Official Title: An Open Label, Single arm, Multicenter, Safety Study of Atezolizumab in Locally Advanced or Metastatic Urothelial or Non-Urothelial Carcinoma of the Urinary Tract

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STATISTICAL ANALYSIS PLAN

TITLE: **AN OPEN LABEL, SINGLE ARM, MULTICENTER, SAFETY STUDY OF ATEZOLIZUMAB IN LOCALLY ADVANCED OR METASTATIC UROTHELIAL OR NON-UROTHELIAL CARCINOMA OF THE URINARY TRACT**

PROTOCOL NUMBER: MO29983

STUDY DRUG: Atezolizumab (MPDL3280A; RO5541267)

VERSION NUMBER: 3.0

IND NUMBER: N/A

EUDRACT NUMBER: 2016-002625-11

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted]

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1. BACKGROUND

Bladder cancer is the ninth most common cancer in the world (World Cancer Research Fund International 2016). In 2012, an estimated 14.1 million people worldwide had bladder cancer, of whom 330,380 were newly diagnosed; in the same year, 123,051 deaths were attributable to the disease (International Agency for Research on Cancer 2016; World Cancer Research Fund International 2016). In the United States, estimates are that 76,960 new cases of bladder cancer will be diagnosed in 2016 (about 58,950 in men and 18,010 in women), and 16,390 deaths will occur due to the disease (American Cancer Society 2016).

This study is being conducted to evaluate the safety of atezolizumab as second-line treatment for locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract. The study will also evaluate treatment efficacy and explore potential tumor biomarkers related to atezolizumab.

The aim of the Statistical Analysis Plan (SAP) for independent Data Monitoring Committee (iDMC) is to state the scope and extent of iDMC analyses.

This SAP is based on the Study Protocol MO29983:

- version 1.0, 21 Jul 2016
- version 2.0, 25 Aug 2016
- version 3.0, 23 Nov 2016
- version 4.0, 31 Jan 2017 (Canada only)
- version 5.0, 19 May 2017
- version 6.0, 06 Jul 2017 (Canada only)
- version 7.0, 22 Feb 2018
- version 8.0, 07 Mar 2018 (Canada only)
- version 9.0, 08 Oct 2018
- version 10.0, 08 Oct 2018 (Canada only)
- version 11.0, 22 Oct 2019
- version 12.0, 22 Oct 2019 (Canada only)
- version 13.0, 03 Mar 2021
- version 14.0, 04 Mar 2021 (Canada only)
- version 15.0, 17 Dec 2021
- version 16.0, 17 Dec 2021 (Canada only)

2. STUDY DESIGN

Study MO29983 is an open label, single-arm, multicenter study of the safety of atezolizumab as second-line treatment for patients with locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract. The study includes evaluation of the efficacy of atezolizumab and potential tumor biomarkers associated with atezolizumab.

Study screening will take place within 28 days prior to initiation of study treatment. Eligible patients will be enrolled and begin treatment with 1200 mg atezolizumab intravenous (IV) every 3 weeks. The single agent study treatment will continue until investigator-assessed loss of clinical benefit, unacceptable toxicity, investigator or patient decision to withdraw from therapy, or death (whichever occurs first).

During the study treatment period, patients will be followed for safety based on adverse event (AE) assessments including vital signs, physical findings and clinical laboratory test results. Efficacy will be evaluated by the investigator according to both Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and modified RECIST. Exploratory biomarker analyses will be conducted based on primary tumor tissue or biopsied metastatic tumor tissue collected at baseline and an optional tumor sample collected at the second study treatment cycle.

Following discontinuation of study treatment, safety assessments will be conducted 30 days after the last study drug administration or until initiation of other anti-cancer therapy (whichever occurs first). Thereafter, patients will be followed for disease progression (unless this has already occurred), serious adverse events (SAEs), AEs of special interest, anti-cancer therapy and survival. Follow-up will continue for up to four years after the last patient is enrolled in the study.

2.1 PROTOCOL SYNOPSIS

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

2.2 OUTCOME MEASURES

The primary objective of this study is to evaluate the safety of atezolizumab. The secondary objectives of the study include evaluation of the efficacy of atezolizumab. Additional secondary study objectives include the evaluation of efficacy of atezolizumab according to patient-reported outcomes (PROs).

2.2.1 Primary Efficacy Outcome Measures

Not applicable for this study.

2.2.2 Secondary Efficacy Outcome Measures

The following endpoints are defined to evaluate efficacy:

- Overall survival (OS), defined as the time from initiation of study treatment to death from any cause.
- Progression-free survival (PFS), defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause, whichever occurs first. PFS will be calculated based on disease status evaluated by

investigator according to RECIST v1.1 and also by disease status evaluated by the investigator according to modified RECIST

- Overall response rate (ORR), defined as the proportion of patients with a best overall response of either complete response (CR) or partial response (PR). ORR will be calculated based on disease status evaluated by investigator according to RECIST v1.1 and also by disease status evaluated by the investigator according to modified RECIST
- Disease control rate (DCR), defined as the sum of the CR, PR and stable disease (SD) rates. DCR will be calculated based on disease status evaluated by investigator according to RECIST v1.1 and also by disease status evaluated by the investigator according to modified RECIST
- Duration of response (DoR), defined as the time from first occurrence of a documented response to disease progression or death from any cause, whichever occurs first. Duration of response will be calculated based on disease status evaluated by investigator according to RECIST v1.1 and also by disease status evaluated by the investigator according to modified RECIST

Additional secondary study objectives include the evaluation of efficacy of atezolizumab to the following PROs:

- Change from baseline in health-related quality of life (HRQoL), as assessed using the EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30).
- EuroQol EQ-5D-5L-assessed utility.

2.2.3 Exploratory Efficacy Outcome Measures

Not applicable for this study.

2.2.4 Pharmacokinetic Efficacy Outcome Measures

Not applicable for this study.

2.2.5 Safety Outcome Measures

The following endpoints are defined to evaluate safety:

- Nature, severity, duration, frequency and timing of AEs.
- Changes in vital signs, physical findings, and clinical laboratory results during and following atezolizumab administration.

2.3 DETERMINATION OF SAMPLE SIZE

This is a single-arm safety study. There is no formal statistical hypothesis and all analyses will be descriptive. The results for the primary safety variables will be presented via percentages and corresponding 95% Clopper-Pearson confidence intervals (CIs).

A sample size of approximately 1000 patients is planned for this study. The precision of (e.g., rare) AE incidence estimates presented by two-sided exact 95% Clopper-Pearson CIs are shown in Table 1.

Table 1 Two-Sided Clopper-Pearson 95% Confidence Intervals for Adverse Event Rate Estimates

Number of Patients with at Least One Event (Expected) N=1000	Expected Event Rate (%)	Lower limit of CI (%)	Upper limit of CI (%)
12	1.2	0.62	2.09
10	1.0	0.48	1.83
8	0.8	0.35	1.57
6	0.6	0.22	1.3
5	0.5	0.16	1.16
4	0.4	0.11	1.02
3	0.3	0.06	0.87
2	0.2	0.02	0.72
1	0.1	0.00	0.56

CI = confidence interval.

Therefore, for a sample size of 1000 patients and an expected AE incidence of 0.5%, based on the half-width of the Clopper-Pearson 95% CI, the true AE rate can be estimated with a precision of: ±(1.16% – 0.16%)/2 % = ±0.5 %.

2.4 ANALYSIS TIMING

The primary analysis will occur 6 months after the last patient has been enrolled.

The final analysis will occur at the end of the study, i.e., approximately 4 years after enrollment of the last study patient.

In addition, iDMC interim safety reviews occurred 3 months after the first patient was enrolled and 3 months after 500 patients were enrolled and followed up for safety.

Table 2 Analysis Timing

Analysis	Timing of Analysis
First iDMC review	At least 3 months after enrollment of the first patient
Second iDMC review	After 500 patients who reach at least 3-month follow-up
Optional / additional iDMC reviews	Defined by iDMC at any time during the study period
Primary analysis	6 months after the last patient has been enrolled
Final analysis	End of the study, i.e., approximately 4 (48 month) years after enrollment of the last study patient

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Not applicable; study is not randomized.

3.2 INDEPENDENT REVIEW FACILITY

No IRF will be included in this study.

3.3 DATA MONITORING

The iDMC will share with the Sponsor the responsibility to monitor overall patient safety and/or efficacy of the Investigational Medicinal Product (IMP) with the objective to minimize patient exposure to unnecessary risk. The iDMC will notably review all AEs, SAEs and AEs of special interest and cumulative safety data including any death event during the scheduled interim analyses.

The details of the data summaries that will be produced for iDMC are described in the SAP on hand (required data for review by iDMC is outlined in the iDMC Charter).

4. STATISTICAL METHODS

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point, frequency counts and percentages; 95% exact Clopper-Pearson CI will also be provided when relevant. Missing data will be considered when calculating percentages. Therefore, the percentages will be based on the total number of patients in the corresponding population and not on the number of non-missing values.

Unless otherwise specified, time periods are always calculated in months. If the duration is given in days, the number of days will be divided by 365.25 and multiplied by 12 to have the period shown in months.

Continuous data will be summarized using descriptive statistics. Missing data will not be imputed, unless otherwise stated. The number of observations being included as well as the number of missing observations will be given. Further the mean, standard deviation, median, lower (25%) and upper (75%) quartile, minimum and maximum will be used to describe the data. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower and upper quartiles will be reported to one more decimal place than the raw data recorded in the database, and the standard deviation to two more decimal places.

Time to event data will be estimated by the Kaplan-Meier approach with the corresponding 95% CIs.

Two-sided 95% CIs for point estimates will be calculated and presented to one more decimal places than the raw data.

All outputs (tables, listings, figures) will be produced using the statistical analysis software SAS®, version 9.3 or higher. The generated outputs will be incorporated into a Microsoft® Word 2010 document using portrait or landscape orientation, whatever is appropriate, and afterwards printed to PDF.

Mapping of unscheduled visits:

In case of an unscheduled assessment prior to the date of first study drug administration, the unscheduled assessment will be assigned to the baseline visit.

