PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PLACEBO–CONTROLLED, DOUBLE–BLIND STUDY OF ATEZOLIZUMAB (ANTI–PD–L1 ANTIBODY) AS ADJUVANT THERAPY IN PATIENTS WITH RENAL CELL CARCINOMA AT HIGH RISK OF DEVELOPING METASTASIS FOLLOWING NEPHRECTOMY**
PROTOCOL NUMBER:	WO39210
VERSION NUMBER:	10
EUDRACT NUMBER:	2016–001881–27
IND NUMBER:	119039
NCT NUMBER:	NCT03024996
TEST PRODUCT:	Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann–La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
12-Nov-2021 15:44:41	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	Date Final	Country	Version	Date Final
10	See electronic date stamp on title page.	—	—	—
9	7 February 2021	China	9	15 March 2021
8	15 February 2020	China	8	15 February 2020
7	5 December 2018	China	7	12 December 2018
6	20 September 2018	—	—	—
4	1 March 2018	France	5	15 March 2018
3	16 December 2016	France	4	5 May 2017
2	15 September 2016	—	—	—
1	29 April 2016	—	—	—

PROTOCOL AMENDMENT, VERSION 10:
RATIONALE

Protocol WO39210 has been amended to change the primary endpoint of Independent Review Facility (IRF)-assessed disease-free survival (DFS) to investigator-assessed DFS. The protocol has also been updated to align with the Atezolizumab Investigator's Brochure, Version 18. Additional clarifications and changes to the protocol, along with a rationale for each change, are summarized below:

- Benefit–risk assessment and guidance on concomitant administration of coronavirus disease 2019 vaccines with atezolizumab have been modified to align with the standard language (Sections 1.4 and 4.4.1).
- Language has been updated throughout the protocol to change the endpoint of IRF-assessed DFS to investigator-assessed DFS as the investigators assessment of recurrence better approximates treatment benefit in real world clinical practice (Sections 2, 3.3.6, 6.1.1, 6.1.2, 6.4, 6.4.1, 6.4.3, and 6.10.1).
- The secondary efficacy endpoint of investigator-assessed DFS will be changed to IRF-assessed DFS. IRF-assessed DFS will be continued to minimize potential investigator bias to evaluate the treatment benefit in patients without retrospectively identified baseline disease (Sections 2, 3.3.6, 6.4.2, and 6.4.3).
- A new secondary endpoint of IRF-assessed event-free survival (EFS) has been added to ensure the assessment of treatment benefit in patients that were retrospectively identified by the IRF as having baseline disease. Additional language has been added to define the new secondary endpoint of IRF-assessed EFS (Sections 2, 3.3.6, 6.4.2, and 6.4.3).
- The endpoint for immunogenicity objective, “To evaluate the immune response to atezolizumab” has been updated to better align the protocol with real world practice (Section 2).
- The definition of “Distant metastasis–free survival” in secondary efficacy objective endpoint has been updated to provide more clarification (Section 2).
- The exploratory objective, “to assess surgical outcomes including complication rates” and its corresponding endpoint has been removed (Section 2).
- The responsibilities of the Principal Investigator and the role of the Medical Monitor (MM) during study conduct have been clarified (Sections 4.2.2.1, 4.2.2.2, 4.5.5, 4.5.6.2, 5.1.2, Appendices 7 and 11).
- Language has been updated to clarify the use of public record searches for survival follow-up following withdrawal of consent (Sections 4.5.10 and 4.6.1, Appendix 1).
- The Medical Monitor information has been updated (Section 5.4.1).
- The name of “Serious Adverse Event/Adverse Event of Special Interest Reporting Form” has been updated to “Clinical Trial Adverse Event/Special Situations Form” (Sections 5.4.2.1, 5.4.2.2, and 5.6)

- Language has been updated to include time to clinically confirmed deterioration analysis to allow for analyzing all FKSI-19 data captured. Subgroup analysis will be performed to test the consistency of the results (Section 6.9.1).
- The medical term “primary biliary cirrhosis” has been replaced by the term “primary biliary cholangitis” to align with the updated preferred term in MedDRA (Appendix 7).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator’s Brochure, Version 18 (Appendix 11).
- The management guidelines referencing Grade 4 myositis have been removed because Version 4.0 of the Common Terminology Criteria for Adverse Events does not have a Grade 4 category for myositis. Instructions regarding recurrent Grade 3 events have been modified accordingly (Appendix 11).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PLACEBO–CONTROLLED, DOUBLE-BLIND STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) AS ADJUVANT THERAPY IN PATIENTS WITH RENAL CELL CARCINOMA AT HIGH RISK OF DEVELOPING METASTASIS FOLLOWING NEPHRECTOMY**
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NCT NUMBER:	NCT03024996
TEST PRODUCT:	Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann–La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) AS ADJUVANT THERAPY IN PATIENTS WITH RENAL CELL CARCINOMA AT HIGH RISK OF DEVELOPING METASTASIS FOLLOWING NEPHRECTOMY**
PROTOCOL NUMBER:	WO39210
VERSION NUMBER:	10
EUDRACT NUMBER:	2016–001881–27
IND NUMBER:	119039
NCT NUMBER:	NCT03024996
TEST PRODUCT:	Atezolizumab (RO5541267)
PHASE:	III
INDICATION:	Renal cell carcinoma
SPONSOR:	F. Hoffmann–La Roche Ltd

