Official Title: A Phase III, Open-Label, Multicenter, Randomized Study of Atezolizumab (Anti−PD-L1 Antibody) Versus Observation as Adjuvant Therapy in Patients With High-Risk Muscle-Invasive Urothelial Carcinoma After Surgical Resection

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STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI−PD−L1 ANTIBODY) VERSUS OBSERVATION AS ADJUVANT THERAPY IN PATIENTS WITH HIGH-RISK MUSCLE-INVASIVE UROTHELIAL CARCINOMA AFTER SURGICAL RESECTION**

PROTOCOL NUMBER: WO29636

STUDY DRUG: Atezolizumab (MPDL3280A; RO5541267)

VERSION NUMBER: 1

IND NUMBER: 120827

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SPONSOR: F. Hoffmann-La Roche Ltd.

PLAN PREPARED BY: [redacted], Ph.D.

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STATISTICAL ANALYSIS PLAN APPROVAL

Name	Reason for Signing	Date and Time (UTC)
[redacted]	Company Signatory	01-Feb-2019 16:59:25

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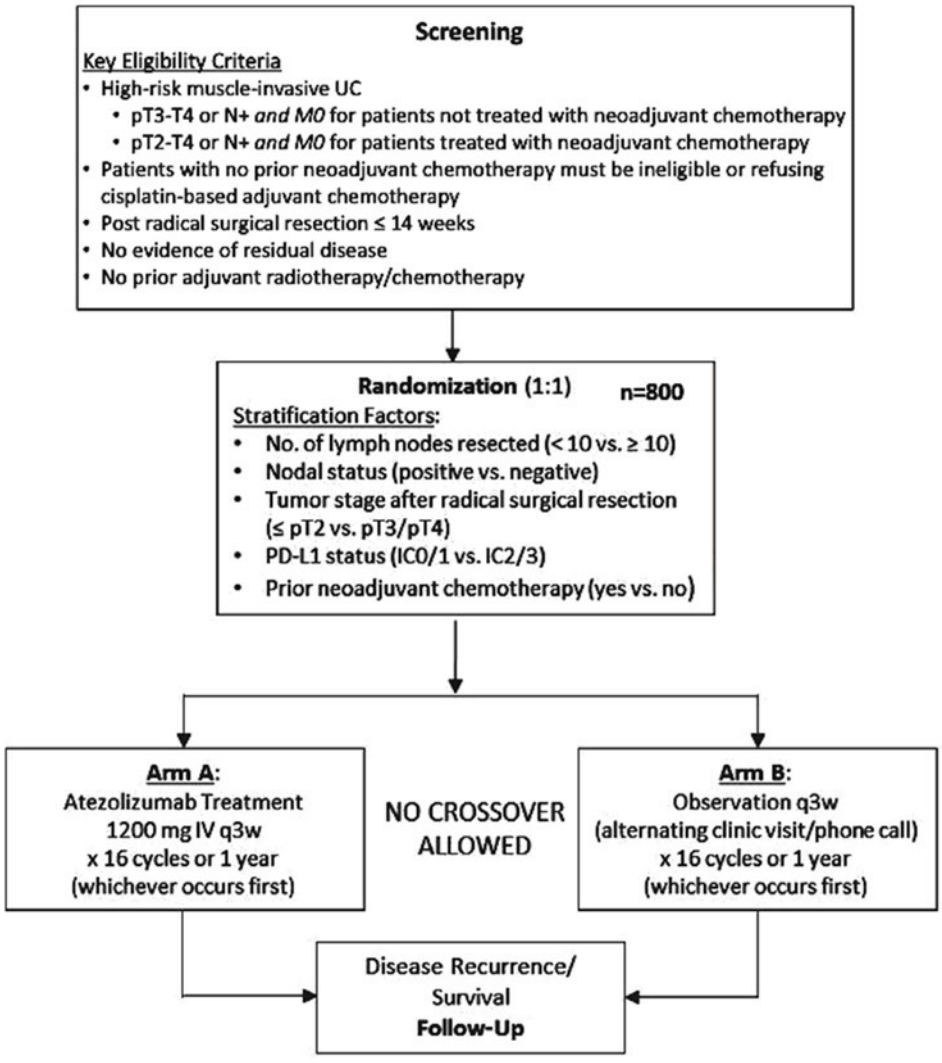
1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study WO29636 (IMvigor010). The analyses described in this SAP will supersede those specified in Protocol WO29636.

2. STUDY DESIGN

Study WO29636 is a global Phase III, open–label, randomized, controlled trial designed to evaluate the efficacy and safety of adjuvant treatment with atezolizumab compared with observation in patients with muscle invasive urothelial carcinoma (UC), who are at high risk for recurrence following resection. The study schema is provided in Figure 1.

Figure 1 Study Schema



IC = tumor–infiltrating immune cell; IV = intravenous; n = number; PD-L1 = programmed death-ligand 1; q3w = every 3 weeks; UC = Urothelial carcinoma.

Patients were randomized to one of the following arms in a 1:1 ratio:

- Arm A (experimental arm): atezolizumab 1200 mg q3w
- Arm B (control arm): observation

The randomization was stratified by the following factors: number of lymph nodes resected (<10 vs. ≥ 10), nodal status (positive vs. negative), tumor stage after surgical resection ($\leq$pT2 vs. pT3/pT4), PD-L1 status (IC0/1 vs. IC2/3), and prior neo–adjuvant chemotherapy (yes vs. no).

Note: The study design was revised in Protocol Version (v) 6 from a diagnostically selected population with PD–L1 status (tumor–infiltrating immune cell [IC] score measured in tumor) of IC2/3 to include all patients regardless of PD–L1 status. Age–adjusted Charlson comorbidity index, which was a stratification factor prior to Protocol v6, was removed as a stratification factor in Protocol v6 and replaced with PD–L1 status (IC0/1 vs IC2/3). Patients enrolled prior to Protocol v6 have been categorized as IC2/3 for stratification purposes.

For patients in Arm A, atezolizumab will be administered intravenously (IV) on Day 1 of each 21-day cycle for 16 cycles (up to 1 year). In Arm B, patients will continually undergo observation starting on Day 1 of each 21-day cycle for 16 cycles (up to 1 year).

Treatment/observation will be discontinued in the event of disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor. Patients in the control arm will not be allowed to cross over to receive atezolizumab treatment within this study.

All patients will undergo scheduled assessments for tumor recurrence at baseline and every 12 weeks (approximately every 4 cycles) in the first year following randomization. Upon completion of the treatment/observation period, surveillance for tumor recurrence will be performed every 12 weeks for years 2-3; every 24 weeks for years 4-5; and at year 6 (approximately 48 weeks after the last assessment in year 5). In the absence of a disease-free survival (DFS) event (defined as any of the following: local [pelvic] recurrence of UC; upper urinary tract or urethral recurrence of UC; distant metastasis of UC; or death from any cause), surveillance for tumor recurrence should continue regardless of whether patients start new anticancer therapy, until withdrawal of consent, loss to follow-up, or study termination by the Sponsor, whichever occurs first.

The primary efficacy endpoint is DFS as assessed by the investigator and the key secondary endpoint is overall survival (OS). See Section 2.2 for further details on primary efficacy endpoints, as well as secondary and other safety, pharmacokinetic (PK), and exploratory endpoints.

There are no interim analyses planned for DFS and two interim analyses are planned for OS in this study. See Section 2.3 for detailed analysis timing.

An external independent Data Monitoring Committee (iDMC) was convened to evaluate safety data on an ongoing basis.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details on study assessments, see the Schedule of Assessments in Appendix 2.

2.2 DETERMINATION OF SAMPLE SIZE

Approximately 800 patients will be randomized in this study.

2.2.1 Type I Error Control

The Type I error (alpha) for this study is 0.05 (two-sided). Type I error will be controlled for the primary endpoint of DFS and the key secondary endpoint of overall survival (OS).

To control the Type I error at alpha = 0.05 (two–sided) for DFS and OS endpoints, the treatment arms will be compared in a hierarchical fashion as follows:

- If the DFS analysis results are statistically significant at alpha = 0.05 (two–sided), then the analysis of OS will be performed at alpha = 0.05 (two–sided) and the interim analysis boundaries for OS (see Section 2.3.2) will be calculated according to alpha = 0.05 (two–sided).