In case of an unscheduled assessment after or on the date of first study drug administration, the unscheduled assessment will be assigned to the most recent visit performed.

If a patient has more than one assessment assigned to a same visit, the latest value assigned to the visit will be used, when presenting data in summary tables by visit. In listings by patient by visit all assessments (scheduled and unscheduled) will be presented.

Unscheduled visits will not be considered at all for tabulations of vital signs. In listings, these visits will appear as unscheduled without remapping.

Mapping of progression visits:

If the patient progresses, the visit where the first occurrence of tumor progression is recorded (earliest of the dates of the RECIST component indicating tumor progression) will be defined as the progression visit.

4.1 ANALYSIS POPULATIONS

In the study, two populations are distinguished: Safety Population and Intent-To-Treat (ITT) Population. The analysis for the iDMC will be provided based on the Safety Population.

4.1.1 Randomized Population

Not applicable.

4.1.2 Per Protocol Population

Not applicable for the analyses described in this SAP.

4.1.3 Pharmacokinetic-Evaluable Population

Not applicable for the analyses described in this SAP.

4.1.4 Safety Population

The analysis population for this study will include all enrolled patients who have received at least one dose of atezolizumab. The safety population will be used for all baseline and safety analyses, unless otherwise stated.

4.1.5 Intent-to-treat population

The ITT population will include all patients who have signed informed consent and met all eligibility criteria. The ITT population will be used for all efficacy analyses, unless otherwise stated. (According to the Protocol, should the difference between the ITT and safety populations have been 5 or fewer patients – which was not the case –, all efficacy analyses would have been based only on the safety population).

4.2 ANALYSIS OF STUDY CONDUCT

Disposition of patients

Patients will be considered as having treatment discontinued when the “Study Completion/Early Discontinuation” has been captured for the treatment phase.

Patients will be considered as having discontinued/completed the study when the “Study Completion/Early Discontinuation” has been captured for the follow-up phase or the treatment phase and it was indicated as the final study period.

The disposition of patients will be summarized as follows:

Enrolled patients:

- Number of patients who signed informed consent and met all eligibility criteria, i.e. number of patients in the ITT Population

- Number and percentage of patients who have received at least one dose of atezolizumab, i.e. number and percentage of patients in the Safety Population (out of the ITT Population)
- Number and percentages of patients who have permanently discontinued atezolizumab, overall and by reasons for discontinuation (out of the Safety Population)
- Number and percentages of patients who have permanently discontinued atezolizumab by cycle and by reasons for discontinuation (out of the Safety Population). Discontinuations will be associated with the number of cycles the patient received, a cycle being counted when dose >0. A summary table and figure will be provided.
- Number and percentages of patients who have discontinued the study, overall and by reasons for discontinuation (out of the ITT Population)
- Number and percentages of patients by region, country and site number (out of the ITT population and Safety population)

Following by-patient listing including site, patient identifier and relevant data will be provided:

- Enrolled patients

Protocol violations

A by-patient listing of major protocol violations will be provided.

4.3 ANALYSIS OF BASELINE CHARACTERISTICS

Demography and baseline characteristics will be summarized using descriptive statistics and frequency tables, respectively, based on the safety population at Baseline.

A baseline value will be defined as the last available value before or on the date of first study drug administration, as follows:

- Assessment with a date prior to the date of first study drug administration
- Assessment with a date equal to the date of first study drug administration, if either
    - It is the screening/baseline visit
    - In case of assessments on the same date as the drug administration, it will be assumed that these were performed before the actual time of drug intake.

Demography:

- Descriptive statistics of age in years, age categories (<65, ≥65 -<85 and ≥85 years), age categories (<80 and ≥80 years)
- Frequency tables of sex, ethnicity and race

Baseline characteristics

- Non-cancer General Medical History
    - Number and percentages of patients with history of any medical condition overall and by status of medical condition and by System Organ Class (SOC) and Preferred Terms (PT)
- History of Cancer
    - Descriptive statistics of time from primary diagnosis to start of study treatment, frequency tables of histological tumor type, non-urothelial tumors sub-type, squamous neoplasms sub-type, glandular neoplasms sub-type, neuroendocrine sub-type, histological grade, location, TNM classification and stage of tumor at primary diagnosis and at study entry, descriptive statistics of time from primary diagnosis to diagnosis of metastatic disease
- Prior Tumor Surgery
    - Frequency of patients with prior tumor surgery before entering the study
    - Frequency tables of surgery setting and surgery purpose
- Prior Cancer Radiotherapy
    - Frequency tables therapy setting and given boost
- Prior Systemic Cancer Therapy
    - Frequency tables of therapy intent, highest line of therapy, and information regarding platinum treatment. Patients who received prior adjuvant/neoadjuvant chemotherapy will be considered as having 0 lines of treatment for metastatic disease (irrespective of the line(s) of therapy entered in eCRF).
- General Surgery and Procedure History (Non-Cancer)
    - Number and percentages of patients with any relevant surgeries or procedures
- Autoimmune disease
    - Number and percentages of patients who have any history of autoimmune disease
    - Number and percentages of patients with resolved diseases, ongoing diseases with treatment and ongoing diseases without treatment
- Serology Local
    - HIV test
        - Number and percentages of patients with negative, positive and not done HIV tests
        - Number and percentages of patients with a final negative or positive HIV tests
        - Descriptive statistics of HIV Load for final positive HIV tests
        - Number and percentages of patients suffering from AIDS

- Hepatitis Testing
    - Number and percentages of patients with negative, positive and not done tests regarding Hepatitis B Surface Antigen
    - Number and percentages of patients with negative, positive and not done tests regarding Anti Hepatitis B Core Antibody
    - Number and percentages of patients with negative, positive and not done tests regarding Anti Hepatitis B Surface Antibody
    - Number and percentages of patients with negative, positive and not done tests regarding anti-HCV Antibody
    - Number and percentages of patients with negative, positive and not done tests regarding anti-HCV RNA
    - Number and percentages of patients with negative, positive and not done tests regarding anti-HBV DNA

- Female Reproductive Status and Local Pregnancy Test
    - Frequency table of female reproductive status
    - Frequency table of sample type (urine, serum)
    - Frequency of patients with a final negative or positive test result
- Tobacco Use History
    - Number and percentages of patients by tobacco use history and by sex (males vs females)
    - Descriptive statistics of smoking duration in years
- Electrocardiogram (ECG)
    - Descriptive statistics of heart rate [beats/min], PQ (PR) duration [ms], QRS duration [ms], QT duration [ms], QTcF [ms]
    - Frequency table of ECG result
- Eastern cooperative oncology group (ECOG) Performance Status
    - Frequency table of ECOG score
- Age-adjusted Charlson Comorbidity Index (AACI)
    - Descriptive statistics of the calculated total score
    - Frequency table of the calculated total score
- Brain magnetic resonance imaging/computed tomography (MRI/CT) status
    - Frequency of patients with knowledge, symptoms or suspicion of central nervous system (CNS) metastases
    - Frequency of patients with performed MRI/CT Scan
    - Frequency of patients with present metastasis
    - Descriptive statistics of number of metastasis
- Renal impairment at baseline

- Descriptive statistics of creatinine clearance
- Frequency of patients with/without renal impairment

- PD-L1 expression
  - PD-L1 expression by IHC class (IC0 to IC3)
  - PD-L1 expression: IC0/1 or IC2/3

Renal dialysis reported at baseline is defined as 'No' for all patients included with protocol version < 5 (regardless if any or no dialysis reported or no information given). For patients included with protocol version 5 or higher, if patient reports dialysis at Screening or Cycle 1 Day 1, then renal dialysis is set to 'Yes', otherwise if no dialysis is reported or if information is missing then renal dialysis is set to 'No'.

The time from diagnosis of primary disease to start of study treatment will be calculated in units of years as the difference between the date of start of study treatment and date of diagnosis of primary disease plus 1, divided by 365.25. For the calculation of the time from diagnosis of primary disease to start of study treatment, replacement rules will be applied in case the date of diagnosis of primary disease is incomplete. If day and month are missing, they will be imputed by June 30th to allow for time calculation, if only the day is missing, it will be imputed by 15. If after imputation, the date of diagnosis of primary disease is later than the start date of study treatment, then it will be set to the start date of study treatment.

The time from diagnosis of primary disease to diagnosis of metastatic disease will be calculated in units of years as the difference between the date of occurrence of metastatic disease and date of diagnosis of primary disease plus 1, divided by 365,25. For the calculation of the time from diagnosis of primary disease to diagnosis of metastatic disease, replacement rules will be applied for both dates in case dates are incomplete. If day and month are missing, they will be imputed by June 30th, if only the day is missing, it will be imputed by 15. If after imputation, the date of diagnosis of primary disease is later than the date of diagnosis of metastatic disease, then it will be set to the date of diagnosis of metastatic disease.

Creatinine clearance at baseline will be calculated using the Cockcroft-Gault formula:

$$Creatinineclearance[mL/\min] = \frac{(140 - age[years]) \times weight[kg] \times (0.85\ if\ \ female\ or\ 1.0\ if\ \ male)}{72 \times serum\ creatinine[mg/dL]}$$

A patient will be defined as having renal impairment in case creatinine clearance at baseline is < 30 mL/min.

By-patient listing of demographic and baseline characteristics as listed above will be provided based on the Safety Population. Prior intravesical therapy will also be listed.

For assessments listed above performed at baseline and post-baseline timepoints, the corresponding listings will include both baseline and post-baseline assessments.