Objectives and Endpoints

This is a Phase III, multicenter, randomized, placebo–controlled, double-blind study (IMmotion010) to evaluate the efficacy and safety of atezolizumab versus placebo in patients with renal cell carcinoma (RCC) who are at high risk of disease recurrence following resection. Specific objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoints
Primary Efficacy Objective	
• To evaluate the efficacy of adjuvant treatment with atezolizumab	• *Investigator*-assessed DFS, defined as the time from randomization to death from any cause or the first documented recurrence assessed by *investigator, whichever occurs first. Recurrence is* defined as any of the following: Local recurrence of RCC New primary RCC Distant metastasis of RCC

Objectives	Corresponding Endpoints
Secondary Efficacy Objective	
• To evaluate the efficacy of adjuvant treatment with atezolizumab	• Overall survival, defined as the time from randomization to death from any cause • Investigator-assessed DFS *in patients with PD-L1 expression status IC1/2/3** • *IRF-assessed DFS, defined as the time from randomization to death from any cause or the first documented recurrence assessed by IRF, whichever occurs first.* • IRF-assessed DFS in patients with *PD-L1 expression status* IC1/2/3* • *IRF-assessed event-free survival (EFS), defined as the time from randomization to death from any cause, or the first documented recurrence in patients without baseline disease by IRF or the first documented disease progression in patients identified as having baseline disease by IRF, whichever occurs first. Disease progression is defined as either unequivocal progression of baseline disease or new unequivocal lesions.* • Disease-specific survival, defined as the time from randomization to death from RCC • Distant metastasis–free survival, defined as the time from randomization to *death from any cause or* the date of diagnosis of distant (i.e., non-locoregional) metastases assessed by investigator*, whichever occurs first.* • 1–, 2–, and 3–year investigator-assessed DFS rate, defined as the probability of patients being alive and free of recurrence assessed by investigator *at* Year 1, 2, and 3 after randomization • *1–, 2–, and 3–year IRF-assessed DFS rate, defined as the probability of patients being alive and free of recurrence assessed by IRF at Year 1, 2, and 3 after randomization*
Safety Objective	
• To evaluate the safety and tolerability of atezolizumab in the adjuvant setting	• Incidence, nature, and severity of adverse events graded according to NCI CTCAE v4.0 • Changes in vital signs and clinical laboratory results
Pharmacokinetic Objective	
• To characterize the PK profile of atezolizumab	• Serum concentration of atezolizumab at specified timepoints

Objectives	Corresponding Endpoints
Immunogenicity Objectives	
• To evaluate the immune response to atezolizumab	• *Prevalence of anti-drug antibodies (ADAs) to atezolizumab at baseline and incidence of ADAs to atezolizumab after treatment*
• To explore the potential relationship of the immunogenic response	• Relationship between ADA *status* and PK (i.e., minimum serum concentration), safety, and efficacy *endpoints*
Exploratory Objectives	
• To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease recurrence *and overall survival*	• Tumor *and circulating* biomarkers (including, but not limited to PD-L1, PD-1, *prevalence of immune subsets, circulating factors, genomic mutations, gene expression, gene expression signatures of tumor and immune biology, and molecular subtypes),* as defined by IHC or qRT-PCR, NGS, and/or other methods will be correlated with efficacy measures.
• To document patients' perspective regarding treatment tolerability and health-related quality of life	• The Functional Assessment of Cancer Therapy Kidney Symptom Index 19 (FKSI-19)
• To measure health status for health economic modeling	• EQ–5D–5L questionnaire as a measure of patient reported health status to derive utilities
• To evaluate the efficacy of adjuvant treatment with atezolizumab among patients with tumor Fuhrman Grade 4 or sarcomatoid histology (defined by investigator-assessed conventional histopathology)	• *Investigator*-assessed DFS in patients with tumor Fuhrman Grade 4 or sarcomatoid histology (defined by the investigator-assessed conventional histopathology).