2.2.2 Primary Endpoint: Disease-Free Survival

The analysis of the primary endpoint of DFS will take place when approximately 377 DFS events have occurred in the intent–to–treat (ITT) population (defined in Section 4.1.1) and at least 12 months after the last patient is enrolled have elapsed.

The estimated number of events required for the analysis is based on the following assumptions:

- Two-sided, log-rank test at the 0.05 significance level (two-sided)
- 80% power
- 1:1 randomization ratio
- Median DFS for the control (observation) arm of 20 months and estimated median DFS in the atezolizumab arm of 26.7 months (corresponding to a HR of 0.75)
- No interim analysis for DFS

Accrual of the planned 800 patients is projected to occur over 32 months, assuming a ramp-up period of 13 months to a projected accrual rate of 35 patients per month. On the basis of these assumptions, and the projected probability of loss to follow-up for DFS of approximately 32% over 24 months after enrollment, the required number of DFS events is projected to occur at Month 50 from the time the first patient is randomized.

Also on the basis of these assumptions, it is projected that an observed HR of 0.82 or lower will result in a statistically significant difference between treatment arms (i.e., an HR of 0.82 will be the minimally detectable difference at the analysis; this corresponds to an improvement of 4.5 months in median DFS, from 20 months in the control [observation] arm to 24.5 months in the atezolizumab arm).

2.2.3 Secondary Endpoint: Overall Survival

The final analysis of the secondary endpoint of OS will take place when approximately 428 deaths have occurred in the ITT population on the basis of the following assumptions:

- Two-sided, log-rank test at the 0.05 significance level (two-sided)
- 80% power
- 1:1 randomization ratio
- Median OS for the control (observation) arm of 34 months and estimated median OS in the atezolizumab arm of 44.7 months (corresponding to HR of 0.76)
- Two interim analyses for OS (see Section 2.3.2 for details)

On the basis of these assumptions, the projected probability of loss to follow–up for OS of approximately 24% over 24 months after enrollment, and projected accrual, the required number of OS events for the final analysis of OS is projected to occur 95 months from the time the first patient is randomized. It is projected that an observed HR of 0.82 or lower will result in a statistically significant difference between treatment arms (i.e., an HR of 0.82 will be the minimally detectable difference at the analysis; this corresponds to an improvement of 7.4 months in median OS, from 34 months in the control [observation] arm to 41.4 months in the atezolizumab arm).

2.3 ANALYSIS TIMING

2.3.1 Primary Analysis Timing for DFS

No interim analyses are planned for the primary endpoint of DFS in this study. The analysis of the primary endpoint DFS will take place when approximately 377 DFS events have occurred in the ITT population and at least 12 months after the last patient is enrolled have elapsed. Based on the assumptions described in Section 2.2.2, the required number of DFS events is projected to occur at Month 50 from the time the first patient is randomized.

2.3.2 Interim and Final Analysis Timing for OS

There are no interim analyses planned for DFS, and a total of three analyses of OS will be performed by the Sponsor (two interim analyses and one final analysis; see Table 1 below for details about each analysis).

The first interim analysis of OS will be performed at the time of the DFS analysis. On the basis of the projected median OS for each treatment arm and the projected time of the final analysis of DFS, it is projected that approximately 280 deaths (35% of 800 patients)

will have occurred at the first interim analysis of OS, which corresponds to approximately 65% of the 428 deaths required for the final analysis of OS. It is projected that an observed HR of 0.74 or lower will result in a statistically significant difference between treatment arms at this analysis.

The second interim analysis of OS will be performed when approximately 342 deaths (43% of 800 patients) have occurred, which corresponds to 80% of the 428 deaths required for the final analysis of OS. The required number of OS events for the second interim analysis of OS is projected to occur at Study Month 63 from the time the first patient is randomized. It is projected that an observed HR of 0.78 or lower will result in a statistically significant difference between treatment arms at this analysis.

The final analysis of OS will take place when approximately 428 OS events have occurred in the ITT population. Based on the assumptions described in Section 2.2.3, the required number of OS events is projected to occur at Month 95 from the time the first patient is randomized. It is projected that an observed HR of 0.82 or lower will result in a statistically significant difference between treatment arms at this analysis.

The boundary for statistical significance at each interim analysis and the final analysis will be determined based on the Lan-DeMets implementation of the O'Brien–Fleming use function (Lan and DeMets 1983). For example, with $\alpha = 0.05$ (two–sided) and using the two–sided log–rank test, if 280 deaths have occurred at the time of the first OS interim analysis, statistical significance will be declared if $p \leq 0.011$; if 342 deaths have occurred at the time of the second OS interim analysis, statistical significance will be declared if $p \leq 0.021$; and if 428 deaths have occurred at the time of the final OS analysis, statistical significance will be declared if $p \leq 0.042$. The projected p–value boundary for statistical significance above is based on the number of projected events; actual boundary p–values will be calculated at the time of analysis based on the actual number of events observed in the ITT population.

Table 1 Overall Survival Interim and Final Analysis Characteristics

	ITT population n = 800
Target HR	0.76
median (observation arm)	34 months
median (atezolizumab arm)	44.7 months
Power	80%
Alpha level (two-sided)	0.05
Projected enrollment complete	Study Month 32
First interim OS (to be performed at time of final DFS analysis)	—
Projected cutoff date [a]	Study Month 50
Projected number of events (% of final events)	280 (65%)

	ITT population n = 800
Projected MDD [b]	0.74
Projected boundary (p-value) [c]	$p \leq 0.011$
Second interim OS	—
Number of events (% of final events)	342 (80%)
Projected cutoff date [a]	Study Month 63
Projected MDD [b]	0.78
Projected boundary (p-value) [c]	$p \leq 0.021$
Final OS	—
Number of events (% of final events)	428 (100%)
Projected cutoff date [a]	Study Month 95
Projected MDD [b]	0.82
Projected boundary (p-value) [c]	$p \leq 0.042$

DFS = disease-free survival; HR = hazard ratio; MDD = minimally detectable difference; OS = overall survival

Note: The projected probability of loss to follow-up for OS of approximately 24% over 24 months after enrollment

[a] Study month at which required number of events are projected to occur, where Study Month 1 is the month the first patient is enrolled. Analysis results will be available after data cleaning

[b] The largest observed HR that is projected to be statistically significant

[c] The projected boundary for statistical significance for the number of events shown (actual boundary to be calculated at time of analysis based on actual number of events).

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Eligible patients will be randomized in a 1:1 ratio to either receiving atezolizumab (arm A) or observation (arm B) with the use of a stratified permuted–block randomization.

The randomization will be stratified for the following factors:

- PD–L1 status (IC0/1 vs. IC2/3)
- Nodal status (positive vs. negative)
- Tumor stage after surgical resection ($\leq$pT2 vs. pT3/pT4)
- Prior neo–adjuvant chemotherapy (yes vs. no)
- Number of lymph nodes resected (<10 vs. ≥ 10)

3.2 DATA MONITORING

An independent Data Monitoring Committee (iDMC) will be convened to evaluate safety data until the analysis of the primary endpoint (DFS), after which iDMC review of the study data will be discontinued. The iDMC will evaluate study safety data on a periodic

basis, approximately every 6 months after enrollment of the first patient. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. The Sponsor will remain blinded to the results until the analysis of the primary endpoint of DFS. All summaries and analyses by treatment arm for the iDMC review will be prepared by an external independent data coordinating center.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

4.1.1 Intent–To–Treat Population

The ITT population is defined as all randomized patients, whether or not the patient received the assigned treatment (atezolizumab/observation).

4.1.2 Safety Population

The safety population is defined as patients who received at least one dose of atezolizumab, and all patients who did not receive any dose of atezolizumab who had at least one post-baseline safety assessment (e.g., adverse event, lab, vital signs, ECG, etc.), regardless of their assigned treatment (atezolizumab/observation).

4.1.3 Pharmacokinetic–Evaluable Population

The pharmacokinetic–evaluable population is defined as all patients who received any dose of atezolizumab and who have evaluable pharmacokinetic (PK) samples.

4.1.4 ADA-Evaluable Population

The anti-drug antibodies (ADA)–evaluable population is defined as all patients treated with atezolizumab who have at least one post–baseline ADA result.

4.1.5 Patient–Reported Outcome–Evaluable Population

The patient-reported outcome (PRO) evaluable population is defined as all randomized patients with baseline and at least one post–baseline PRO assessment.