Derivations for selected prior platinum regimens are as follows (on regimens level):

Selected prior platinum regimens	
Gemcitabine + Cisplatin	If patient has at least at least one combination of (Gemcitabine or Gemcitabine hydrochloride) + Cisplatin within a prior systemic cancer therapy
Gemcitabine + Carboplatin	If patient has at least one combination of (Gemcitabine or Gemcitabine hydrochloride) + Carboplatin within a prior systemic cancer therapy
Methotrexate + Vinblastine + Cisplatin + Adriamycin (MVAC)	If patient has at least one combination of (Methotrexate or Methotrexate sodium) + Vinblastine + Cisplatin + (Adriamycin or Doxorubicin or Doxorubicin hydrochloride) within a prior systemic cancer therapy
Methotrexate + Vinblastine + Cisplatin (MCV)	If patient has at least one combination of (Methotrexate or Methotrexate sodium) + Vinblastine + Cisplatin, not together with (Adriamycin or Doxorubicin or Doxorubicin hydrochloride) nor (Epirubicin or Epirubicin hydrochloride), within a prior systemic cancer therapy
Methotrexate + Vinblastine + Cisplatin + Epirubicin (MVEC)	If patient has at least one combination of (Methotrexate or Methotrexate Sodium) + Vinblastine + Cisplatin + (Epirubicin or Epirubicin hydrochloride) within a prior systemic cancer therapy

Derivations for selected regimens for patients who never had prior platinum are as follows (on patient-level)

Patients who never had prior platinum regimens	Number of patients
Patients with Single-agent Gemcitabine	If patient has at least one prior systemic cancer therapy with Gemcitabine or Gemcitabine Hydrochloride alone
Patients with Single-agent Vinflunine	If patient has at least one prior systemic cancer therapy with Vinflunine alone
Patients with Other Regimens	If patient has neither therapy with Gemcitabine or Gemcitabine Hydrochloride alone nor Vinflunine alone but any other non-platinum based prior systemic cancer therapy

4.4 EFFICACY ANALYSIS

4.4.1 Primary Efficacy Endpoint

Not applicable for this study.

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 Overall Survival

Overall survival (OS) is defined as date of death (due to any cause) or censoring minus date of start of study treatment + 1. Patients who never received treatment are censored with time equal to 1 day.

Date of death is found either in the “Death Attributed to Progressive Disease” form, in the “Study Completion/Early Discontinuation” form (discontinuation date if death) or in the “Adverse Event” form. For patients not known to have died, the date of censoring is based on data from the Survival Follow-Up CRF or on data in the “Study Completion/Early Discontinuation” form:

- “Date of contact” if “Survival status” is “Alive”
- “Date last known to be alive” if “Survival status” is “Lost to Follow-up”
- “Date withdrew consent for survival status” if “Survival status” is “Withdrew consent”.
- Date of study discontinuation in case the patient discontinued the study

  The date of censoring will be the maximum of those dates.

  In case the patient withdrew consent or is lost to follow-up, but corresponding dates were not entered and only the date of contact is filled in on the Survival follow-up form, then the date of contact will be used instead.

  If the date of censoring is still missing, the last date where the patient is known to be still alive (from any CRF page) will be used.

  For patients known to have died but whose date of death is missing, the date will be imputed as the last date where the patient is known to be still alive (from any CRF page), but the imputed date will be marked as a death not a censoring.

  For patients known to have died but whose date of death is partial, take the latest of the last date where the patient is known to be still alive (from any CRF page) and a completion of the partial date where the missing components are taken as 1 for day and January for month. The imputed date will be marked as a death not a censoring.

Survival status up to the discontinuation date for OS analysis is summarized as number and percentage of patients who

- died
- were still in survival follow-up (still alive)
- discontinued the survival follow-up (e.g., withdrew consent, lost to follow-up, discontinued study).

A Kaplan-Meier (KM) curve for OS is presented including the

- number of patients at risk for death (decreasing over time)
- cumulative number of deceased patients (increasing over time)
- cumulative number of patients censored for OS (increasing over time)

every 6 months.

Two-sided 95% confidence intervals (CIs) for OS probabilities at 6 months timepoints are added to the KM curve. For calculating these CIs:

- KM estimates are transformed to an unrestricted range by the log(-log(x)) function
- calculation of CIs by applying normal approximation methods to the transformed scaled estimates of the survivor function
- re-transformation of CIs to the original scale.

This approach is triggered by option CONFTYPE=LOGLOG in SAS PROC LIFETEST.

If applicable, median OS is estimated together with a two-sided 95% CI according to the method of Brookmeyer and Crowley 1982.

4.4.2.2 Progression-Free Survival

Progression-free survival (PFS) is determined separately on disease status using RECIST v1.1 and modified RECIST, both evaluated by the investigator.

The date of disease progression is derived based on scan/assessment or death dates, not on visit dates. RECIST assessments/scans contributing towards a particular visit may be performed on different dates.

Progression-Free Survival based per RECIST v1.1 assessments:

PFS is defined as date of first occurrence of tumor progression (earliest of the dates of the RECIST component indicating tumor progression) or date of death (in the absence of tumor progression) by any cause or date of censoring, whichever occurs first, minus date of start of study treatment + 1.

For patients not known to have had a tumor progression or died, the date of censoring is the latest date of assessment from their last evaluable RECIST assessment or the date of start of subsequent cancer therapy whichever occurs first. Patients who never received treatment are censored with time equal to 1 day.

If a patient has no evaluable post-screening RECIST assessments, the patient is censored at the day of study treatment initiation unless the patient dies within 18 weeks. In the latter case, the death date will be used as the date of disease progression.

Progression-Free Survival based per modified RECIST assessments:

PFS according to modified RECIST is defined as:

- date of first occurrence of tumor progression after a modified confirmed response if the patient is a responder according to modified RECIST or
- date of first occurrence of tumor progression in case the patient is not a responder according to modified RECIST or
- date of death (in the absence of tumor progression) by any cause or
- date of censoring, whichever occurs first, minus date of start of study treatment + 1.

For patients not known to have had a tumor progression or died after that modified response, the date of censoring is the latest date of assessment from their last evaluable RECIST assessment or the date of start of subsequent cancer therapy whichever occurs first. Patients who never received treatment are censored with time equal to 1 day.

If a patient has no evaluable post-screening RECIST assessments, the patient is censored with time equal to 1 day unless the patient dies within 18 weeks. In the latter case, the death date will be used as the date of disease progression.

The analyses described below are performed separately for PFS based on disease status using RECIST v1.1 and for PFS based on disease status using modified RECIST, both evaluated by the investigator.

Study treatment status at date of disease progression (for patients with disease progression) or at DCO date used for PFS analysis (for patients without disease progression) is summarized. This includes number and percentage of patients who

- were on study treatment at date of disease progression
- discontinued study treatment prior to disease progression
- did not progress and were on study treatment at DCO date
- did not progress and discontinued study treatment.

A KM curve for PFS is presented including the

- number of patients at risk for disease progression (decreasing over time)
- cumulative number of patients with a disease progression (increasing over time)
- cumulative number of patients censored for disease progression (increasing over time)

every 6 months time.

Two-sided 95% CIs for PFS probabilities at 6 months time points are added to the KM curve. For calculating these CIs:

- KM estimates are transformed to an unrestricted range by the log(-log(x)) function
- calculation of CIs by applying normal approximation methods to the transformed scaled
- re-transformation of CIs to the original scale.

This approach is triggered by option CONFTYPE=LOGLOG in SAS PROC LIFETEST.

If applicable, median PFS is estimated together with a two-sided 95% CI according to the method of Brookmeyer and Crowley 1982.

4.4.2.3 Overall Response

Overall response is determined separately on disease status using RECIST v1.1 and modified RECIST, both evaluated by the investigator.

Best overall response will be derived differently for RECIST assessments and for modified RECIST assessments.

Best overall response based on RECIST v1.1 assessments:

The assessment of best overall response includes post-screening RECIST assessments obtained up to

- disease progression

- death from any cause
- last evaluable RECIST assessment in the absence of disease progression or death
- start of a subsequent anti-cancer therapy

whatever occurs first.

A patient with complete response followed by complete response determined on two consecutive investigator assessments (>=4 weeks apart) has confirmed complete response as Best Overall Response.

Otherwise, a patient with complete response followed by partial response or partial response followed by complete response or partial response followed by partial response determined on two consecutive investigator assessments (>=4 weeks apart) has confirmed partial response as Best Overall Response.

Otherwise, if there exists at least an assessment of CR, PR or SD, then the patient has Stable disease as Best Overall Response.

If the patient has confirmed complete or partial response, the patient is an overall responder, otherwise, the patient is an overall non-responder. Therefore, if best overall response is Stable Disease, Progressive Disease, Non-Evaluable disease or missing, the patient is an overall non-responder.

Patients who never received treatment are considered as non-responder.

Best overall response based on modified RECIST assessments:

The assessment of best overall response includes post-screening RECIST assessments obtained up to

- death from any cause
- last evaluable RECIST assessment in the absence of death
- start of a subsequent anti-cancer therapy

whatever occurs first.

For best overall response based on modified RECIST, all RECIST assessments are considered even after progression.

The calculations of best overall response based on modified RECIST assessments is similar to the best overall response based on RECIST v1.1 assessments.

In case there are more than one occurrence of CR (or PR in the absence of CR), the first occurrence of CR (respectively PR) will be considered.

4.4.2.4 Duration of Response

Duration of response (DoR) is determined separately on disease status using RECIST v1.1 and modified RECIST, both evaluated by the investigator

Duration of response based on RECIST v1.1 assessments:

For overall responders, DoR is defined as the time from the date of first occurrence of a confirmed response (CR or PR) to date of tumor progression or death from any cause or to censoring date:

- end of response coincides with the date of tumor progression or death (in the absence of tumor progression) used for the PFS endpoint
- for a patient without disease progression or death following a response, the censored end of response coincides with the PFS censoring date (that is latest RECIST assessment or start of subsequent cancer therapy whichever occurs first)
- DoR is computed as date of PFS event or censoring minus date of first response + 1.

DoR is not defined for overall non-responders.

Duration of response based on modified RECIST assessments:

For overall responders, DoR is defined as the time from the date of first occurrence of a confirmed response (CR or PR) to date of tumor progression following that confirmed response or death from any cause or to censoring date:

- end of response will be the date of tumor progression after that confirmed response or death (in the absence of tumor progression)
- for a patient without disease progression or death following a response, the censored end of response will be the latest RECIST assessment or start of subsequent cancer therapy whichever occurs first.

DoR is not defined for overall non-responders.