ADA=anti-drug antibody; DFS=disease free-survival; *EFS =event free survival,* EQ-5D-5L=EuroQoL 5-Dimension, 5-level version; IC=tumor-infiltrating immune cell; IHC=immunohistochemistry; IRF=Independent Review Facility; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0; NGS=next generation sequencing; PD-1=programmed death-1; PD-L1=programmed death ligand-1; PK=pharmacokinetic; qRT-PCR=quantitative reverse transcriptase=polymerase chain reaction; RCC=renal cell carcinoma

**PD-L1 IC0 is defined as <1% and IC1/2/3 is defined as ≥1% of tumor-infiltrating immune cells (IC) expressing PD-L1 as assessed by immunohistochemistry using SP142 assay.*

Study Design

Description of Study

This is a Phase III, multicenter, randomized, placebo–controlled, double–blind study designed to evaluate the efficacy and safety of adjuvant treatment with atezolizumab versus placebo in patients with RCC who are at high risk for disease recurrence following resection.

Male and female patients aged ≥18 years of age who have histologically confirmed RCC and who have undergone nephrectomy and are classified as being at high risk of RCC recurrence are eligible for study participation. Patients who have not developed RCC metastases but are at high risk of recurrence are eligible on the basis of the following TNM/grading criteria as determined by the investigator: T2 Grade 4, T3a Grade 3–4, T3b/c any Grade, T4 any Grade, or TxN+any Grade. Patients with metachronous recurrence no less than 12 months following

nephrectomy who have undergone metastasectomy with a complete resection (R0 resection) of all sites of disease (restricted to lung, soft tissue, and lymph node) and have no evidence of disease recurrence are also eligible. Patients with synchronous metastases who have undergone complete resection of residual disease are eligible in the following circumstances: isolated solitary ipsilateral or contralateral adrenal metastasis treated with adrenalectomy, and lung metastasis resected with a sublobar or lobar resection within 12 weeks of nephrectomy. The TNM/grading eligibility requirements do not apply to patients who enroll on the basis of resected metachronous or synchronous metastasis.

Patients who have received prior neoadjuvant or adjuvant therapy are not eligible for study participation.

Nephrectomy and/or metastasectomy tumor specimens from patients who meet eligibility criteria will be evaluated for PD–L1 expression. Patients must have sufficient amounts of viable tumor for IHC scoring of PD–L1 by the central pathology laboratory in order to be eligible. When tissue from both nephrectomy and metastatic specimens are available, submission of both specimens is recommended. The highest PD-L1 staining score will be used for patients who provide both nephrectomy and metastasectomy specimens.

Approximately 764 patients at high risk for RCC recurrence [see below for high-risk definition]) will be randomized to one of the following arms in a 1:1 ratio:

- Arm A (experimental arm): Atezolizumab 1200 mg every 3 weeks (q3w) for 16 cycles or 1 year (whichever occurs first)
- Arm B (control arm): Placebo q3w for 16 cycles or 1 year (whichever occurs first)

High–risk patients are defined as patients with any of the following:

- T2 Grade 4, T3a Grade 3–4, T3b/c any Grade, T4 any Grade, TxN+ any Grade
- Limited metachronous/synchronous recurrence in patients who undergo complete R0 resection of all sites of disease. These patients will be eligible regardless of their original TNM/grade.

Number of Patients

A total of approximately 764 patients will be enrolled at approximately 215 centers globally.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1
- Able to comply with the study protocol, in the investigator's judgment
- Pathologically confirmed RCC with a component of either clear cell histology or sarcomatoid histology (sarcomatoid differentiation regardless of the primary epithelial subtype) that has not been previously treated in the adjuvant or neoadjuvant setting

    Patients with localized disease with T2 Grade 4, T3a Grade 3–4, T3b/c any grade, T4 any grade and TxN+ any grade are eligible.

    Patients with pulmonary (treated with sub–lobar or lobar resection), lymph node, or soft–tissue metachronous recurrence of disease occurring greater than 12 months following nephrectomy who undergo complete resection (R0; microscopically margin-negative resection in which no gross of microscopic disease remains) and have no evidence of disease following metastasectomy are eligible. Patients with resected CNS, bone, or adrenal metastasis are not eligible.

    Patients with synchronous metastases who have undergone complete resection of residual disease are eligible in the following circumstances: isolated solitary ipsilateral or contralateral adrenal metastasis treated with adrenalectomy and lung metastases treatable with a sub–lobar or lobar resection within 12 weeks of nephrectomy. Patients with resected CNS, bone, or other soft–tissue metastasis are not eligible.

Medical Monitor approval is necessary for patients with resected metachronous and synchronous metastasis.

A TNM/grading high risk classification is not required for patients with metachronous/synchronous recurrence.

- Radical or partial nephrectomy with lymphadenectomy in select patients

  Surgeries may be performed by the open, laparoscopic, or robotic approach.

  Nephrectomy should include a lymph node dissection in patients with suspected nodal metastases on preoperative imaging (e.g., 2 cm) rendering the patient surgically NED (no evidence of disease). For patients with clinical venous involvement or whose tumors are clinically > 10 cm, a lymph node dissection is recommended but not required. The extent of the lymph node dissection will be at the discretion of the treating surgeon.

