 4.5.6 of the protocol for details.

[e] HPV status of tumor tissue determined by any of the following methods: p16 IHC, in situ hybridization, or polymerase chain reaction–based assay. If HPV status by p16 IHC, in situ hybridization, or polymerase chain reaction–based assay is unknown, archival tumor tissue or freshly collected tumor tissue must be tested at screening.

[f] The PRO questionnaires, including selected scales from the EORTC questionnaires (e.g., QLQ-C30 and QLQ-H&N35) and the EQ-5D-5L in its entirety (including the VAS), will be completed by the patients at the investigational site on paper. All PRO questionnaires are required to be administered prior to administration of study treatment and/or prior to any other study assessment(s) involving communication with the clinical staff (e.g., discussion of tumor progression) that could bias patients' rating of their health status (symptoms, signs, functioning, or QoL) to ensure that the validity of the assessment is not compromised and to ensure that data quality meets regulatory requirements. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site, and the hard copy originals of the questionnaires must be maintained as part of the patient's medical record when relevant at the site for source data verification. Reasons for non-completion should be recorded on the eCRF.

[g] It is imperative that the selected scales from the EORTC questionnaires and the EQ-5D-5L in its entirety be completed on Day 1 of Cycle 1 to have a baseline. Each questionnaire will be completed on Day 1 of each cycle, at the treatment discontinuation visit, and at unscheduled visits as clinically indicated. All PRO questionnaires are required to be completed prior to the administration of study treatment and/or prior to any other study assessment(s) that could bias a patient's responses.

[h] After discontinuation of the treatment and in the absence of unequivocal radiographic evidence of disease recurrence or progression, selected scales from the EORTC QLQ-C30 (Physical Function and Global Health Status/QoL) and the EQ-5D-5L (including VAS) will be administered at the same schedule as the tumor assessments until disease recurrence or progression, at the study site or by telephone. *After the confirmation of unequivocal radiographic evidence of disease recurrence or progression*, selected scales from the EORTC QLQ-C30 (Physical Function and Global Health Status/QoL) and the EQ-5D-5L (including VAS) will be administered over the telephone or during clinic *at 3 months (±30 days) and 6 months (±30 days)* by site personnel.

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

[j] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. Ongoing use of tobacco (smoking and smokeless) must also be recorded. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Complete physical examinations are defined in Section 4.5.3 of the protocol.

[k] Perform a limited, symptom-directed examination at every cycle and as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Ongoing use of tobacco (smoking and smokeless) must also be recorded. Limited physical examinations are defined in Section 4.5.3 of the protocol.

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

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[n] Specified screening laboratory test results must be obtained prior to randomization and within 14 days prior to initiation of study treatment.

[o] If screening laboratory assessments were performed within 96 hours prior to Day 1 of Cycle 1, laboratory assessments do not have to be repeated at C1D1. At all cycles subsequent to C1D1, laboratory assessments, ECOG Performance Status, and limited physical examination must be performed within 96 hours prior to administration of drug.

[p] Chemistry panel (serum) includes sodium, potassium, magnesium, chloride, bicarbonate or total carbon dioxide (if considered standard of care for the region), glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, *and* LDH.

[q] 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 of Cycle 1. Either urine or serum pregnancy tests must be performed within 96 hours prior to administration study drug at every cycle during study treatment, at treatment discontinuation, and as clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[r] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 1, 5, 9, etc.).

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

[t] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[u] Urinalysis should be performed as clinically indicated during study treatment.

[v] Blood for DNA isolation will be collected from patients who have consented to optional RBR sampling at baseline (predose on Day 1 of Cycle 1). However, if the RBR genetic blood sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study.

[w] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[x] Biopsy at radiographic disease recurrence or progression should be performed within 40 days after progression or recurrence or prior to the next anti-cancer therapy, whichever is sooner. Patients must sign a separate Optional Biopsy Informed Consent Form to undergo optional biopsies. See Section 4.5.9. of the protocol for tissue sample requirements.