Therefore, in case of disease progression followed by a confirmed response of CR or PR (and no confirmed CR or PR before the disease progression), this confirmed response will be considered as Best overall response and the duration of response will start from this confirmed response until next disease progression or death or censoring.

Additionally, a descriptive KM curve (including estimated median) for DoR is provided based on patients with an overall response.

4.4.2.5 Disease Control

Disease control is determined separately on disease status using RECIST v1.1 and modified RECIST, both evaluated by the investigator.

Disease control rate (DCR) is defined as the sum of the CR, PR and stable disease (SD) rates.

A patient with complete response followed by complete response determined on two consecutive investigator assessments (>=4 weeks apart) has confirmed complete response as Best Overall Response.

Otherwise, a patient with complete response followed by partial response or partial response followed by complete response or partial response followed by partial response determined on two consecutive investigator assessments (>=4 weeks apart) has confirmed partial response as Best Overall Response.

Otherwise, if there exists at least an assessment of CR, PR or SD, then the patient has Stable disease as Best Overall Response.

Patients who never received treatment are considered as non-responder.

4.4.2.6 QLQ-C30 questionnaire

In this study, health-related quality of life (HRQoL) are assessed using the EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30, European Organisation for Research and Treatment of Cancer 2016, Aaronson et al 1993).

The EORTC QLQ-C30 consists of 30 questions, which are combined to produce 5 functional scales (Physical, Role, Cognitive, Emotional, Social), 3 symptom scales (Fatigue, Pain, Nausea/vomiting), 6 individual symptom items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) and a global health status.

A score ranging from 0 to 100 is derived for each of the functional scales, symptom scales, symptom items and the global health status according to the EORTC QLQ-C30 Scoring Manual, 3rd Edition (Fayers et al 2001). In particular:

- higher scores on the global health status and functional scales indicate better health status/function
- higher scores on the symptoms scales and symptom items indicate greater symptom burden.

If at least half the components of a scale are present in a EORTC QLQ-C30 questionnaire, the score is calculated. Otherwise, the score is set to missing.

In addition, the change from baseline (post-baseline value minus baseline value) is calculated for each of the functional scales, symptom scales, symptom items and the global health status.

EORTC QLQ-C30 questionnaire: compliance

EORTC QLQ-C30 questionnaire compliance rate over time is calculated separately for each EORTC QLQ-C30 visit (Day 1 of first 3 study treatment cycles, then with tumor assessments) by using numbers of expected questionnaires as defined below:

- the expected number of EORTC QLQ-C30 questionnaires at a specific EORTC QLQ-C30 visit is either the
  - number of patients attending Day 1 visit of cycles 1, 2 or 3, respectively
  - number of patients attending a tumor assessment visit, respectively

Number of patients with expected questionnaires, all questions completed, at least one question completed and no question at all completed are summarized at each scheduled EORTC QLQ-C30 visit.

EORTC QLQ-C30 questionnaire: summaries by visits

Summaries by visit, including changes from baseline, are provided for the EORTC QLQ-C30 scores for

- each of the 5 functional scales
- each of the 3 symptom scales
- each of the 6 individual symptom items
- the global health status.

EORTC QLQ-C30 questionnaire will not be presented for primary analysis.

4.4.2.7 Utilities collected using the EQ-5D-5L for pharmacoeconomic models

The EuroQol 5-Dimension Questionnaire (EQ-5D-5L) is a self-report health status questionnaire that consists of 6 questions used to calculate a health utility score for use in health economic analysis (Herdman et al 2011; Janssen et al 2013).

There are two components to the EuroQol EQ-5D:

- a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression,
- a visual analogue scale (VAS) that measures health state.

Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction.

Country-specific, published utility functions would allow for creation of a single summary score for health-economic modelling. Such modelling is outside the scope of this SAP.

EQ-5D questionnaire compliance rate over time is calculated separately for each EQ-5D visit (Day 1 of first 3 study treatment cycles, then with tumor assessments) by using numbers of expected questionnaires as defined below:

- the expected number of EQ-5D questionnaires at a specific EQ-5D visit is either the
  - number of patients attending Day 1 visit of cycles 1, 2 or 3, respectively
  - number of patients attending a tumor assessment visit, respectively

Number of patients with expected questionnaires, all questions completed, at least one question completed and no question at all completed are summarized at each scheduled EQ-5D visit.

Summaries by visit, including changes from baseline, are provided for the EQ-D scores for

- each of the 5 dimensions
- the visual analogue scale

EQ-5D questionnaire will not be presented for primary analysis.

4.4.3 Exploratory Efficacy Endpoints

Not applicable for this study.

4.4.4 Sensitivity Analyses

No formal sensitivity analyses are pre-planned.

4.4.5 Subgroup Analyses

Secondary efficacy endpoints are also analyzed by the following subgroups:

- ECOG Performance status: 0–1 vs. 2
- Presence of CNS metastases at baseline: yes vs. no

- Renal impairment at study entry: yes vs. no
- Creatine clearance at study entry (mL/min): 15-<30 vs 30-<60 vs >=60
- Sex: female vs. male
- HIV status: negative vs. positive
- Patients aged ≥65 years: yes vs. no
- Patients aged ≥70 years: yes vs. no
- Patients aged ≥75 years: yes vs. no
- Patients aged ≥80 years: yes vs. no
- Patients aged 65-<75 vs 75-<80 vs >=80
- History of autoimmune disease: yes vs. no
- Progression on, or within 12 months of, prior platinum-based treatment: yes vs. no
- Concomitant steroid treatment ongoing at baseline: yes vs. no
- History of non-urothelial or mixed urinary tract carcinoma histology: yes vs. no
- Tumor location: Ureter vs Renal Pelvis vs all UTUC (Ureter or Renal Pelvis) vs Bladder
- Prior Lines of Treatment for Metastatic Disease (0 vs 1 vs. 2 vs. 3)
- Age-adjusted Charlson comorbidity index (AACI): ≤ 11 vs. > 11
- PD-L1 expression: IC2/3 vs. IC0/1
- PD-L1 expression by IHC Class: IC0 to IC3
- IMvigor211-like patients: yes vs. no
- Region: Australia/Canada/Western Europe vs Eastern Europe vs Other regions

All subgroup analyses are based on the same methods for statistical analyses of the respective secondary efficacy endpoint. Graphical displays such as forest plots are used to visualize the homo-/heterogeneity of secondary efficacy endpoint results across different levels of the subgroups defined above (proportions and 95% CI, or KM medians and corresponding 95% CI as applicable).

The subgroup PD-L1 expression will be derived from the percentage of tumor area infiltrating immune cells as follows:

IC=0 (<1%), IC=1 (≥1% - <5%), IC=2 (≥5% - <10%), IC=3 (≥10%).

The subgroup “IMvigor211-like patients” is defined as follows:
Patients with:

- ECOG Performance status: 0–1
- Presence of CNS metastases at baseline: no
- Renal impairment at study entry: no
- Patient with renal dialysis reported at baseline: no
- HIV status: negative
- History of autoimmune disease: no

- Progression on, or within 12 months of, prior platinum-based treatment: yes
- Concomitant steroid treatment ongoing at baseline: no
- History of non-urothelial or mixed urinary tract carcinoma histology: no
- Prior Lines of Treatment for Metastatic Disease: 0 or 1 or 2
- Patients aged ≥65 years: indifferent
- Patients aged ≥70 years: indifferent
- Patients aged ≥75 years: indifferent
- Patients aged ≥80 years: indifferent
- Age-adjusted Charlson comorbidity index (AACI): indifferent
- PD-L1 expression: indifferent
- Region: indifferent
- Sex: indifferent

All adverse events/deaths tables and RECIST based efficacy tables by subgroup PD-L1 Expression IC2/3 vs IC0/1 will be further broken down by IMvigor211-like patients subgroup.
All RECIST based efficacy tables by subgroup PD-L1 Expression IC0/1 will be further broken down by IMvigor211-like patients subgroup and by Prior Lines of Treatment for Metastatic Disease= 0.
All RECIST based efficacy tables by subgroup PD-L1 Expression by IHC Class (IC0 to IC3) will be further broken down by IMvigor211-like patients subgroup.

All adverse events/deaths tables and RECIST based efficacy tables by subgroup PD-L1 Expression IC2/3 vs IC0/1 will be further broken down by Prior Lines of Treatment for Metastatic Disease: 0 to 3 subgroup.

All RECIST based efficacy tables by subgroup ECOG will be further broken down by the following subgroups:
- Patients aged ≥65 years: yes
- Patients aged ≥70 years: yes
- Patients aged ≥75 years: yes
- Patients aged ≥80 years: yes

Positive and negative associations between subgroups will also be tested pairwise and reported. An association between 2 subgroups is positive when lower limit of 80 % Clopper-Pearson Confidence interval of percentage of patients in subgroup 1 within subgroup 2 is higher than the percentage of patients in subgroup 1 in the whole population. An association between 2 subgroups is negative when upper limit of 80 % Clopper-Pearson Confidence interval of percentage of patients in subgroup 1 within subgroup 2 is lower than the percentage of patients in subgroup 1 in the whole population.

Associations will be tested pairwise among the following 12 subgroups: ECOG Performance status =2, Progression on, or within 12 months of, prior platinum-based

treatment, Concomitant steroid treatment ongoing at baseline, History of non-urothelial or mixed urinary tract carcinoma histology, AACI: > 11, Renal impairment at study entry, female patients, male patients, HIV status positive, History of autoimmune disease, Presence of CNS metastases at baseline, Patients aged ≥ 65 years, Patients aged ≥ 70 years; Patients aged ≥ 75 years, Patients aged ≥ 80 years and PD-L1 expression IC2/3.

Only positive and negative associations will be reported in table.

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable for this study.

4.6 SAFETY ANALYSES

The safety analyses will be conducted on the Safety Population.

4.6.1 Exposure of Study Medication

Data of atezolizumab administration will be summarized using descriptive statistics and frequency tables, respectively, based on the Safety Population, considering all exposure data until the date of last study treatment, as reported for treatment phase on the Study Completion/Early Discontinuation page of the electronic case report form (eCRF).