  For patients with no preoperative evidence of abdominal node involvement and those not at increased risk of nodal metastases, a lymph node dissection is not required.

  Patients must have a negative surgical margin. Positive surgical margin is defined as tumor identified at the inked perinephric fat margin surrounding the nephrectomy specimen (R2), evidence of microscopic disease at the tumor margin (R1), or evidence of tumor histologically invading or adherent to the renal vein wall at the margin. Luminal thrombus without venous wall invasion is not considered a positive margin. The final surgical margin must be free of disease. Contact the Medical Monitor if clarification is required.

  For patients with evidence of thrombus involving the inferior vena cava and/or right atrium (i.e., cavoatrial involvement), a thrombectomy should be performed at the time of the radical nephrectomy.

- Representative formalin–fixed paraffin–embedded (FFPE) resected tumor specimens in paraffin blocks (blocks preferred) or at least 15 unstained slides, with an associated pathology report, for central testing and determined to be evaluable for tumor PD-L1 expression prior to study enrollment

  Up to 5 unstained slides will be used to determine tumor PD–L1 expression. The remaining unstained slides will support exploratory biomarker analysis and objectives

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

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

  The tumor specimen must contain adequate viable tumor tissue to establish PD-L1 expression status.

  Patients who have additional tissue samples from procedures performed at different times (e.g., nephrectomy and metastasectomy) during the course of their renal cell carcinoma will be requested (but not required) to also submit these samples for central testing.

  In situations in which multiple specimens were received from different sites or at different times, the highest score will be used for eligibility.

- Absence of residual disease and absence of metastasis, as confirmed by a negative baseline computed tomography (CT) of the pelvis, abdomen, and chest no more than 4 weeks prior to randomization. Confirmation of disease–free status will be assessed by an independent central radiologic review of imaging data.

- Absence of brain metastasis, as confirmed by a negative CT with contrast or MRI scan of the brain, no more than 4 weeks prior to randomization

  Applicable only to patients who are eligible based upon completely resected metachronous lung, soft tissue or lymph node metastasis, or synchronous lung or adrenal metastasis

- Full recovery from nephrectomy or metastasectomy within 12 weeks from randomization following surgery

  Randomization should occur within 12 weeks after nephrectomy or metastasectomy.
- Adequate hematologic and end–organ function, defined by the following laboratory results obtained within 28 days prior to randomization:

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

  WBC counts > 2500/μL

  Lymphocyte count ≥ 300/μL

  Platelet count ≥ 100,000/μL (without transfusion within 2 weeks prior to Cycle 1, Day 1)

  Hemoglobin ≥ 9.0 g/dL

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

  AST, ALT, and alkaline phosphatase ≤ 2.5 × the upper limit of normal (ULN)

  Serum bilirubin ≤ 1.5 × ULN

  Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.

  INR and aPTT ≤ 1.5 × ULN

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

  Calculated creatinine clearance ≥ 20 mL/min (Cockcroft–Gault formula)
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period for at least 5 months after the last dose of study drug, and agreement to refrain from donating eggs during this same period

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

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

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

<u>Exclusion Criteria</u>

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

- Bilateral synchronous tumors with inheritable forms of RCC including von Hippel-Lindau
- Any approved anti–cancer therapy, including chemotherapy or hormonal therapy, within 3 weeks prior to initiation of study treatment

  Hormone–replacement therapy or oral contraceptives are allowed.
- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days or five half–lives of the investigational agent, whichever is longer, prior to enrollment
- CNS metastases or leptomeningeal disease

- Malignancies other than RCC within 5 years prior to Cycle 1, Day 1

  Patients with low–risk prostate cancer (defined as Stage cT1/T2a, Gleason score ≤6 and PSA ≤10 ng/mL) who are treatment–naive or who have been treated definitively with surgery or radiation and who are currently undergoing 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 (e.g., adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ of the breast treated surgically with curative intent)

  No evidence of recurrence or metastasis by follow-up imaging and any disease-specific tumor markers
- Life expectancy of <24 weeks
- Pregnancy or lactation, or intending to become pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
- Serum albumin <2.5 g/dL
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

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

  Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only are permitted provided that they meet the following conditions:

  Rash must cover less than 10% of body surface area (BSA)

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

  No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
- Patients with prior allogeneic stem cell or solid organ transplantation
- 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 CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class III or greater), myocardial infarction within 3 months prior to initiation of study treatment, unstable arrhythmias, or unstable angina
- Patients with a known left ventricular ejection fraction (LVEF) <40%.