4.2 ANALYSIS OF STUDY CONDUCT

Enrollment, major protocol deviations (including major deviations of inclusion/exclusion criteria), and reasons for discontinuation from the study will be summarized overall and by treatment arm for the ITT population. Study treatment administration and reasons for discontinuation from study treatment will be summarized for patients in the safety population. Length of follow up will be summarized by treatment arm for the ITT population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic variables (age, sex, race/ethnicity), stratification factors (nodal status, number of lymph nodes resected, tumor stage, PD–L1 status, and prior neo–adjuvant chemotherapy) and baseline and disease characteristics (e.g., ACCI, time since initial

diagnosis, time since surgery, surgery–related information, type of urinary diversion, and Eastern Cooperative Oncology Group [ECOG] Performance Status) will be summarized by treatment arm for the ITT population.

Unless otherwise noted, the baseline value of any variable will be defined as the last available value prior to the first administration of study treatment for the atezolizumab arm and prior to Cycle 1 Day 1 date of observation for the observation arm. Descriptive statistics (mean, median, SD, range) will be presented for continuous variables, and frequencies and percentages will be presented for categorical variables.

4.4 EFFICACY ANALYSES

For efficacy analyses, patients will be grouped according to the treatment assigned at randomization by interactive voice/web response system (IxRS), whether or not the assigned treatment was received.

The stratification factors will be the same as the randomization stratification factors (see Section 3.1); however, in order to minimize small strata sizes, only PD-L1 status (IC0/1 vs. IC2/3), nodal status (positive vs. negative) and tumor stage after surgical resection ($\leq$pT2 vs. pT3/pT4) will be used for stratified analysis purposes. Given the mechanism of action of atezolizumab, PD–L1 status will be used for the stratified analysis. Based on the prognostic significance (Protocol Section 3.3.5), prior neo–adjuvant chemotherapy (yes vs. no), and number of lymph nodes resected (<10 vs. ≥ 10) will not be used for the stratified analysis. The eight strata will be applied to all time-to-event endpoints where stratified analyses are planned, including stratified log–rank test and stratified Cox regression model, unless otherwise specified.

Analyses based on stratification factors recorded on the electronic Case Report Form (eCRF) will also be provided if considerable discrepancy is observed between values from IxRS and eCRF records.

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is Investigator-assessed DFS, defined as the time from randomization to the first occurrence of a DFS event, defined as any of the following:

- Local (pelvic) recurrence of UC
- Urinary tract recurrence of UC
- Distant metastasis of UC
- Death from any cause

Data for patients without a DFS event will be censored at the last date the patient was assessed to be alive and recurrence free as determined with radiographic evidence. Data for patients with no post–baseline disease assessment will be censored at the randomization date.

For U.S. registrational purposes, the primary efficacy endpoint of DFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with a DFS event who missed two or more consecutive scheduled assessments immediately prior to the DFS event will be censored at the last date the patient was assessed to be alive and recurrence free as determined with radiographic evidence prior to the missed visits or at the randomization date if there is no post–baseline tumor assessment prior to the DFS event.

DFS will be analyzed in the ITT population. The following analyses will be performed for both DFS endpoints described above. Treatment comparisons will be based on the stratified log-rank test at the two–sided level of significance as described in Section 2.2.1. The stratification factors used for the analysis are described in Section 4.4 and the values will be those recorded in the IxRS. The null and alternative hypotheses can be phrased in terms of the survival functions S_A (t) and S_B (t) in Arm A (atezolizumab) and Arm B (observation), respectively:

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

The HR, λ_A/λ_B, where λ_A and λ_B represent the hazard of experiencing an DFS event in Arm A and Arm B, respectively, will be estimated using a stratified Cox regression model with the same stratification variables used for the stratified log-rank test, and the 95% CI for the HR will be provided. Results from an unstratified analysis will also be provided.

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

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 Overall Survival (OS)

Overall survival is defined as the time from randomization to the date of death from any cause, regardless of whether the death occurs during study treatment or following treatment discontinuation. Data for patients who have not died will be censored at the last date they were known to be alive. Data for patients without post–baseline survival information will be censored at the randomization date. Methods for comparison of OS between treatment arms will be the same as the methods for treatment comparison for the primary efficacy endpoint of DFS.

Three analyses of OS are planned (two interim analyses and one final analysis; see Section 2.3.2 for details). The first interim analysis of OS will occur at the time that the primary endpoint of DFS is analyzed. The Type I error control for the secondary endpoint of OS is described in Section 2.2.1.

4.4.2.2 Disease-Specific Survival (DSS)

DSS is defined as the time from randomization to the date of death from UC. Data for patients who have not died will be censored at the last date they were known to be alive. Data for patients who died from causes other than UC will be censored at the date of death. Methods for comparison of DSS between treatment arms will be the same as the methods for treatment comparison for the secondary efficacy endpoint of OS. For the purposes of evaluating DSS, for each patient death, the cause of death will be assessed as related or not related to UC by the investigator.

4.4.2.3 Distant Metastasis-Free Survival (DMFS)

DMFS is defined as the time from randomization to the date of a DMFS event, defined as diagnosis of distant (i.e., non–locoregional) metastasis or death from any cause. Data for patients without a DMFS event will be censored at the last date the patient was assessed to be alive and free of distant metastasis. Data for patients without post baseline disease assessment will be censored at the randomization date. Methods for comparison of DMFS between treatment arms will be the same as the methods for treatment comparison for the primary efficacy endpoint of DFS.

4.4.2.4 Non-Urinary Tract Recurrence-Free Survival (NURFS)

NURFS is defined as the time from randomization to the date of a NURFS event, defined as diagnosis of non-urinary tract (non–UT) recurrence (i.e., pelvic soft tissue or regional lymph node recurrence, or distant metastasis) or death from any cause. Data for patients without a NURFS event will be censored at the last date the patient was assessed to be alive and free of non–urinary tract recurrence. Data for patients with no post baseline disease assessment will be censored at the randomization date day. Methods for comparison of NURFS between treatment arms will be the same as the methods for treatment comparison for the primary efficacy endpoint of DFS.

4.4.3 Exploratory Efficacy Endpoints

4.4.3.1 DFS and OS Analyses by PD-L1 status

To estimate the treatment benefit for patients with different PD-L1 status (IHC score of IC0/1 and IC2/3), the same stratified analysis used for the primary DFS analysis will also be performed for both DFS and OS in ITT patients within each PD-L1 subgroup (IC0/1 and IC2/3), except that PDL1 status as a stratification factor for the primary DFS analysis will not be used for these stratified analysis.

4.4.3.2 Analyses at Landmark Timepoints

The rates of DFS, OS, DSS, DMFS, and NURFS at various timepoints (i.e., every 6 months after randomization) will be estimated by the Kaplan–Meier methodology for each arm and the 95% CI will be calculated using Greenwood's formula. The 95% CIs for the difference in each of the event rates between the two arms will be estimated using the normal approximation method.

4.4.3.3 Additional DFS and OS Analyses

In order to evaluate the robustness of the primary analyses in the event that proportionality of hazard rates may not be assumed, the following analyses may be performed for DFS and OS.

4.4.3.3.1 Restricted Mean Survival Time (RMST)

The RMST for each treatment arm may be computed for DFS and OS using the area under the corresponding survival curve from baseline to a several timepoints (e.g., 6 months, 12 months, etc.). The difference with its 95% confidence interval will be displayed.

4.4.3.3.2 Weighted Log-rank (WLR) Test

WLR test (Fine 2007) may be performed for both DFS and OS using Fleming and Harrington weight function defined at time t as: $W(t) = S(t)^{\rho}(1 - S(t))^{\gamma}$. The following two combinations of ρ and γ will be considered: $(\rho = 0, \gamma = 1)$ and $(\rho = 1, \gamma = 1)$. Both unstratified and stratified (using stratification factors mentioned in Section 4.4 analyses will be conducted.

4.4.3.4 Biomarker Analyses

The tumor biomarkers include but are not limited to tTMB using the cut-offs of ≥ 10 mutations/MB and ≥ 16 mutations/MB separately (given data availability), PD-L1, CD8, and CD103, as defined by immunohistochemistry (IHC), quantitative reverse transcriptase−polymerase chain reaction (qRT−PCR), or other methods and would be dependent on sufficient tissue availability. Additional pharmacodynamic analyses of predictive, prognostic, and exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to study treatment will be conducted as appropriate. These exploratory analyses may be provided in a separate report.