The duration of treatment will be calculated in units of days as the difference of the start date of treatment until the date of the most recent study treatment at data cut-off plus 1, converted into months as described in section 4.

A treatment cycle is defined as 3 weeks (+/- 3 days) in duration. An atezolizumab treatment cycle will be counted as such if the first atezolizumab administration is given for this cycle.

The relative dose intensity of atezolizumab will be calculated as the total dose administered between the first and the last administration of study treatment divided by the amount of planned dose for this period multiplied by 100.

The total dose will be calculated as the sum of all doses that where administered during the time interval between the first and the last administration of study treatment, as entered on the eCRF.

The planned dose will be calculated as the amount of drug which should have been received during the time interval between the first and the last administration of study treatment based on a dose level of 1200 mg every 3 weeks, accounting for the theoretical duration of the last cycle. Consequently, the calculation of the planned dose will be performed as follows:

$$Planned\ dose\ [mg] = \frac{(last\ dose\ date - first\ dose\ date + 21) \times 1200}{21}$$

Time on treatment will be presented in two ways. First, for the purposes of describing the exposure to atezolizumab at the time of analysis, it will be presented in standard summary form without taking account of censoring. Second, for the purposes of estimating the time spent on treatment phase by the end of the study, it will be analyzed using the Kaplan-Meier method. A patient with a recorded end of treatment phase before or on the cut-off date will be considered as having experienced an end of treatment event on the date of last dose. Patients with ongoing treatment at the cut-off date will be censored at the time of last dose before or on cut-off date.

Duration of follow-up time will also be calculated using the reverse Kaplan-Meier method (that is, using the time variable for the Overall Survival (efficacy) analysis with the censoring flag reversed)

Atezolizumab exposure will be summarized as follows:

- Number of patients with infusion by cycle
- Descriptive statistics for time on treatment [months]
- Kaplan-Meier analysis of time on treatment and corresponding Kaplan-Meier plot
- Number of treatment cycles per patient during study
- Descriptive statistics for relative dose intensity
- Frequency table of treatment cycles by dose (categorized in original, below and above dose [dose = 1200mg, dose < 1200mg, dose > 1200mg])
- Number of patients with injection/infusion modified, overall and by reason for modification.
- Number of patients with dose modification, overall and by reason for modification

A by-patient listing of exposure data including site, patient identifier will be provided based on the Safety Population.

Additionally, for responders, the number of subjects treated after response by the number of cycles of treatment after response and the number of subjects still ongoing treatment at cutoff date will be presented. For progressors, the number of subjects treated after progression by the number of cycles of treatment after progression and the number of subjects still ongoing treatment at cutoff date will be presented. This will be based on the ITT population.

4.6.2 Adverse Events

Verbatim descriptions of AEs will be mapped to latest version of MedDRA thesaurus terms and graded according to the National Cancer Institute Common Terminology Criteria version 4.0 (NCI CTCAE v4.0).

Multiple occurrences of the same event will be counted once at the maximum severity.

The following AEs will be initially considered as AEs of special interest:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal Insufficiency, hypothyroidism/hyperthyroidism and hypophysitis
- Hepatitis
- Transaminitis Grade ≥ 2 (Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3x ULN and bilirubin >2x ULN) OR AST/ALT >10x ULN
- Systemic lupus erythematosus
- Neurological: Guillian-Barre Syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Vasculitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release, HLH and MAS
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7 of the protocol)
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Cardiac toxicities of Grade ≥ 2 (e.g., atrial fibrillation, myocarditis, pericarditis)
- Autoimmune flare of Grade ≥ 3

Beside the listed AEs of special interest, Roche will provide a list of MedDRA Preferred Terms (basket) during the study to identify the AEs of special interest for the statistical analysis.

Treatment-emergent AEs (TEAEs) will be defined as any AEs with an onset date after the start date and time of first administration of study treatment and up to 30 days after

the date of last administration of study treatment (For SAEs and AEs of special interest up to 90 days).

AEs with onset on first dosing date, not recorded as starting before study treatment administration will be considered as TEAEs. Similarly, AEs with onset date prior first dosing date but worsening/change recorded on or after first dosing date will be considered as TEAEs.

Only TEAEs will be included in summary tables. AEs which are not treatment-emergent will only be included in the AE listings.

Patient rates for AEs will be presented and accompanied by the respective two-sided 95% Pearson-Clopper CIs.

In any AE summary tables, number and percentage of patients reporting at least one AE will be provided. In AE summary tables by SOC and PT, the number of reported events will be presented additionally.
Every occurrence of an AE in any patient will be counted in the total number of events.

In tables presenting frequency of AEs by worst grade, only the event with the highest grade will be counted when there are multiple occurrences of a same AE in one patient.

A missing NCI CTCAE grade will be imputed as follows: for a fatal AE, as Grade 5; for a non-fatal AE, as Grade 4.

A summary table will be provided presenting:

- Number and percentage of patients with any TEAE
- Number and percentage of patients with any Serious TEAE
- Number and percentage of patients with any related TEAE
- Number and percentage of patients with any related Serious TEAE
- Number and percentage of patients with any TEAE leading to study drug discontinuation
- Number and percentage of patients with any grade 3 to 4 TEAE
- Number and percentage of patients with any grade 5 TEAE
- Number and percentage of patients with any AESI
- Number and percentage of patients with any grade 3 to 5 AESI
- Number and percentage of deaths, overall and by reason
- Number and percentage of deaths on study treatment (i.e. within 30 days post last study treatment administration), overall and by reason

Following safety data will be summarized:

- TEAEs by SOC, PT and by worst grade
- TEAEs of grade 3 to 5, by PT and by worst grade
- TEAEs of grade 5, by PT
- TEAEs leading to study drug discontinuation, by SOC and PT
- TEAEs leading to study discontinuation, by SOC and PT
- TEAEs related to study drug, by SOC, PT and worst grade
- Serious TEAEs by SOC, PT and worst grade
- Serious TEAEs related to study drug, by SOC and PT
- AEs of special interest by category, PT and worst grade (with additional column for AESI of grade >=3)

Death cases will be summarized as follows:

- Number of death events, overall and by primary cause of deaths, occurrence of an autopsy, number of death events within 30 days/ later than 30 days to 90 days and later than 90 days after first study treatment administration, number of death events within 30 days/ later than 30 days to 90 days and later than 90 days after last study treatment administration
- Number of death events by number of cycles started (1 cycle, 2 cycles, 3 cycles, 4 cycles, 5 cycles or more and broken down by number of days since last dose: <=30 days, >30-<=90 days or >90 days) and by primary cause of death and occurrence of an autopsy. A death event will be associated with the number of cycles the patient received, a cycle being counted when dose >0. A summary table and the corresponding figure will be provided.

By-patient listings based on the safety population will be provided for the following types of AEs:

- TEAEs and AEs who do not meet the criteria of TEAEs
- AEs of special interest
- AEs leading to permanent treatment discontinuation
- SAEs
- Fatal AEs (i.e. grade 5 AEs)

In addition, a by-patient listing of death case will be provided based on the Safety Population. Deaths events will be categorized in days since first dose and days since last dose: ≤30 days, >30 - ≤90 days or >90days in this listing.

In the above listings, information relative to the following subgroups of interest will be included:

- ECOG Performance status: 0–1 vs. 2 (the category 2 includes patients who recorded status 2 at screening but 3 at baseline)

- Progression on, or within 12 months of, prior platinum-based treatment: yes vs. no
- Concomitant steroid treatment ongoing at baseline: yes vs. no
- History: non-urothelial or mixed urinary tract carcinoma histology vs urothelial
- AACI: ≤ 11 vs. > 11
- Renal impairment at study entry: yes vs. no
- Sex: female vs. male
- HIV status: negative vs. positive
- History of autoimmune disease: yes vs. no
- Presence of CNS metastases at baseline: yes vs. no
- Patients: < 65 years vs. ≥ 65 years
- Patients: < 70 years vs. ≥ 70 years
- Patients: < 75 years vs. ≥ 75 years
- Patients: < 80 years vs. ≥ 80 years
- Prior Lines of Treatment for Metastatic Disease: 0 vs 1 vs. 2 vs. 3
- PD-L1 expression: IC2/3 vs. IC0/1
- PD-L1 expression: IC0 to IC3
- IMvigor211-like patients: yes vs. no
- Regions: Australia/Canada/Western Europe vs Eastern Europe vs Other regions

In addition, the AE summary table described previously in this section will be repeated for each of the above subgroups.

A by-patient listing of immune-related thyroid disorders on the safety population will also be provided.

4.6.3 Laboratory Data

Assessments of laboratory parameters including hematology, chemistry, coagulation and thyroid panel will be performed as follows:

- For parameters with corresponding NCI-CTCAE grading, shift tables will be provided displaying baseline versus worst NCI-CTCAE grade on treatment (last date of treatment + 21 days)
- For parameters with no corresponding NCI-CTCAE grading, summary statistics will be provided for baseline values, actual values and the change from baseline values at post-baseline time points

Additionally, by-patient listings of all laboratory data, including site and patient identifier will be generated based on the safety population. A by-patient listing of ALT, AST,

alkaline phosphatase (AP) and total bilirubin assessments for potential Hy´s law cases will also be provided.

4.6.4 Vital Signs, Height and Weight

Summary statistics of vital signs including Systolic and Diastolic blood pressure, respiratory rate, pulse rate and temperature will be provided for baseline values, actual values and the change from baseline values at post-baseline time points.

Baseline for vital signs will be defined as follows:

- Select Vital signs at “Cycle 1 Day 1 - Within 60 min before Infusion” if (date/time of measurement and date/time of first treatment are both given and date/time of vital sign ≤ date/time of first treatment) OR if ((time of measurement or time of first treatment missing) and measurement and first treatment are on same date)
- Otherwise select closest measurement before first treatment (i.e. last Screening measurement as we do not consider unscheduled visits).

Vital signs information will be presented by a by-patient-by-visit listing, including site, patient identifier, date of assessment and study day, cycle, height, weight, Systolic and Diastolic blood pressure, respiratory rate, pulse rate as well as body temperature.