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

- Positive test for HIV

  Documentation of HIV testing is required. The most recent testing must have occurred within 3 months prior to randomization. If such testing has not been done, it must be performed during screening.
- Patients with active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

  Documentation of HBsAg, hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), and hepatitis C virus (HCV) antibody testing is required. The most recent testing must have occurred within 3 months prior to randomization. If such testing has not been done, it must be performed during screening

  Patients with a positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening are eligible. The HBV DNA test will be performed only for patients who have a positive total HBcAb test.

  Patients with a positive HCV antibody test followed by a negative HCV RNA test at screening are eligible. The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- Active tuberculosis
- Severe infections within 4 weeks prior to initiation of study treatment including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Receipt of therapeutic oral or intravenous (IV) antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease or for dental extraction) are eligible.
- Major surgical procedure within 4 weeks prior to initiation of study treatment or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis.
- Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment

  Patients must agree not to receive live, attenuated influenza vaccine, or any other live, attenuated vaccine, within 28 days prior to initiation of study treatment, during treatment, or within 5 months after the last dose of study drug.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- Prior treatment with CD137 agonists, anti–CTLA–4, anti–programmed death–1 (PD-1), or anti–PD–L1 therapeutic antibody or pathway-targeting agents
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferons or interleukin–2) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to initiation of study treatment
- Treatment with systemic immunosuppressive medications (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to initiation of study treatment or anticipated need for systemic immunosuppressive medications during the study

  Patients who have received acute, low-dose (≤ 10 mg/day oral prednisone or equivalent), systemic immunosuppressant medications (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.

  The use of corticosteroids (≤ 10 mg oral prednisone or equivalent), physiologic replacement doses of glucocorticoids, and mineralocorticoids (e.g., fludrocortisone for non-autoimmune adrenal insufficiency) is allowed.

End of Study

The end of this study is defined as when the required numbers of deaths have been observed for the final analysis of overall survival (OS) in the intent–to–treat (ITT) population. Additionally, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from randomization of the first patient to the end of the study, is projected to be approximately 88 months.

Investigational Medicinal Products

The investigational medicinal product for this study is atezolizumab.

Test Product (Investigational Drug)

Atezolizumab

Atezolizumab 1200 mg will be administered IV q3w for 16 cycles or 1 year (whichever occurs first).

Comparator

Placebo

The placebo will be identical in appearance to atezolizumab and comprise the same excipients but without atezolizumab Drug Product. Placebo will be administered IV q3w for 16 cycles or 1 year (whichever occurs first).

Non–Investigational Medicinal Products

None

Statistical Methods

Primary Analysis

The primary efficacy endpoint is *investigator*-assessed DFS, defined as the time from randomization to *death from any cause or the* first documented recurrence assessed by *investigator, whichever occurs first. Recurrence is defined as any of the following: local recurrence of RCC, new primary RCC and distant metastasis of RCC.*

Data for patients without an *investigator*-assessed DFS event will be censored at the last date the patient was assessed to be alive and *investigator*-assessed recurrence free (or, for patients with no post-baseline disease assessment, at the randomization date).

Appropriate sensitivity analyses will be conducted for *investigator*-assessed DFS.

For U.S. registration purposes, the primary efficacy endpoint of *investigator*-assessed DFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with an *investigator*-assessed DFS event who missed two or more scheduled assessments immediately prior to the *investigator*-assessed DFS event will be censored at the last tumor assessment prior to the missed visits.

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

Kaplan-Meier methodology will be used to estimate for each treatment arm the *investigator-assessed* DFS rate at specific timepoints (e.g., every 6 months or yearly) and to estimate median DFS; *Kaplan–Meier* curves will be produced. Brookmeyer–Crowley methodology will be used to construct the 95% CI for the median DFS for each treatment arm.

Determination of Sample Size

Type I Error Control

Type I error rate for this study is 0.05 (two–sided). To control the type I error rate at alpha = 0.05 (two–sided) for the primary endpoint of *investigator*-assessed DFS and the key secondary

endpoint of OS, the treatment arms will be compared in a hierarchical fashion. The analysis hierarchy will be *investigator*-assessed DFS followed by OS. *One* planned final analysis of *investigator*-assessed DFS *and* a total of three *planned* analyses of OS (two interim analyses and one final analysis) *will be performed by the Sponsor*. The analysis hierarchy will be implemented as follows:

Step 1: *Investigator*-assessed DFS will be evaluated at alpha = 0.05 (two–sided). The final analysis will be conducted when approximately 334 DFS events have occurred. The *investigator*-assessed DFS endpoint will be considered positive in the ITT population if statistical significance is achieved at the *DFS* final analysis.