4.4.4 Sensitivity Analyses

4.4.4.1 Sensitivity Analyses on DFS for Patients in Any Treatment Arm Receiving Protocol Prohibited Anti–Cancer Therapy

The impact of protocol prohibited anti-cancer therapy on DFS may be assessed depending on the number of patients who receive such therapy before a DFS event. If $> 5\%$ of patients received protocol prohibited anti-cancer therapy before a DFS event in any treatment arm, data for these patients will be censored at the last disease assessment date before they received such therapy in DFS analyses that may be performed for the comparisons between treatment arms.

4.4.4.2 Sensitivity Analyses on OS for Patients in Observation Arm Receiving Atezolizumab or Similar Immunotherapy

The impact on OS by patients in observation arm subsequently receiving atezolizumab or another immunotherapy considered similar to atezolizumab in its mechanism of action may be assessed, depending on the number of such patients. If more than 5% of

patients in observation arm have received atezolizumab or a similar immunotherapy, the following analyses may be performed to compare treatment arms at each of the interim analyses and final analysis, as applicable:

- OS in the observation arm will be discounted according to a range of possible effects on OS after having received atezolizumab or another immunotherapy (e.g., 10%, 20%, 30%, etc.)
- Additional sensitivity analyses may be conducted if deemed necessary

4.4.5 Subgroup Analyses

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

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

- Age at randomization ($<$65 years vs. $\geq$65 years)
- Race (non–white vs. white)
- Sex (female vs. male)
- Region (North America, Europe, Asia, Australia)
- PD-L1 status (IC0/1 vs. IC2/3)
- Number of lymph nodes resected ($<$10 vs.$\geq$10)
- Nodal status (positive vs. negative)
- Tumor stage after resection ($\leq$ pT2 vs. pT3/pT4)
- Prior neo–adjuvant chemotherapy (yes vs. no)
- Age-adjusted Charlson comorbidity index (ACCI) (0-1, 2-3, $\geq$4)
- ECOG performance status at randomization (0 vs. 1-2)
- Primary disease (MIBC vs. UTUC)
- Type of urinary diversion (ileal conduct, orthotopic, other)

Similar analyses will be performed as appropriate for OS.

4.5 SAFETY ANALYSES

Unless specified otherwise, the safety analyses described below will be conducted for the safety population (see Section 4.1.2), with patients grouped according to whether any atezolizumab treatment was received (i.e., patients who received any dose of atezolilzumab will be included in the atezolizumab arm).

4.5.1 Exposure of Study Medication

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

4.5.2 Adverse Events

Verbatim descriptions of adverse events will be mapped to Medical Dictionary for Regulatory Activities (MedDRAterms). Treatment emergent events (defined as events occurring on or after the first dose of atezolizumab, or, for patients in the observation arm, after the date of randomization) will be summarized by MedDRA term, appropriate MedDRA levels, and NCI CTCAE (National Cancer Institute, Common Terminology Criteria for Adverse Events) v4.0 grade. For each patient, multiple occurrences of the same event will be counted once at maximum severity reported will be used in the summaries. Adverse events will be summarized regardless of relationship to study drug as assessed by the investigator. All adverse events, adverse events leading to withdrawal of study drug, adverse events leading to dose interruption, Grade ≥ 3 adverse events, serious adverse events, adverse events related to study drug, adverse events of special interest, and immune–mediated adverse events will be summarized. Deaths and cause of death will be summarized.

4.5.3 Laboratory Data

Laboratory data will be classified according to NCI CTCAE v4.0. Highest NCI CTCAE v4.0 grade post-baseline will be reported and shift tables from baseline to worst value during the study post–baseline will be presented. Selected laboratory tests will be summarized descriptively over time including changes from baseline.

A Hy's law analysis will be provided. The potential Hy's law quadrant is defined as alanine aminotransferase or aspartate aminotransferase increases above 3-fold the upper limit of normal (ULN) with concomitant total bilirubin increases above 2-fold the ULN.

4.5.4 Vital Signs

Changes in selected vital signs will be summarized by treatment arm and by change over time including change from baseline.

4.6 PHARMACOKINETIC ANALYSES

Atezolizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized according to the blood sampling schedule (C_{max} will be reported for Cycle 1 only; C_{min} will be evaluated at Cycles 1, 2, 3, and 4; every 8 cycles starting on Cycle 8; and both at treatment discontinuation and at 120 days [± 30 days] after the last dose of atezolizumab). Descriptive statistics will include means, medians, ranges, and SDs, as appropriate. Additional PK analyses will be conducted as appropriate.

4.7 IMMUNOGENICITY ANALYSES

Incidence of ADAs against atezolizumab will be summarized. The analyses of pharmacokinetics, key efficacy, and safety by ADA status will be conducted to explore the potential impact of immunogenicity. ADA results will be summarized and listed by patient for patients in Arm A only.

4.8 PATIENT-REPORTED OUTCOME ANALYSES

PROs will primarily be evaluated by treatment arm (as assigned at randomization) in the ITT population. Sensitivity analyses may be conducted in the PRO-evaluable population.

Completion rates will be calculated as the number of completed assessments divided by the number of expected assessments at each time point.

Summary statistics (e.g., mean, median, SD, interquartile range, minimum, maximum) for the EuroQol 5-dimension, 5-level version (questionnaire; EQ-5D-5L) descriptive system (i.e., health utilities and individual items) and the visual analogue scale (VAS) scores and score changes from baseline will be presented for each time point.

Longitudinal mixed models (e.g., repeated measures, linear) will estimate least-squares mean change from baseline in EQ-5D-5L VAS scores by treatment arm and differences between arms at each assessment time point and/or at landmark time points. Within–and between–group differences will be evaluated descriptively.

4.9 MISSING DATA

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

4.10 EXPLORATORY ANALYSES

Exploratory outcome measures defined in the protocol other than the analyses specified in Section 4.4.3 are outside of the scope of this SAP and will not be included in the Clinical Study Report.

5. REFERENCES

Brookmeyer, Ron, and John Crowley. "A confidence interval for the median survival time." *Biometrics* (1982): 29-41.

Fine, Gil D. "Consequences of delayed treatment effects on analysis of time-to-event endpoints." *Drug Information Journal*41.4 (2007): 535-539.

Gordon Lan, K. K., and David L. DeMets. "Discrete sequential boundaries for clinical trials." *Biometrika* 70.3 (1983): 659-663.

Lewis, Steff, and Mike Clarke. "Forest plots: trying to see the wood and the trees." *BMJ: British Medical Journal* 322.7300 (2001): 1479.

Appendix 1
Protocol Synopsis

TITLE:	**A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) VERSUS OBSERVATION AS ADJUVANT THERAPY IN PATIENTS WITH HIGH-RISK MUSCLE-INVASIVE UROTHELIAL CARCINOMA AFTER SURGICAL RESECTION**
PROTOCOL NUMBER:	WO29636
VERSION NUMBER:	8
EUDRACT NUMBER:	2014-005603-25
IND NUMBER:	120827
TEST PRODUCT:	Atezolizumab (MPDL3280A; RO5541267)
PHASE:	III
INDICATION:	Muscle-invasive urothelial carcinoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives:

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of adjuvant atezolizumab treatment in patients with muscle-invasive urothelial carcinoma (UC) as measured by disease-free survival (DFS)

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of adjuvant atezolizumab treatment, as measured by overall survival (OS)
- To evaluate the efficacy of adjuvant atezolizumab treatment, as measured by disease-specific survival (DSS)

PROTOCOL AMENDMENT APPROVAL

- To evaluate the efficacy of adjuvant atezolizumab treatment, as measured by distant metastasis-free survival (DMFS)
- To evaluate the efficacy of adjuvant atezolizumab treatment, as measured by non-urinary tract recurrence-free survival (NURFS)

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab in the adjuvant setting
- To evaluate the incidence of anti-therapeutic antibodies (ATAs) against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

Pharmacokinetic Objective

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

- To characterize the pharmacokinetics of atezolizumab

Patient-Reported Outcome Objective

The patient-reported outcome (PRO) objective for this study is as follows:

- To assess health status as measured by the EuroQol 5-dimension, 5-level version (EQ-5D-5L) questionnaire

Exploratory Objective

The exploratory objective for this study is as follows:

- To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease recurrence

Study Design

Description of Study

Study WO29636 is a global Phase III, open-label, randomized, controlled trial designed to evaluate the efficacy and safety of adjuvant treatment with atezolizumab compared with observation in patients with muscle-invasive UC, who are at high risk for recurrence following resection.