4.6.5 Concomitant medications

Subsequent anti-cancer therapies will be summarized overall and by type of anti-cancer therapy on the Safety Population.

By-patient listings including site and patient identifier will be provided for each of the following type of therapies based on the Safety Population:

- Concomitant Medications (separately for corticosteroids, immunosuppressive medications and any other medications)
- On-study Surgery and Procedure (Non-Cancer)
- On-Study Cancer Radiotherapy
- On-Study Tumor Surgery data.
- Subsequent anti-cancer therapies

4.6.6 Biomarker Endpoints

Not applicable for this study.

4.7 MISSING DATA

Missing or partial dates of death are imputed as described in Section 4.4.2.1 for Overall Survival analysis.

Missing NCI CTCAE grade will be imputed as described in Section 4.6.2 for Adverse events.

4.8 INTERIM ANALYSES

There was no formal interim analysis in the study. However, regular safety data reviews were performed by iDMC.

The iDMC interim safety reviews occurred 3 months after the first patient was enrolled and 3 months after 500 patients were enrolled and followed up for safety.

Analysis	Timing of Analysis
First iDMC review	Three months after enrollment of the first patient
Second iDMC review	After 500 patients who reach at least 3 months follow up
Optional iDMC reviews	Defined by iDMC at any time during the study period

5. REFERENCES

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Appendix 1

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN LABEL, SINGLE ARM, MULTICENTRE, SAFETY STUDY OF ATEZOLIZUMAB IN LOCALLY ADVANCED OR METASTATIC UROTHELIAL OR NON-UROTHELIAL CARCINOMA OF THE URINARY TRACT**
PROTOCOL NUMBER:	MO29983
VERSION NUMBER:	9
EUDRACT NUMBER:	2016-002625-11
IND NUMBER:	120827
TEST PRODUCT:	Atezolizumab (MPDL3280A; RO5541267)
PHASE:	IIIB
INDICATION:	Advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study is being conducted to evaluate the safety of atezolizumab as second-line treatment for locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract. The study will also evaluate treatment efficacy and explore potential tumor biomarkers related to atezolizumab. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective

The primary objective of this study is to evaluate the safety of atezolizumab based on the following endpoints:

- Nature, severity, duration, frequency and timing of adverse events (AEs)
- Changes in vital signs, physical findings, and clinical laboratory results during and following atezolizumab administration

Secondary Objectives

The secondary objectives of the study include evaluation of the efficacy of atezolizumab based on the following disease response endpoints:

- Overall survival (OS), defined as the time from initiation of study treatment to death from any cause
- Progression-free survival (PFS), defined as the time from initiation of study treatment to the first occurrence of disease progression or death from any cause, whichever occurs first. PFS will be calculated based on disease status evaluated by the investigator according to RECIST v1.1, and also by disease status evaluated by the investigator according to modified RECIST
- Overall response rate (ORR), defined as the proportion of patients with a best overall response of either complete response (CR) or partial response (PR). ORR will be calculated based on disease status evaluated by the investigator according to RECIST v1.1, and also by disease status evaluated by the investigator according to modified RECIST

- Disease control rate (DCR), defined as the sum of the CR, PR and stable disease (SD) rates. DCR will be calculated based on disease status evaluated by the investigator according to RECIST v1.1, and also by disease status evaluated by the investigator according to modified RECIST
- Duration of response (DoR), defined as the time from first occurrence of a documented response to disease progression or death from any cause, whichever occurs first. Duration of response will be calculated based on disease status evaluated by the investigator according to RECIST v1.1, and also by disease status evaluated by the investigator according to modified RECIST

Additional secondary study objectives include the evaluation of efficacy of atezolizumab according to the following patient-reported outcomes (PROs; Appendix 4):

- Change from baseline in health-related quality of life (HRQoL), as assessed using the EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30)
- EuroQol EQ-5D-5L-assessed utility

Exploratory Objectives

Exploratory study objectives may include evaluations of atezolizumab efficacy according to additional efficacy endpoints.

Biomarker Objectives

The biomarker objectives of the study are as follows:

- To evaluate PD-L1 prevalence based on retrospective evaluation of PD-L1 expression in tumor tissue measured by IHC. PD-L1 testing may be conducted on a subset of samples at local laboratories for inter-laboratory concordance evaluation
- The study also includes exploratory biomarker objectives to examine centrally assessed biomarkers and biomarker profiles in tumor tissue, and to correlate these with safety and/or efficacy outcomes. Biomarkers and biomarker profiles may be assessed using various methodologies including, but not limited to, IHC (single and multiplex, e.g., PD-L1 expression and immune cell infiltration analyses), RNA and DNA analysis (e.g., mutation and expression analyses)

Study Design

Description of Study

Study MO29983 is an open label, single-arm, multicenter study of the safety of atezolizumab as second-line treatment for patients with locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract. The study includes evaluation of the efficacy of atezolizumab and potential tumor biomarkers associated with atezolizumab. An overview of study design is shown in the Synopsis Figure.

Study screening will take place within 28 days prior to initiation of study treatment. Eligible patients will be enrolled and begin treatment with 1200 mg atezolizumab IV every 3 weeks. The single agent study treatment will continue until investigator-assessed loss of clinical benefit, unacceptable toxicity, investigator or patient decision to withdraw from therapy, or death (whichever occurs first).

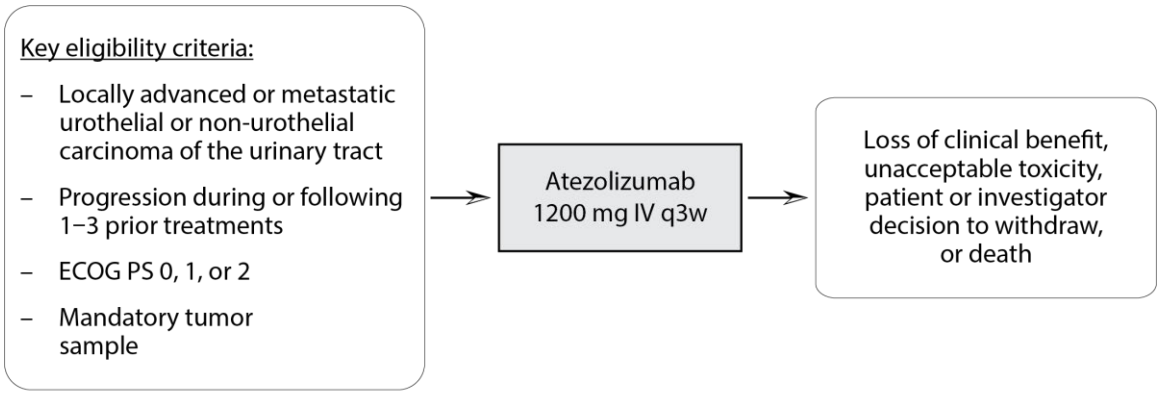
During the study treatment period, patients will be followed for safety based on AE assessments including vital signs, physical findings and clinical laboratory test results. Efficacy will be evaluated by the investigator according to both RECIST v1.1 (Appendix 3) and modified RECIST (Appendix 2). Exploratory biomarker analyses will be conducted based on primary tumor tissue or biopsied metastatic tumor tissue collected at baseline and an optional tumor sample collected at the second study treatment cycle.

Following discontinuation of study treatment, safety assessments will be conducted 30 days after the last study drug administration or until initiation of other anti-cancer therapy (whichever occurs first). Thereafter, patients will be followed for disease progression (unless this has

already occurred), SAEs, AEs of special interest, anti-cancer therapy and survival. Follow-up will continue for up to four years after the last patient is enrolled in the study.

An iDMC established for the study reviewed all AEs, SAEs and AEs of special interest and cumulative safety data.

Synopsis Figure. Study Schema



ECOG PS, Eastern Cooperative Oncology Group performance status; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; GC, gemcitabine and cisplatin.

Number of Patients

Approximately 1000 patients with locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract who progressed on one to three prior combination lines of systemic therapy for inoperable, locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract will be enrolled in this study. Patients who discontinue the study prior to study treatment initiation will not be replaced.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed informed consent form
2. Age ≥ 18 years
3. Is, according to the investigator's judgment, able to comply with the study protocol
4. Histologically documented locally advanced (T4b, any N; or any T, N 2−3) or metastatic (M1, Stage IV) urothelial or non-urothelial carcinoma of the urinary tract
   - Urinary tract carcinoma includes carcinoma of the bladder, ureter, urethra, and renal pelvis
   - Primary non-urothelial carcinoma includes all sub-types listed in the WHO classification (see Appendix 8)
     - Bellini collecting duct tumors are allowed if independently reviewed by two expert pathologists from different sites
   - Lymphoma, sarcoma, and renal cell carcinoma are excluded
5. Patients with measurable and/or non-measurable disease according to RECIST v1.1 are allowed

6. Must have progressed during or following treatment with at least one (and not more than 3) prior treatments for inoperable, locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract
   - Patients who received prior adjuvant/neoadjuvant chemotherapy and progressed within 12 months of treatment will be considered as having a first line of treatment for metastatic disease
   - Patients who were intolerant to prior systemic treatment are allowed as long as they had received at least 2 treatment cycles
   - Platinum- or non-platinum-based chemotherapy regimens are allowed
   - Low-dose chemotherapy given as radiosensitizer for curative treatment of localized disease does not count as a line of systemic chemotherapy

7. Representative formalin-fixed paraffin-embedded (FFPE) tumor specimen block available for submission
   - Only tissue from core needle (with ≥ 3 cores), punch, incisional, excisional, or forceps biopsies will be accepted. Fine-needle aspiration, brushing, bone tissue, and lavage samples are not acceptable
   - If an appropriate tumor specimen is not available, a sample will be collected by biopsy during the study screening period
   - ONLY at sites where local laws and regulations prohibit the sending of tumor specimen blocks to an outside central laboratory, specimen slides are acceptable. A minimum of 15 unstained serially-cut sections must be prepared and sent per tumor sample. For details, please refer to the Sample Handling Manual