[y] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with oral or IV contrast) of the chest and abdomen and CT scans (with oral or IV contrast) or MRI (with contrast) of the head and neck region. If a CT scan with contrast is contraindicated (e.g., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI with contrast scans of the abdomen and head and neck region must be performed. All measurable and non-measurable lesions should be assessed and documented at screening. If both a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance or contrast allergy) and MRI is contradicted (e.g., in patients with claustrophobia), non-contrast CT scans of the chest, abdomen, and head and neck region may be performed only upon prior approval from the Medical Monitor.

[z] The same radiographic modality (e.g., CT scan with contrast) and procedures (e.g., the same contrast protocol for CT scans) used at screening must be used for subsequent tumor assessments. Imaging of the head and neck region and chest must be performed at every scheduled tumor assessment. Imaging of the abdomen and bone must be performed as clinically indicated, and imaging of the abdomen must also be done upon disease recurrence or progression in the head and neck and/or chest. All measurable and non-measurable lesions should be re-assessed at each subsequent timepoint. Progression of patients with evidence of residual disease at baseline (as assessed by screening scans) will be assessed by the investigator using RECIST v1.1. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Disease recurrence in patients with no evidence of disease at baseline (as assessed by screening scans) will be determined by the investigator based on unequivocal radiographic evidence of recurrence (local recurrence, new second primary SCCHN lesion, or development of distant metastasis). At any time that disease recurrence or progression is clinically suspected, protocol required imaging must be performed expeditiously outside the schedule timepoints, even if not mandated in the schedule of activities. In cases of equivocal evidence of recurrence or progression, recurrence or progression must be confirmed by repeat tumor assessments after 9 weeks or earlier as clinically indicated. Tumor assessments will continue regardless of whether study drug is given, held, or discontinued (even if a new follow-up anti-cancer therapy is started) until death, disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis), disease progression (per RECIST v1.1), loss to follow-up, the end of Year 5, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

[aa] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment until the treatment discontinuation visit.

[bb] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment. 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 trial-related procedures until a final outcome can be reported.

[cc] Patients should 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 4 days after randomization. The initial infusion of study drug will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[dd] After discontinuation of treatment, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits. In addition (but not instead of), study staff may also use a public information source (e.g., county records) to obtain information about survival status. Patients who have discontinued study drug (for any reason) in the absence of disease recurrence (per unequivocal radiographic evidence of local recurrence, new second primary SCCHN lesion, or development of distant metastasis) or disease progression (per RECIST v1.1) must complete survival follow-up on the same schedule as the radiographic assessments until the protocol-defined criterion for ending radiographic assessments is met. After both treatment and radiographic assessments are discontinued, survival follow-up must occur approximately every 3 months or more frequently until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from survival follow-up, this request must be documented in the source documents and signed by the investigator. If a patient withdraws from the study (i.e. survival follow-up), the study staff may use a public information source (e.g., county records) to obtain information about survival status.

Appendix 3 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Fluid Samples for All Enrolled Patients in Arms A and B

Visit	Timepoint	Sample Type
Day 1 of Cycle 1	Predose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, and blood [a]) • Blood sample for RBR (optional) [b]
	30 (± 10) minutes after end of atezolizumab infusion	• Atezolizumab PK (serum)
Day 1 of Cycle 2	Predose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)
Day 1 of Cycle 4	Predose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)
Day 1 of Cycle 8	Predose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)
Day 1 of Cycle 16	Predose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma and serum)

ADA=anti-drug antibody; PK=pharmacokinetic; RBR=Research Biosample Repository.

Note: Except for Day 1 of Cycle 1, 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 ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[a] If this blood sample is not collected during the Day 1, Cycle 1 *visit*, it may be collected at any other visit during the conduct of the clinical study.

[b] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. The blood sample for the RBR will be collected predose on Day 1 of Cycle 1. However, if this sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study.