Male and female patients aged ≥ 18 years with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 who have histologically confirmed muscle-invasive UC (also termed TCC) of the bladder or upper urinary tract (i.e., renal pelvis or ureters) are eligible. Patients with upper urinary tract urothelial carcinoma (UTUC) will be limited to no more than approximately 10% of the study population.

Patients with bladder as the site of primary involvement must have undergone radical cystectomy with lymph node dissection. Patients with UTUC as the site of primary involvement must have undergone radical nephroureterectomy (RNU) with excision of the bladder cuff regardless of the location of the tumor in the upper urinary tract. RNU must include lymph node dissection.

Patients who have received prior neoadjuvant chemotherapy are eligible, but must have tumor staging of ypT2–4a or ypN+ (ypT2-4 or ypN+ for patients with UTUC) and M0 at pathological examination of the surgical resection specimen. Patients who have not received prior neoadjuvant chemotherapy must be ineligible for or declined treatment with cisplatin-based adjuvant chemotherapy and have tumor staging of pT3–4a or pN+ (pT3-4 or pN+ for patients with muscle-invasive UTUC) and M0.

Tumor specimens from surgical resection (i.e., radical cystectomy, RNU, or lymph node dissection) from patients who have signed the Informed Consent Form will be evaluated for PD-L1 expression by IHC. Only patients whose tumors have sufficient amounts of viable tumor and are evaluable for PD-L1 expression as confirmed by a central pathology laboratory prior to enrollment of the patient in the study will be eligible.

Patients will be randomized to one of the following arms in a 1:1 ratio:

- Arm A (experimental arm): atezolizumab 1200 mg q3w
- Arm B (control arm): observation

Randomization will be stratified by the following factors:

- Number of lymph nodes resected (<10 vs. ≥ 10)
- Nodal status (positive vs. negative)
- Tumor stage after surgical resection ($\leq$pT2 vs. pT3/pT4)
- PD-L1 IHC status (IHC score of IC0/1 vs. IHC score of IC2/3)
- Prior neoadjuvant chemotherapy (yes vs. no)

Randomization $must$ occur within 14 weeks after surgical resection of the primary tumor and study drug administration should begin within 7 calendar days after randomization.

For patients in Arm A, atezolizumab will be administered intravenously (IV) on Day 1 of each 21-day cycle for 16 cycles (up to 1 year). In Arm B, patients will continually undergo observation starting on Day 1 of each 21-day cycle for 16 cycles (up to 1 year). Treatment/observation will be discontinued in the event of disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor.

To ensure the same frequency of study assessments between the treatment arms, including assessments for disease recurrence and safety, patients in Arm B will be required to undergo q3w medical contacts for assessments during the first year, which will consist of formal clinic visits alternating with clinical contacts (either via telephone call or formal outpatient clinic visit) for symptom and adverse event assessment.

Patients in the control arm will not be allowed to cross over to receive atezolizumab treatment within this study.

All patients will undergo scheduled assessments for tumor recurrence at baseline and every 12 weeks (approximately every 4 cycles) in the first year following randomization. Upon completion of the treatment/observation period, surveillance for tumor recurrence will be performed every 12 weeks for Years 2–3; every 24 weeks for Years 4–5; and at Year 6 (approximately 48 weeks after the last assessment in Year 5). In the absence of a DFS event (defined as any of the following: local [pelvic] recurrence of UC; upper urinary tract or urethral recurrence of UC; distant metastasis of UC; or death from any cause), surveillance for tumor recurrence should continue regardless of whether patients start new anticancer therapy, until withdrawal of consent, loss to follow-up, or study termination by the Sponsor, whichever occurs first. For patients with muscle-invasive bladder cancer (MIBC), surveillance for tumor recurrence will include physical examination, laboratory evaluation, and imaging studies of the chest, abdomen, upper urinary tracts, and pelvis. Disease recurrence will be as determined by the investigator based on radiographic evidence (visual appearance of UC with histological confirmation is acceptable for recurrence in bladder). For patients with UTUC, surveillance for tumor recurrence must include physical examination, cystoscopy, urine cytology and imaging studies of the chest, abdomen, and pelvis. A confirmatory tumor biopsy is mandatory at the time of disease recurrence. Cases for which biopsy results definitively rule out recurrence of UC will not be considered as disease recurrence for this study.

Safety assessments will include the incidence, nature, and severity of adverse events, changes in vital signs, and laboratory abnormalities graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of ATAs to atezolizumab. A sample of archived tumor tissues, as well as serum and plasma samples, will be collected for future exploratory biomarker assessments.

An external independent Data Monitoring Committee (iDMC) will evaluate safety data according to policies and procedures detailed in an iDMC Charter.

Number of Patients

Approximately 800 patients will be enrolled in the study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Ability to comply with protocol
- Age $\geq$ 18 years
- Histologically confirmed muscle-invasive UC (also termed TCC) of the bladder or upper urinary tract (i.e., renal pelvis or ureters)

Patients with mixed histologies are required to have a dominant transitional cell pattern.

- TNM classification (UICC/AJCC 7th edition) at pathological examination of surgical resection specimen as follows:

For patients treated with prior neoadjuvant chemotherapy: tumor stage of ypT2 -4a or ypN+ (ypT2-4 or ypN+ for patients with UTUC) and M0

For patients who have not received prior neoadjuvant chemotherapy: tumor stage of pT3–4a or pN+ (pT3-4 or pN+ for patients with UTUC) and M0

- Surgical resection of muscle-invasive UC of the bladder, or UTUC upper tract

For patients with MIBC, radical cystectomy may be performed by the open, laparoscopic, or robotic approach. Cystectomy must include bilateral lymph node dissection, the extent of which will be at the discretion of the treating surgeon but optimally should extend at a minimum from the mid common iliac artery proximally to Cooper's ligament distally, laterally to the genitofemoral nerve, and inferiorly to the obturator nerve. The method of urinary diversion for patients undergoing cystectomy will be at the discretion of the surgeon and choice of the patient.

Patients with a negative surgical margin (i.e., R0 resection) or with carcinoma in situ (CIS) at the distal ureteral or urethral margin will be eligible.

Patients with a positive R2 margin (which is defined as a tumor identified at the inked perivesical fat margin surrounding the cystectomy specimen) or R1 margin (which is defined as evidence of microscopic disease identified at the tumor margin), except for CIS at the distal ureteral or urethral margin, will be excluded.

For patients with UTUC, RNU with excision of the bladder cuff is required and may be performed by the open or laparoscopic approach. RNU must include lymph node dissection (LND), the extent of which will be at the discretion of the treating surgeon but optimally should include the para-aortic, paracaval or interaortocaval nodes from the renal hilum to the inferior mesenteric artery in renal pelvis and proximally ureteral tumors, or nodes from the renal hilum to the bifurcation of the common iliac artery and ipsilateral pelvic nodes in mid and lower ureteral tumors, respectively.

Patients must have a negative surgical margin (i.e., R0 resection). Patients with a positive R1 or R2 surgical margin will be excluded.

- Patients who have not received prior platinum-based neoadjuvant chemotherapy, have refused, or are ineligible (“unfit”) for cisplatin-based adjuvant chemotherapy

Patients who have received at least two cycles of a platinum-containing regimen will be considered as those who have received prior neoadjuvant chemotherapy.

Cisplatin ineligibility is defined by any one of the following criteria:

Impaired renal function (glomerular filtration rate [GFR] $<$ 60 mL/min); GFR should be assessed by direct measurement (i.e., creatinine clearance or ethyldediaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine (Cockcroft-Gault formula)

A hearing loss (measured by audiometry) of 25 dB at two contiguous frequencies

Grade 2 or greater peripheral neuropathy (i.e., sensory alteration or parasthesis including tingling)

ECOG performance status of 2

- Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens from surgical resection (i.e., radical cystectomy, nephroureterectomy, or lymph node dissection) in paraffin blocks (blocks preferred) or at least 15 unstained slides, with an associated pathology report, for central testing and determined to be evaluable for tumor PD-L1 expression prior to study enrollment

Patients with fewer than 15 unstained slides available at baseline (but no fewer than 10) may be eligible following discussion with Medical Monitor.

Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.

Tumor tissue of bladder or upper tract should be of good quality based on total and viable tumor content and must contain a muscle invasive component (i.e. T2 or greater) of the tumor as verified by local pathology review. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.In situations where multiple specimens were received from different sites or at different times, the score from the surgical resection of the primary tumor or lymph node dissection specimen will be used for both primary and secondary analyses.

- Muscle-invasive UC with PD-L1 expression per IHC prospectively determined on the surgical resection or lymph node dissection tumor specimens by a central laboratory
- Absence of residual disease and absence of metastasis, as confirmed by a negative baseline computed tomography (CT) or magnetic resonance imaging (MRI) scan of the pelvis, abdomen, and chest no more than 4 weeks prior to randomization.

For patients with MIBC, imaging of the upper urinary tracts must include one or more of the following: intravenous pyelogram (IVP), CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy or MRI urogram, and must be completed no more than 4 weeks prior to randomization.

For patients with UTUC, cystoscopy and urine cytology must be completed no more than 4 weeks prior to randomization, however upper tract imaging is not needed.

Other examinations should be performed as clinically indicated.

For patients with both primary MIBC and primary UTUC, imaging of the upper urinary tracts, cystoscopy, and urine cytology is not required.

- Full recovery from cystectomy or nephroureterectomy within 14 weeks following surgery
- ECOG performance status of ≤ 2
- Life expectancy ≥ 12 weeks
- Adequate hematologic and end-organ function, as defined by the following laboratory results obtained within 14 days prior to the first study treatment:

ANC ≥ 1500 cells/μL (without granulocyte colony–stimulating factor support within 2 weeks prior to Cycle 1, Day 1)

WBC counts $> 2500/\mu L$

Lymphocyte count $\geq 300/\mu L$

Platelet count $\geq 100{,}000/\mu L$ (without transfusion within 2 weeks prior to Cycle 1, Day 1)

Hemoglobin ≥ 9.0 g/dL

Patients may be transfused or receive erythropoietic treatment to meet this criterion.

AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ the upper limit of normal (ULN)

Serum bilirubin $\leq 1.0 \times$ ULN

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

PTT/PT $\leq 1.5 \times$ ULN or INR $< 1.7 \times$ ULN

This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.

Calculated creatinine clearance ≥ 20 mL/min (Cockcroft-Gault formula)

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 5 months after the last dose of atezolizumab*, and agreement to 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, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

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

Exclusion Criteria

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

Cancer-Specific Exclusion Criteria:

- Any approved anti-cancer therapy, including chemotherapy, or hormonal therapy within 3 weeks prior to initiation of study treatment

Hormone-replacement therapy or oral contraceptives are allowed.

- Adjuvant chemotherapy or radiation therapy for UC following surgical resection

Patients who have received primary chemoradiation for bladder preservation before cystectomy are eligible and will be treated as the same as patients who have received prior neoadjuvant chemotherapy.

Postsurgical intrapelvic/intravesical chemotherapy or BCG is not allowed for patients with UTUC.

- Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 28 days or five half-lives of the drug, whichever is longer, prior to enrollment
- Malignancies other than UC within 5 years prior to Cycle 1, Day 1

Patients with high risk UTUC (defined as tumor stage ypT2–4a or ypN+) within 5 years prior to Cycle 1 Day 1 will be ineligible after the UTUC limit of approximately 10% has been met.

Patients with localized low risk prostate cancer (defined as Stage ≤ T2b, Gleason score ≤ 7, and PSA at prostate cancer diagnosis ≤ 20 ng/mL [if measured]) treated with curative intent and without prostate-specific antigen (PSA) recurrence are eligible.

Patients with low risk prostate cancer (defined as Stage T1/T2a, Gleason score ≤ 7 and PSA ≤ 10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible.

Patients with 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, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent)

No evidence of recurrence or metastasis by follow-up imaging and any disease-specific tumor markers

General Medical Exclusion Criteria:

- Pregnancy or breastfeeding
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.

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

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

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

- Serum albumin < 2.5 g/dL
- Positive test for HIV
- Patients with active hepatitis B virus (HBV; chronic or acute; defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBc Ab] and absence of HBsAg) are eligible. HBV DNA must be obtained in these patients prior to Cycle 1, Day 1.

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

- Active tuberculosis
- Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia

Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1

- Receipt of therapeutic oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1

Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible.

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

Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction $< 50\%$ must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

- Major surgical procedure other than for diagnosis within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study
- Prior allogeneic stem cell or solid organ transplant
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study

Influenza vaccination should be given during influenza season only (approximately October through May in the Northern Hemisphere and approximately April through September in the Southern Hemisphere). Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to randomization, during treatment or within 5 months following the last dose of atezolizumab (for patients randomized to atezolizumab).

- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications

Medication-Related Exclusion Criteria:

- Prior treatment with CD137 agonists or immune checkpoint–blockade therapies, including anti-CD40, anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including but not limited to interferons, IL-2) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1, or anticipated requirement for systemic immunosuppressive medications during the trial

Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea, multiple doses for contrast allergy) may be enrolled in the study.

The use of inhaled or low-dose (e.g., ≤ 10 mg/day prednisone) corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, and mineralocorticoids (e.g., fludrocortisone for adrenal insufficiency) and low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

End of Study

The end of the study as planned will occur when the required number of events for the final analysis of OS has occurred (projected to be approximately Month 95 from FPI). However, the Sponsor may decide to terminate the study at any time.

Length of Study

The study is expected to last approximately 8 years after the first patient is randomized.

Outcome Measures

Efficacy Outcome Measures

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

- Investigator-assessed DFS, defined as the time from randomization to the time of first occurrence of a DFS event, defined as any of the following:

Local (pelvic) recurrence of UC (including soft tissue and regional lymph nodes)

Urinary tract recurrence of UC (including all pathological stages and grades)

Distant metastasis of UC

Death from any cause

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

- OS, defined as the time from randomization to the date of death from any cause
- DSS, defined as the time from randomization to the date of death from UC per investigator assessment of cause of death
- DMFS, defined as the time from randomization to the date of diagnosis of distant (i.e., non-locoregional) metastases or death from any cause
- NURFS, defined as the time from randomization to the time of first occurrence of a NURFS event, defined as any of the following:

Local (pelvic) recurrence of UC (including soft tissue and regional lymph nodes)

Distant metastasis of UC

Death from any cause

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events graded according to NCI CTCAE v4.0

- Changes in vital signs and clinical laboratory results
- Incidence of ATA response to atezolizumab and potential correlation with PK, pharmacodynamic, safety, and efficacy parameters

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Maximum observed serum atezolizumab concentration (C_{max}) after infusion on Day 1 of Cycle 1
- Minimum observed serum atezolizumab concentration (C_{min}) prior to infusion on Day 1 of Cycles 1, 2, 3, and 4; every 8 cycles starting on Cycle 8; at treatment discontinuation; and at 120 days (±30 days) after the last dose of atezolizumab

Patient-Reported Outcome Measure

The PRO outcome measure for this study is as follows:

- EQ-5D-5L as a measure of patient-reported health status

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Status of tumor immune-related or disease type−related exploratory biomarkers in archival and/or freshly obtained tumor tissues and association with disease recurrence
- Status of exploratory biomarkers in plasma, whole blood, or serum (including but not limited to cytokines such as IL-6) collected before or during treatment with atezolizumab or at recurrence and association with disease recurrence

Investigational Medicinal Products

Test Product (Investigational Drug)

The dose level of atezolizumab to be tested in this study is 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) administered by IV infusion every 3 weeks (21 [±3] days) for 16 cycles or 1 year (whichever occurs first).

Statistical Methods

Primary Analysis

The primary efficacy endpoint is investigator-assessed DFS, defined as the time from randomization to the time of first occurrence of a DFS event, defined as any of the following: local (pelvic) recurrence of UC; urinary tract recurrence of UC; distant metastasis of UC; or death from any cause. Data for patients without a DFS event will be censored at the last date the patient was assessed to be alive and recurrence free as determined with radiographic evidence. Data for patients with no post-baseline disease assessment will be censored at the randomization date.

For United States registrational purposes, the primary efficacy endpoint of DFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with a DFS event who missed two or more scheduled assessments immediately prior to the DFS event will be censored at the last tumor assessment as determined with radiographic evidence prior to the missed visits. Type I error control will be applied to this analysis of DFS.