Step 2: If the *investigator*-assessed DFS results are statistically significant at the *DFS* final analysis, alpha = 0.05 will be passed to the analysis of OS. At the *time of the investigator*-assessed DFS final analysis, *the first OS interim analysis will be performed and* it is projected that approximately 190 deaths will have occurred. The second interim and final analyses *of* OS will be conducted when approximately 222 and 254 deaths have occurred, respectively. For control of the familywise error rate at level 0.05, OS will be evaluated on the basis of the generalized Haybittle–Peto boundary (Haybittle 1971) for statistical significance, with *alpha boundaries for the two* interim *and* final analysis specified as the following: 0.036, 0.036, and 0.011. *If the investigator*-assessed DFS results are not statistically significant at the *DFS* final analysis, formal treatment comparison of OS will not be performed.

Investigator-Assessed Disease-Free Survival

The final analysis of the primary endpoint of *investigator*-assessed DFS will take place when approximately 334 DFS events have occurred (44% of 764 patients) on the basis of the following assumptions:

- Log–rank test (two–sided)
- Type I error rate (alpha) of 0.05 (two–sided)
- 1:1 randomization ratio
- 5% loss to follow–up over 24 months
- Median DFS for the control (placebo) arm of 47 months and estimated median DFS in the atezolizumab arm of 67 months (corresponding to a HR of 0.70, under the proportional hazard assumption)
- 90% power

Accrual of the planned 764 patients is projected to occur over 33 months, assuming a ramp–up period of 8 months. On the basis of these assumptions, the required number of DFS events for final analysis is projected to occur at Month 67 after the first patient is randomized; minimum follow–up at the time of the *investigator*-assessed DFS *final* analysis will be 34 months. Also on the basis of these assumptions, it is projected that an observed HR of ≤ 0.80 at the final analysis will result in a statistically significant difference (i.e., minimally detectable difference) between treatment arms. An HR of 0.80 corresponds to an improvement of 12 months in median DFS, from 47 months in the control (placebo) arm to 59 months in the atezolizumab arm.

Overall Survival

The final analysis of the secondary endpoint of OS will take place when approximately 254 deaths have occurred (33% of 764 patients), on the basis of the following assumptions:

- Log–rank test (two–sided)
- Type I error rate (alpha) of 0.05 (two–sided)
- 1:1 randomization ratio
- 2% loss to follow–up over 24 months for OS
- Two interim analyses for OS will take place when approximately 190 and 222 deaths have occurred, respectively
- Alpha boundary is set to be 0.036, 0.036, and 0.011 for the three analyses of OS
- Median OS for the control (placebo) arm of 100 months and estimated median OS in the atezolizumab arm of 143 months (corresponding to HR of 0.70)
- 75% power

On the basis of these assumptions and projected accrual, the required number of OS events for the final analysis of OS is projected to occur at Month 88 from the time the first patient is randomized. Also on the basis of these assumptions, it is projected that an observed HR of $\leq$0.73 and 0.75 at the first and second interim analyses, and HR of $\leq$0.72 at the final analysis of OS, respectively, will result in a statistically significant difference (i.e., minimally detectable difference) between treatment arms.

Interim Analyses

There is no planned interim efficacy analysis of the primary endpoint of *investigator*-assessed DFS for this study. A total of three analyses of OS will be performed (two interim analyses and one final analysis). OS will be evaluated on the basis of the generalized Haybittle–Peto boundary (Haybittle 1971) for statistical significance, with p–*value boundaries* at each interim or final analysis specified as the following: 0.036, 0.036, and 0.011.

The first interim analysis of OS will be performed at the time of the *investigator*-assessed DFS analysis (projected to occur at Month 67 after the first patient is randomized), if DFS is statistically significant. On the basis of the projected median OS for each treatment arm, the projected number of deaths observed at the DFS analysis is approximately 190 deaths (25% of 764 patients), which corresponds to approximately 75% of the number of deaths required for the final analysis of OS. The observed HR of OS that is projected to result in a statistically significant difference between treatment arms at the DFS analysis is less than or equal to 0.73.

The second interim analysis of OS will be performed when approximately 222 deaths have occurred (29% of 764 patients), corresponding to approximately 87.5% of the number of deaths required for the final analysis of OS. The required number of OS events for the second interim analysis of OS is projected to occur at Month 77. The observed HR that is projected to result in a statistically significant difference between treatment arms at this analysis is OS HR 0.75 or lower.

The boundary for statistical significance at the OS interim and final analyses will be adjusted based on the actual number of events observed. Specifically, if at the DFS analysis, the observed number of OS events is significantly less than the projected 190 events, a nominal alpha value (1E–05) will be spent at the first OS interim analysis and the team will conduct another interim analysis of OS when 190 events have occurred.

Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct an additional interim efficacy analysis beyond what is specified in the protocol (e.g., an additional interim analysis of OS). This is because the external data such as results for other atezolizumab or competitor studies may indicate the need for an unplanned interim analysis (e.g., due to a treatment effect that is substantially larger than currently assumed). Below are the specifications in place to ensure that the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details (including type I error control) for the analysis, will be documented in the Statistical Analysis Plan (SAP), and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC Charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy) if necessary, and the iDMC Charter will also be made available to relevant health authorities.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
anti–HBc	antibody to hepatitis B core antigen
ADA	anti–drug antibody
CRS	cytokine-release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
DFS	disease–free survival
DMFS	distant metastasis–free survival
DSS	disease–specific survival
DOR	duration of response
EAU	European Association of Urology
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	*event-free survival*
ESMO	European Society for Medical Oncology
FDG	fluorodeoxyglucose
FFPE	formalin–fixed paraffin–embedded
FKSI–19	Functional Assessment of Cancer Therapy Kidney Symptom Index–19
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
IC	tumor–infiltrating immune cell
ICH	International Conference on Harmonisation
iDMC	Independent Data Monitoring Committee
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board

Abbreviation	Definition
IRF	Independent Review Facility
IRR	infusion–related reaction
ITT	intent to treat
IV	Intravenous
IxRS	interactive voice/Web response system
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NED	no evidence of disease
NGS	next–generation sequencing
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PD–1	programmed death–1
PD–L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression–free survival
PK	Pharmacokinetic
PRO	patient–reported outcome
q3w	every 3 weeks
R0	complete surgical resection
RBR	Research Biosample Repository
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SSIGN	stage, size, grade, and necrosis
TKI	tyrosine kinase inhibitor
TNF	tumor necrosis factor
TNM	tumor, lymph node, metastasis (classification)
ULN	upper limit of normal
UISS	University of California Los Angeles integrated staging system
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VHL	von Hippel–Lindau gene
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON RENAL CELL CARCINOMA

Metastatic renal cell carcinoma (RCC) is the most lethal urologic cancer and the sixth leading cause of cancer deaths in developed nations. Worldwide in 2012 there were an estimated 337,860 new diagnoses and approximately 143,369 deaths secondary to RCC (Ferlay et al. 2015). In the United States in 2016, it is estimated that there will be 62,700 new cases and 14,240 deaths attributable to cancers of the kidney and renal pelvis (American Cancer Society 2016). In developed nations, the average age-adjusted incidence of RCC is approximately 12 in 100,000 men and 5 in 100,000 in women (Patel et al. 2006). The RCC age–adjusted incidence has been rising for the past 30 years within the United States and most European nations at an annual rate of approximately 3% (Chow et al. 2010). Active and passive smoking, hypertension, genetics, and obesity have been identified as risk factors and may contribute to the rising incidence. In addition, the rising use of medical imaging has led to increased detection of asymptomatic lesions and an ensuing rise in incidence rates.

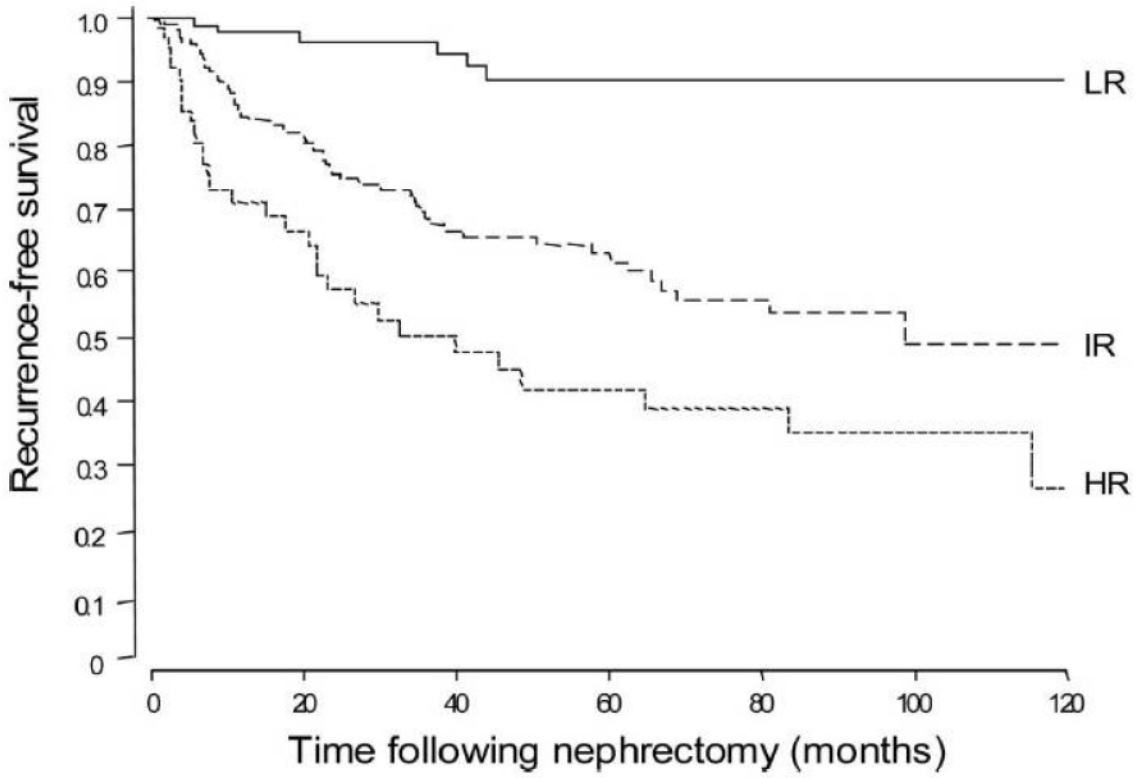
RCC has several histologic types, each arising from distinct regions of the renal epithelia, caused by a distinct set of gene mutations and exhibiting a unique clinical course. The most common types of epithelial renal tumors include the following: clear-cell RCC (75%), type 1 (5%) and type 2 (10%) papillary, chromophobe (5%), and oncocytoma (5%) (Motzer et al. 1997). Both sporadic and inherited forms of clear-cell RCC are strongly associated with mutations in the von Hippel–Lindau (VHL) gene. Clear-cell RCC is a highly vascular tumor that arises from epithelial elements within proximal tubules of nephrons. An early event during the evolution of clear–cell RCC is loss of function mutation of the VHL gene (Latif et al. 1993). Inactivation of the VHL gene leads to overexpression of vascular endothelial growth factor (VEGF), a growth hormone which functions to stimulate growth and angiogenesis. Sarcomatoid transformation/histologic changes can occur in any subtype of RCC and portends a poor prognosis (Ljungberg et al. 2015).