8. Eastern Cooperative Oncology Group (ECOG) Performance Status 0, 1 or 2
9. Life expectancy ≥ 12 weeks
10. Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 2 weeks prior to the first study treatment:
    - Absolute neutrophil count ≥ 1500 cells/μL (without granulocyte colony-stimulating factor support within 2 weeks prior to the first study treatment)
    - White blood cell count > 2500/μL
    - Lymphocyte count ≥ 500/μL
    - Platelet count ≥ 100,000/μL (without transfusion within 2 weeks prior to the first study treatment)
    - Hemoglobin ≥ 9.0 g/dL (patients may be transfused or receive erythropoietic treatment to meet this criterion)
    - Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase ≤ 2.5 times the upper limit of normal (ULN), with the following exceptions:

      Patients with documented liver metastases: AST and/or ALT ≤ 5 × ULN

      Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN

    - Serum bilirubin ≤ 1.5 ×ULN. Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled
    - Calculated creatinine clearance ≥ 15 mL/min (Cockcroft-Gault formula)
    - International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 ×ULN. This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation must be on a stable dose

11. Patients with treated, asymptomatic central nervous system (CNS) metastases are eligible, provided they meet all of the following criteria:
    - Evaluable disease outside the CNS

- No history of intracranial or spinal cord hemorrhage
- No evidence of significant vasogenic edema
- No stereotactic radiation within 7 days or whole-brain radiation or neurosurgical resection within 2 weeks before the start of study treatment
- Have had a screening CNS radiography ≥ 2 weeks since completion of radiotherapy or surgical resection
- Radiographic demonstration of interim stability (i.e. no progression) between the completion of CNS-directed therapy and the screening radiographic study

Note: Patients on stable doses of anticonvulsants or on prednisone doses (or dose equivalents) of ≤ 20 mg/day are allowed

12. 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
    - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)
    - Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical 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:

13. Treatment with more than three prior lines of systemic therapy for inoperable, locally advanced or metastatic urothelial or non-urothelial carcinoma of the urinary tract
14. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 4 weeks prior to study treatment initiation
    - Patients who were in another clinical trial with therapeutic intent within 4 weeks of study treatment initiation but were not on active drug in that prior trial are eligible
    - Patients who were in another clinical trial with therapeutic intent within 4 weeks of study treatment initiation but were in the follow-up phase of that prior trial and had stopped receiving active drug 4 or more weeks before study treatment initiation are eligible
15. Treatment with chemotherapy within 2 weeks prior to study treatment initiation
16. Treatment with radiotherapy ongoing at the time of study entry (for CNS-directed radiotherapy, please refer to Inclusion Criterion 11)
17. Pregnant or lactating, or intending to become pregnant during the study
    - Women who are not postmenopausal (postmenopausal defined as ≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 2 weeks prior to initiation of study drug
18. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)

19. Malignancies other than the one studied in this protocol within 5 years prior to Cycle 1, Day 1
    - Patients with localized low risk prostate cancer (defined as Stage ≤ pT2b, Gleason score ≤ 7, and prostate-specific antigen [PSA] at prostate cancer diagnosis ≤ 20 ng/mL) treated with curative intent and without PSA recurrence are eligible
    - Patients with pre-existing low risk prostate cancer (defined as Stage T1/T2a, Gleason score ≤ 6, 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

20. Significant cardiovascular disease, such as New York Heart Association cardiac disease ≥ Class III, myocardial infarction within 3 months, unstable arrhythmias, or unstable angina
    - Patients with known coronary artery disease 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

21. Significant renal disorder indicating a need for renal transplant
22. Signs or symptoms of severe infection within 2 weeks prior to initiation of study treatment, including but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
23. Major surgical procedure within 4 weeks prior to study treatment initiation or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis
24. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
25. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
26. History of autoimmune disease (Appendix 5) are allowed if controlled and on stable treatment (i.e., same treatment, same dose) for the last 12 weeks, with the exception of:
    - Patients taking concurrent abatacept or belatacept treatment, unless therapy has been withdrawn for > 8 weeks
    - Patients with a history of serious or life threatening immune-related events
    - No more than 1 concomitant autoimmune disease at the time of study entry is allowed unless one of them is:

      Autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone

      Controlled Type I diabetes mellitus on a stable dose of insulin regimen

      A medical history of such entities as atopic disease or childhood arthralgias, where the clinical suspicion of autoimmune disease is low. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis)

      Vitiligo

27. Prior allogeneic stem cell or solid organ transplantation
28. History of idiopathic pulmonary fibrosis (including pneumonitis, drug-induced pneumonitis, organizing pneumonia (i.e. bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest computed tomography (CT) scan

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

29. Patients with active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C
    - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible
    - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA

30. Active tuberculosis
31. Administration of a live, attenuated vaccine within 4 weeks prior to study treatment initiation
    - Influenza vaccination should be given during influenza season only (e.g., approximately October to March in the Northern Hemisphere and April through September in the Southern Hemisphere) and must not be a live, attenuated vaccine.
    - Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to study treatment initiation or at any time during the study treatment, and so for 5 months thereafter

32. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti−CTLA-4, anti−PD-1, and anti−PD-L1 therapeutic antibodies
    - Patients who have received prior treatment with anti-CTLA-4 may be enrolled provided at least 5 half-lives (approximately 75 days) have elapsed from the last dose of anti−CTLA-4 to the first dose of atezolizumab and there was no history of severe immune-related adverse effects from anti-CTLA-4 (NCI CTCAE Grade 3 or 4)

33. Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to initiation of study treatment
    - Prior cancer vaccines and cellular immunotherapy are permitted

34. Specifically for patients <u>without</u> autoimmune disease: 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 agents) within 2 weeks prior to study treatment initiation or anticipated requirement for systemic immunosuppressive medications during the study treatment period
    - For patients with CNS metastases, use of prednisone at a dose (or dose equivalent) of ≤ 20 mg/day is acceptable
    - Chronic use of prednisone or equivalent should be discussed with the Medical Monitor
    - The use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency and topical steroids for cutaneous diseases are allowed.

    Note: For patients with autoimmune disease, immunosuppressive medications are permitted if the patient has controlled autoimmune disease and stable treatment (i.e., same treatment, same dose) for the previous 12 weeks.

End of Study

The end of study will occur when all patients enrolled have either died, withdrawn consent, are lost to follow up, or have been followed for 48 months since the last study patient is enrolled, whichever occurs first.

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 6 years.

Investigational Medicinal Product

The investigational medicinal product (IMP) for this study is atezolizumab.

Formulation, Packaging, and Handling

The atezolizumab drug product will be provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20.0 mL (1200 mg) of atezolizumab solution, but may contain more than the stated volume to enable delivery of the entire 20.0 mL volume. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

Atezolizumab must be refrigerated at 2°C–8°C (36°F–46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

For further details, see the Atezolizumab Pharmacy Manual and Investigator's Brochure.

Dosage, Administration, and Compliance

The dose of atezolizumab in this study will be 1200 mg administered by intravenous infusion every 3 weeks (21 [± 3] days). No dilution of the vial contents is required.

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

For more detailed information on drug preparation, storage and administration, refer to the Atezolizumab Investigator's Brochure and Pharmacy Manual.

The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated AEs, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated, and within 30 (± 10) minutes after the infusion.

Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The management of infusion-related reactions will be according to severity as follows:

- In the event that a patient experiences a mild (NCI CTCAE Grade 1) infusion-related event, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should continue to deliver the infusion at the reduced rate for 30 (± 10) minutes. If tolerated, the infusion rate may then be increased to the original rate
- In the event that a patient experiences a moderate infusion-related event (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the patient should have his or her infusion immediately interrupted and should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the infusion-related event

- For severe or life-threatening infusion-related events (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening infusion-related events will not receive further infusion and will be further managed as clinically indicated until the event resolves

For anaphylaxis precautions, see Appendix 6.

Guidelines for dosage modification, treatment interruption or discontinuation, and the management of specific adverse events are provided in Section 5.1.2.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Please refer to the Pharmacy Manual for detailed instructions on drug preparation, storage and administration.

Concomitant Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Permitted Therapy

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine and/or famotidine or another H2 receptor antagonist, as per standard practice (equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists; see Appendix 6).

Systemic corticosteroids and tumor necrosis factor−α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab, but may be administered at the discretion of the treating physician after consultation with the Medical Monitor (see Exclusion Criterion 23 [Section 4.1.2]). If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for cycles ≥ 2 at the discretion of the treating physician after consultation with the Medical Monitor. The use of inhaled corticosteroids for COPD and mineralocorticoids (e.g., fludrocortisone) and low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as an appetite stimulant is acceptable while the patient is enrolled in the study.

Colony-stimulating factors, such as granulocyte colony-stimulating factor and erythropoietin, should only be used according to manufacturers' labels and the ASCO and ASCO/ASH guidelines (Smith et al. 2006; Rizzo et al. 2010).

Influenza vaccination should be given during influenza season only (approximately October to March in the Northern Hemisphere) and must not be a live, attenuated vaccine. Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to study treatment initiation or at any time during the study treatment, and for 5 months thereafter.

Patients who use hormonal therapy with gonadotropin-releasing hormone agonists or antagonists for prostate cancer, oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy (see Section 4.1.2) should continue their use.

All concomitant medications should be reported to the investigator and recorded on the appropriate eCRF.

Prohibited Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, or investigational agents (except for maintenance therapies outlined in Section 4.1.1 and 4.1.2)
  - After completion of Cycle 1, certain forms of radiotherapy may be considered for palliation if patients are deriving benefit (e.g., treatment of known bone metastases or symptomatic hematuria)

- Traditional herbal medicines are not recommended because the ingredients of many herbal medicines are not fully studied, and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity
- Patients who are receiving a receptor activator of nuclear factor kappa B ligand inhibitor (denosumab) prior to enrollment must be willing and eligible to receive a bisphosphonate instead while on study; denosumab could potentially alter the activity and the safety of atezolizumab
- Patients should not receive abatacept or belatacept treatment (those who were receiving it must stop it > 8 weeks before study entry)

Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during atezolizumab treatment, and for 5 months after the discontinuation of atezolizumab.