DFS will be analyzed in the ITT population. The following analyses will be performed for both DFS endpoints described above. DFS will be compared between treatment arms using the stratified log-rank test. The hazard ratio (HR) for recurrence or death will be estimated using a stratified Cox proportional hazards model and the 95% CI for the HR will be provided. The stratification factors will *be the same as* the randomization stratification factors; *however, stratification factors may be combined for analysis purposes if necessary to minimize small stratum cell sizes. Combination of stratification factors, if any, would be specified in the Statistical Analysis Plan (SAP) prior to analysis*. The stratification factors will be obtained from the IxRS at the time of randomization. Results from an unstratified analysis will also be

provided. Kaplan-Meier methodology will be used to estimate median DFS for each treatment arm; Kaplan-Meier curves will be produced. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median DFS for each treatment arm. The DFS rate at various timepoints (i.e., every 6 months after randomization) will be estimated by Kaplan-Meier methodology for each treatment arm, and the 95% CI will be calculated using Greenwood's formula.

The following additional analyses will be performed for both DFS endpoints described above:

- Analyses at landmark *time*points
- Subgroup analyses

Determination of Sample Size

Approximately 800 patients will be randomized in this study.

The type I error (alpha) for this study is 0.05 (two-sided). Type I error will be controlled for the primary endpoint of DFS and the key secondary endpoint of OS. To control the Type I error at alpha = 0.05 (two-sided) for DFS and OS endpoints, the treatment arms will be compared in a hierarchical fashion as follows: If the DFS analysis results (as defined for United States registrational purposes) are statistically significant at alpha = 0.05 (two-sided), then the analysis of OS will be performed at alpha = 0.05 (two-sided) and the interim analysis boundaries for OS will be calculated according to alpha = 0.05 (two-sided).

The analysis of the primary endpoint of DFS will take place when approximately 377 DFS events have occurred *and at least 12 months after the last patient is enrolled have elapsed. The estimated number of events required for the analysis is based on* the following assumptions:

- Two-sided log-rank test at the 0.05 significance level (two-sided)
- 80% power
- 1:1 randomization ratio
- Median DFS for the control (observation) arm of 20 months and estimated median DFS in the atezolizumab arm of 26.7 months (corresponding to a HR of 0.75)
- No interim analysis of DFS

Accrual of the planned 800 patients is projected to occur over 32 months, assuming a ramp-up period of 13 months to a projected accrual rate of 35 patients per month. On the basis of these assumptions, and the projected probability of loss to follow-up for DFS of approximately 32% over 24 months after enrollment, the required number of DFS events is projected to occur at Month 50 from the time the first patient is randomized. Also on the basis of these assumptions, it is projected that an observed HR of 0.82 or lower will result in a statistically significant difference between treatment arms (i.e., an HR of 0.82 will be the minimally detectable difference at the analysis; this corresponds to an improvement of 4.5 months in median DFS, from 20 months in the control [observation] arm to 24.5 months in the atezolizumab arm).

The final analysis of the secondary endpoint of OS will take place when approximately 428 deaths have occurred on the basis of the following assumptions:

- Two-sided log-rank test at the 0.05 significance level (two-sided)
- 80% power
- 1:1 randomization ratio
- Median OS for the control (observation) arm of 34 months and estimated median OS in the atezolizumab arm of 44.7 months (corresponding to HR of 0.76)
- Two interim analyses of OS

On the basis of these assumptions, the projected probability of loss to follow-up for OS of approximately 24% over 24 months after enrollment, and projected accrual, the required number of OS events for the final analysis of OS is projected to occur 95 months from the time the first patient is randomized. It is projected that an observed HR of 0.82 or lower will result in a statistically significant difference between treatment arms (i.e., an HR of 0.82 will be the minimally detectable difference at the analysis; this corresponds to an improvement of 7.4

months in median OS, from 34 months in the control [observation] arm to 41.4 months in the atezolizumab arm).

Two interim analyses of OS are planned.

Interim Analyses

No interim efficacy analyses of DFS are planned for this study.

A total of three analyses of OS will be performed by the Sponsor (two interim analyses and one final analysis). The final analysis of OS will be performed when approximately 428 deaths (54% of 800 patients) have occurred in the ITT population. On the basis of accrual projections and projected median OS for each treatment arm, the final analysis of OS is projected to occur 95 months from the time the first patient is randomized. The interim analysis boundaries for statistical significance at each interim analysis will be determined on the basis of the Lan-DeMets implementation of the O'Brien-Fleming use function.

The first interim analysis of OS will be performed at the time of the DFS analysis. On the basis of the projected median OS for each treatment arm and the projected time of the final analysis of DFS, it is projected that approximately 280 deaths (35% of 800 patients) will have occurred at the first interim analysis of OS, which corresponds to approximately 65% of the 428 deaths required for the final analysis of OS. It is projected that an observed HR of 0.74 or lower will result in a statistically significant difference between treatment arms at this analysis.

The second interim analysis of OS will be performed when approximately 342 deaths (43% of 800 patients) have occurred, which corresponds to 80% of the 428 deaths required for the final analysis of OS. The required number of OS events for the second interim analysis of OS is projected to occur 63 months from the time the first patient is randomized. It is projected that an observed HR of 0.78 or lower will result in a statistically significant difference between treatment arms at this analysis.

The interim analyses of OS will be performed by the Sponsor. The boundary for statistical significance at each interim analysis and the final analysis will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming use function. For example, with $\alpha = 0.05$ (two-sided) and using the two-sided log-rank test, if 280 deaths have occurred at the time of the first OS interim analysis, statistical significance will be declared $p \leq 0.011$; if 342 deaths have occurred at the time of the second OS interim analysis, statistical significance will be declared if $p \leq 0.021$; and if 428 deaths have occurred at the time of the final OS analysis, statistical significance will be declared if $p \leq 0.042$.

An iDMC will be convened to evaluate safety results approximately every 6 months after enrollment of the first patient until the analysis of the primary endpoint (DFS).

Appendix 2
Schedule of Assessments

	Both Arms	Arm A (Atezolizumab)		Arm B (Observation)			Both Arms
	Screening for Randomization	All Cycles	Discontinuation [a]	Cycles 1, 3, 5, 7, 9, 11, 13, and 15	Cycles 2, 4, 6, 8, 10, 12, 14, and 16	Discontinuation [a]	
Study Procedures	Days –28 to –1	Day 1 (±3 Days for Cycles ≥2) [b]	≤30 Days after Last Dose	Day 1 (±3 Days for Cycles ≥2) [b]	Day 1 (±3 Days) [b]	≤30 Days after Last Visit	Follow-Up
Signed Informed Consent Form(s) [c]	x						
Review of eligibility criteria	x						
Medical, surgical, and cancer histories, including demographic information [d]	x						
Pregnancy test [e]	x	x	x				
ECOG performance status	x	x [f]	x	x [f]		x	
Age-adjusted Charlson comorbidity index (ACCI)	x						
Complete physical examination [g]	x		x			x	
Limited physical examination [g]		x [f]		x [f]			
Weight	x	x	x	x		x	
Height	x						
Vital signs [h]	x	x	x	x		x	
12-lead electrocardiogram [i]	x	x	x				
HIV, HCV serology [j]	x						
Hematology [k]	x	x [f]	x	x [f]		x	
Serum chemistry [l]	x	x [f]	x	x [f]		x	
Coagulation panel (aPTT, INR)	x		x			x	

Appendix 2
Schedule of Assessments (cont.)