Patients are not allowed to receive immunostimulatory agents, including but not limited to interferon (IFN)-α, IFN-γ, or IL-2, during the entire study. These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.

With the exception of autoimmune disease patients, patients should not receive immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of atezolizumab.

Systemic corticosteroids, immunosuppressive medications, and TNF-□ inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-□ inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-□ inhibitors may be administered at the discretion of the investigator after consultation with the Medical Monitor. If feasible, alternatives to these agents should be considered.
Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy.

Patients with CNS metastases are allowed to receive anticonvulsants and steroid treatments if the dose of prednisone is ≤ 20 mg / day (or equivalent).

In addition, all patients (including those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.

The above list of medications is not necessarily comprehensive. The investigator should consult the prescribing information for any concomitant medication and contact the Medical Monitor if questions arise regarding medications not listed above.

Statistical Methods

All qualitative data will be presented in contingency tables, using absolute and relative frequencies, unless otherwise stated. Percentages will be rounded to the first decimal place, and therefore may not always add up to 100%. When applicable, 95% confidence intervals (CI) will be presented with estimates of proportions.

All quantitative data will be summarized via relevant descriptive statistics, such as number of observations with available measurements, mean, standard deviation, median, first and third quartiles (Q1 and Q3) when applicable, and minimum and maximum.

Time to event data will be summarized via Kaplan-Meier (KM) estimates/curves and median with corresponding 95% CI.

All analyses will be performed in SAS, version 9.3.

Primary Analysis

The primary endpoint of the study is the incidence of treatment-emergent AEs. Verbatim descriptions of AEs will be mapped to MedDRA thesaurus terms and graded according to the National Cancer Institute Common Terminology Criteria version 4.0. Multiple occurrences of the same event will be counted once at the maximum severity.

Other safety variables will include:

- Drug exposure (treatment duration, number of doses, dose intensity and dose modifications/discontinuations, with reasons)
- All AEs
- SAEs
- AEs (grade 3–5)
- AEs of special interest
- AEs leading to study drug discontinuation or interruption
- Changes in vital signs from baseline
- Changes in physical findings from baseline
- Changes in selected laboratory parameters from baseline
- Deaths and cause of death
- Concomitant medications

The incidence of AEs will be summarized by frequency tables. Corresponding 95% Clopper-Pearson confidence intervals (CIs) will be presented, as applicable. Time to first incidence of selected event types will also be estimated and presented graphically using the Kaplan-Meier method.

Treatment exposure, discontinuation rate, and cause of death will be analyzed by frequency tables. When appropriate, median time on treatment will be estimated by the Kaplan-Meier approach or univariate statistics, presenting mean, median, quartiles, minimum, maximum and standard deviation.

Changes in vital signs and physical findings from baseline will be tabulated and presented graphically when applicable.

Worst grades for laboratory parameters and newly occurring Grade 3 and 4 laboratory values during treatment will be summarized by frequency tables.

Concomitant medications recorded during the study will be summarized by frequency tables.

Determination of Sample Size

This is a single-arm safety study. There is no formal statistical hypothesis and all analyses will be descriptive. The results for the primary safety variables will be presented via percentages and corresponding 95% Clopper-Pearson CIs.

A sample size of approximately 1000 patients is planned for this study. The precision of rare AE incidence estimates presented by two-sided exact 95% Clopper-Pearson CIs are shown in the Synopsis Table.

Synopsis Table. Two-Sided Clopper-Pearson 95% Confidence Intervals for Adverse Event Rate Estimates

Number of Patients with at Least One Event (Expected) N=1000	Expected Event Rate (%)	Lower limit of CI (%)	Upper limit of CI (%)
12	1.2	0.62	2.09
10	1.0	0.48	1.83
8	0.8	0.35	1.57
6	0.6	0.22	1.3
5	0.5	0.16	1.16
4	0.4	0.11	1.02
3	0.3	0.06	0.87
2	0.2	0.02	0.72
1	0.1	0.00	0.56

CI = confidence interval.

Therefore, for a sample size of 1000 patients and an expected AE incidence of 0.5%, based on the half-width of the Clopper-Pearson 95% confidence interval, the true AE rate can be estimated with a precision of: ±(1.16% – 0.16%)/2 % = ±0.5 %.

Interim Analyses

An Independent Data Monitoring Committee (iDMC) conducted interim reviews of accumulated safety data. The first review was performed three months after enrollment of the first patient. The iDMC performed another overall safety review after 500 patients have been followed up for 3 months.

Appendix 2
Schedule of Assessments

	Screening Period [a]		Treatment Period	Treatment Discontinuation	Follow-Up Period
	Day –28 to Day –1	Day -14 to -1	Day 1 (±3 days) of each 3 week treatment cycle	30 (±7) days from last treatment or at initiation of other anti-cancer therapy (whichever occurs first)	
Informed Consent [a]	x				
Review of eligibility criteria	x				
Medical history and demographics [b]	x				
Age-adjusted Charlson comorbidity index	x				
12-lead ECG [c]	x		as clinically indicated		
Tumor sample	x [d] (mandatory)		Cycle 2, Day 1 (optional) [e]		
Weight	x		x	x	
Height	x				
Complete physical examination [f]	x			x	
Limited physical examination [f]			x [g]		
ECOG Performance Status	x		x [g]	x	
Vital signs [h]	x		x	x	
HIV, HBV, HCV serology [i]	x		as clinically indicated		
Hematology [j]		x	x [g]	x	
Coagulation (aPTT, INR)		x		x	
TSH, free T3, free T4			Every other cycle		
Serum chemistry [k]		x	x [g]	x	

	Screening Period [a]		Treatment Period	Treatment Discontinuation	Follow-Up Period
	Day –28 to Day –1	Day -14 to -1	Day 1 (±3 days) of each 3 week treatment cycle	30 (±7) days from last treatment or at initiation of other anti-cancer therapy (whichever occurs first)	
Urinalysis [l]		x	x [g]	x	
Pregnancy test [m]		x	x		
Tumor assessment [n]	x		Every 9 weeks ± 3 business days for 54 weeks from study treatment start; thereafter every 12 weeks ± 6 business days until confirmed PD or until study discontinuation (for patients who continue to receive atezolizumab following disease "pseudo-progression")		
EORTC QLQ-C30			Day 1 of first 3 cycles then with tumor assessments	x	
EQ-5D-5L			Day 1 of first 3 cycles then with tumor assessments	x	
Concomitant medications [o]	x		x	x	
Adverse events [p]	x		x	x	x
Study drug infusion			x		
Survival and anti-cancer therapy [q]				x	x

Abbreviations: aPTT: activated partial thromboplastin time; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer; INR: international normalized ratio; PD: progressive disease.

Note: Unless otherwise indicated, assessments scheduled on the study treatment days should be performed prior to initiation of study treatment infusion.

a. Written informed consent is required for performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry (except where otherwise specified) may be used for screening assessments rather than repeating such tests.

b. Medical history includes surgical and cancer histories. Cancer history includes stage, date of diagnosis, and prior anti-cancer treatment. Reproductive status and smoking history should also be captured. Demographic information includes age, sex, and self-reported race/ethnicity.

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

d. A representative formalin-fixed paraffin-embedded (FFPE) archival tumor block must be submitted. If an archival tumor block is not available, a tumor FFPE block obtained by biopsy during screening must be submitted. Only tissue from core needle (with ≥ 3 cores), will be accepted. Cytological samples (such as, for example, from fine-needle aspirations) and bone tissue are not acceptable. ONLY at sites where local laws and regulations prohibit the sending of tumor specimen blocks to an outside central laboratory, slides (≥15) are acceptable.
Only for patients eligible for the study and who submitted archival tissue, an optional tumor biopsy may be taken during screening.

e. For patients who underwent screening biopsy, an optional tumor sample ideally from the same lesion may be taken at Cycle 2, Day 1 (± 1 week), if feasible.

f. A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

g. ECOG Performance Status, limited physical examination, and local laboratory assessments may be obtained ≤ 96 hours before Day 1 of each cycle. It is not necessary to repeat these assessments again prior to Cycle 1 if they have been conducted for screening within this time period.

h. Vital signs include respiratory rate, heart rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Treatment cycle Day 1 vital sign assessments will be done prior to study treatment.

i. HIV testing will be performed in accordance with national and/or institutional guidelines. HBV serology includes HBsAg testing. HCV serology includes anti-HCV antibody testing and, if indicated due to anti-HCV antibody positivity, PCR testing for HCV RNA. See Section 4.5.7.

j. Hematology consists of CBC (including RBC count), hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. A manual differential may be done if clinically indicated.

k. Serum chemistry includes glucose, BUN or urea, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.

l. Urinalysis includes specific gravity, pH, glucose, protein, ketones, and blood.

m. A 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. On-study pregnancy tests performed every treatment cycle can be conducted with serum or urine.

n. The same radiographic procedure should be used throughout the study for each patient. A CT (with contrast) or MRI of the head must be included in screening tumor assessments for patients with known or suspected CNS disease. Results must be reviewed by the investigator before dosing at the next cycle. Patients who continue treatment beyond radiographic disease progression assessed per RECIST v1.1 should be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 9 weeks. If the scan frequency is every 12 weeks, a follow-up scan is recommended at 9 weeks (± 2 weeks) as an unscheduled tumor assessment or earlier if clinically indicated. Investigators may perform additional scans or more frequent assessments if clinically indicated.

o. Concomitant medications include any prescription medications, over-the-counter medications, or herbal remedies. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

p. After informed consent has been obtained, but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all SAEs and AEs of special interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other AEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period, the investigator should report any SAEs or AEs of special interest believed to be related to prior study drug treatment. The investigator should follow each AE 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 SAEs considered to be related to study drug or study-related procedures until a final outcome can be reported.

q. Survival and new anti-cancer therapy follow-up information will be collected via telephone contact, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, end of study, patient withdrawal or study termination by the Sponsor, whichever occurs first.

Title: MO29983 SAP 3.0 20221214 Sign-Off			
Sponsor Project Number:	MO29983	**PAREXEL Project Number:**	231986
Sponsor Name:	F.Hoffmann-La Roche Ltd		

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