	Both Arms	Arm A (Atezolizumab)		Arm B (Observation)			Both Arms
	Screening for Randomization	All Cycles	Discontinuation [a]	Cycles 1, 3, 5, 7, 9, 11, 13, and 15	Cycles 2, 4, 6, 8, 10, 12, 14, and 16	Discontinuation [a]	
Study Procedures	Days –28 to –1	Day 1 (±3 Days for Cycles ≥2) [b]	≤30 Days after Last Dose	Day 1 (±3 Days for Cycles ≥2) [b]	Day 1 (±3 Days) [b]	≤30 Days after Last Visit	Follow-Up
Urinalysis [m]	x	x [n,f]	x	x [n]		x	
TSH, free T3, free T4	x	x [o,f]	x				
Auto-antibody testing [p]		x	x				
Serum sample for ATA assessment		See Protocol Appendix 2					
Serum sample for PK sampling		See Protocol Appendix 2					
Blood samples for biomarkers		See Protocol Appendix 2					
Optional whole blood sample for RCR [q]		x [q]		x [q]			
Study drug infusion [r]		x					
Archival/screening FFPE tumor tissue specimen or 15 unstained slides [s]	x						
Fresh biopsy (mandatory sample [t] and optional RCR sample [u])		At the time of radiographic confirmation of disease recurrence [t,u]					
Assessments for UC recurrence [v]	x	Every 12 weeks following randomization (± 7 days; at approximately every four cycles) in first 3 years; every 24 weeks (±10 days) for Years 4 and 5; and at Year 6 (± 10 days), until death, disease recurrence, loss to follow-up, end of Year 6, or withdrawal of consent.					
Concomitant medications [w]	x	x	x	x	x	x	
Adverse events [x]	x	x	x	x	x	x	
Telephone contact [y]					x		

Appendix 2
Schedule of Assessments (cont.)

	Both Arms	Arm A (Atezolizumab)		Arm B (Observation)			Both Arms
	Screening for Randomization	All Cycles	Discontinuation [a]	Cycles 1, 3, 5, 7, 9, 11, 13, and 15	Cycles 2, 4, 6, 8, 10, 12, 14, and 16	Discontinuation [a]	
Study Procedures	Days –28 to –1	Day 1 (±3 Days for Cycles ≥2) [b]	≤30 Days after Last Dose	Day 1 (±3 Days for Cycles ≥2) [b]	Day 1 (±3 Days) [b]	≤30 Days after Last Visit	Follow-Up
Survival and anticancer therapy follow-up [z]							x
Patient-reported outcomes [aa]		x [bb]	x	x		x	x

Note: For Arm A, assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] Patients will be asked to return to the clinic for a discontinuation visit not more than 30 days after the decision to discontinue treatment/observation early, or after the end of the one-year treatment/observation period.

[b] *After five cycles have been completed, one cycle may be delayed by 1 week (i.e., 28 days instead of 21 days for one cycle) for one time to allow for vacations.*

[c] Written informed consent is required for performing any study-specific tests or procedures. Written informed consent (on the main study Informed Consent Form) can be obtained outside the 28 days screening period prior to randomization. Prior to signing the main consent form for the study, patients may specifically allow for the collection and testing of archival or fresh tumor tissue by signing the pre-screening consent form. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to randomization (except where otherwise specified) may be used for screening assessments rather than repeating such tests.

[d] Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Demographic information includes sex, age, and self-reported race/ethnicity.

[e] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Cycle 1 Day 1. Starting from Cycle 3, either serum or urine pregnancy test (positive urine test results will be confirmed with a serum pregnancy test) must be performed every two cycles during the study treatment, and as clinically indicated thereafter.

[f] ECOG performance status, limited physical examination and local/central lab assessments may be obtained ≤ 96 hours before Day 1 of each cycle.

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

Appendix 2
Schedule of Assessments (cont.)

[h] Vital signs include heart rate, respiratory rate, blood pressures, and temperature and will be performed as standard of care if clinically indicated for patients randomized to the observation arm. For patients randomized to the atezolizumab treatment arm, for the first infusions of study drug, the patient's vital signs should be determined up to 60 minutes before the start of infusion, and if clinically indicated, during and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs will be recorded if clinically indicated or if symptoms occurred in the prior infusion.

[i] ECG recordings will be obtained during screening and when clinically indicated during study. ECGs for each patient should be obtained from the same machine wherever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

[j] See Section 4.5.6 for serology tests. HIV testing to be performed in accordance with national and/or institutional guidelines. HBV DNA must be collected on or before Cycle 1, Day 1 in patients who have negative serology for hepatitis B surface antigen and positive serology for anti HBc.

[k] Blood samples collected to monitor safety will be collected in patients randomized to both arms. Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. Refer to Section 4.1.1 for a list of laboratory results to be obtained within 14 days prior to the first dose of study treatment.

[l] Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin. Refer to Section 4.1.1 for a list of laboratory results to be obtained within 14 days prior to the first dose of study treatment.

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

[n] On Day 1 of Cycle 3 and every two cycles thereafter.

[o] On Day 1 of Cycle 5 and every four cycles thereafter.

[p] Baseline sample to be collected on Cycle 1, Day 1 prior to the first dose of study treatment. For patients who show evidence of immune mediated toxicity, additional samples will be collected, and all samples will be analyzed centrally. Includes anti-nuclear antibody, anti-double stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti neutrophil cytoplasmic antibody.

[q] Whole blood for DNA isolation will be collected from patients who have consented to optional RCR sampling at baseline (pre-dose C1D1). If, however, the RCR 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.

[r] Patients in Arm A will receive their first dose of study drug the day of randomization if possible. If this is not possible, the first dose should occur no later than 7 days after randomization. The initial dose of atezolizumab treatment will be delivered over 60 (±15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. Atezolizumab treatment may be continued for a maximum of 16 cycles (or 12 months, whichever occurs first) until disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor.

Appendix 2
Schedule of Assessments (cont.)

[s] Tumor tissue from radical surgical resection should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status). Prior to signing the main consent form for the study, patients may specifically allow for the collection and testing of archival or fresh tumor tissue by signing the prescreening Informed Consent Form. After signing of the Informed Consent Form, retrieval and submission of archival tumor sample can occur outside the 28-day screening period.

[t] All patients will undergo a mandatory tumor biopsy sample collection at the time of radiographic confirmation of disease recurrence (see Section 4.5.5). Acceptable samples include resections; core needle biopsies for deep tumor tissue or lymph nodes; or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. For core needle biopsy specimens, at least three cores should be submitted for evaluation.

[u] For patients who have consented to collection of optional biopsies on the Optional Collection of Samples for RCR Informed Consent Form, optional tumor biopsy samples may be collected by core needle or excisional/punch biopsy per investigator discretion. Optional biopsy tissue will be stored in the RCR. Not applicable for sites that have not been granted approval for RCR sampling.

[v] Surveillance for tumor recurrence must include physical examination and imaging studies of the chest, abdomen, upper urinary tracts, and pelvis. Other examinations such as laboratory or urine cytology should be performed as clinically indicated. Recurrence assessment at Year 6 will be performed at approximately 48 weeks after the last one in Year 5. See Section 4.5.5 for details of assessment requirements.

[w] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to written informed consent should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

[x] After informed consent has been obtained but prior to randomization, only serious adverse events caused by a protocol-mandated intervention should be reported. Upon randomization into study, patients who experience a serious adverse event or protocol-defined adverse events of special interest will be followed for safety for 90 days following their last dose of study drug or until they receive another anti-cancer therapy, whichever comes first. Patients who experience all other adverse events will be reported for patients until 30 days after the last dose of study treatment (for Arm A) or the last day in the observation period (approximately Day 365 for Arm B), or until initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators should ensure any deaths, serious adverse events, or other adverse events of concern are reported if they are later assessed to be related to atezolizumab 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 atezolizumab treatment or trial-related procedures until a final outcome can be reported.

[y] This clinic contact can be either via telephone call or formal clinic visit.

Appendix 2
Schedule of Assessments (cont.)

[z] Survival follow-up information will be recorded via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 7 days) until death, loss to follow-up, or study termination by Roche. All patients (irrespective of which arm they are randomized to) will be followed for survival and new anticancer therapy information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *Patients who have completed the treatment or observation phase and continue in disease recurrence follow-up do not need to begin survival follow-up until a DFS event has occurred but must still be followed for new anti-cancer therapy.*

[aa] The PRO questionnaire EQ-5D-5L will be completed by the patients at the investigational site. All PRO questionnaires are required to be administered prior to administration of study treatment (Arm A) and/or prior to any other study assessment(s) to ensure that the validity of the instrument 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. After discontinuation of the treatment/observation period, for patients who have not experienced disease recurrence, the EQ-5D-5L will be administered at the same schedule as the assessments for disease recurrence (see Section 4.5.5). The EQ-5D-5L will also be recorded at 6, 12, and 24 weeks after disease recurrence per telephone interview by trained site staff and in compliance with best practices and recommendations by EuroQol. Study personnel will record patient responses on a paper copy of the EQ-5D-5L during the telephone interview as record of source documentation.

[bb] Odd-numbered cycles only (i.e., Cycles 1, 3, 5, 7, 9, 11, 13, and 15).