1.1.1 Early–Stage Renal Cell Carcinoma

In the adjuvant setting, prognosis is affected by pathologic, clinical, and molecular factors. Pathologic factors include the anatomic tumor, lymph node, metastasis (TNM) classification, Fuhrman nuclear grade, RCC subtype, sarcomatoid features, microvascular invasion, and tumor necrosis (Sun et al. 2011; Ljungberg et al. 2015). For localized RCC, several risk scores and nomograms have been used, including the Mayo Clinic stage, size, grade, and necrosis (SSIGN) score, Leibovich score (LS) (modified SSIGN score), the University of California Los Angeles (UCLA) integrated staging system (UISS), and the Karakiewicz nomogram. All of these risk scores and nomograms include assessment of TNM and Fuhrman grade. Clinical factors such as patient symptoms and performance status appear prognostic in some scoring systems (Sun et al. 2011). Molecular markers, including a 16–gene assay, are still under investigation (Rini et al. 2015).

UISS is a validated prognostic index that incorporates TNM staging, Fuhrman grading, and performance status (Zisman et al. 2001, 2002). This index is superior to stage alone in differentiating a patient's survival. It classifies patients into low–, intermediate–, and high-risk groups and has been externally validated in a large study of 4204 patients at eight academic centers (Patard et al. 2004). For localized RCC, the 5–year survival rates were 92%, 67%, and 44% for low, intermediate, and high risk patients, respectively. In a UCLA–specific study of 559 patients, the index also differentiated recurrence risk for localized RCC, with 5–year recurrence–free rates of 90.4% (low risk = LR), 61.8% (intermediate risk = IR), and 41.9% (high risk = HR), respectively (Lam et al. 2005); see Figure 1. Simplification of this system to staging and grading has been employed to assess recurrence risk in five of six recent adjuvant RCC studies (Pal and Haas 2014); see Table 1.

Figure 1 Kaplan–Meier Estimate of Recurrence–Free Survival following Nephrectomy among UISS Risk Groups



Source: Lam et al. 2005.

Table 1 Completed and Ongoing Studies of Adjuvant Targeted Treatment in Patients with Localized Renal Cell Carcinoma

Study (Sponsor)	Randomization	Duration of Therapy (Years)	N	Start Date	End Date[a]	Primary Endpoint	Clear Cell Required	Details
ASSURE (ECOG)	Sunitinib versus sorafenib versus placebo	1	1943	April 2006	September 2010	DFS	No	Eligibility: pT1bN0M0 (Grades 3–4) or pT2-4N1-3M0 RCC Histology: Any Accrual approximately 50% complete
ATLAS (Pfizer)	Axitinib versus placebo	3	592	April 2012	June 2017	DFS	Yes	Eligibility: pT2–4N0M0 or pTxN1M0 RCC
EVEREST (SWOG)	Everolimus versus placebo	1	1218	April 2011	October 2021	DFS	No	Eligibility: pT1bN0M0 (Grades 3–4) or pT2–4N1-3M0 RCC Histology: Any Accrual ~50% complete
PROTECT (GSK)	Pazopanib versus placebo	1	1500	November 2010	April 2016	DFS	Yes	Eligibility: pT2N0M0 (Grades 3–4) or pT3–4N0M0 or pTxN1M0 RCC
SORCE (MRC)	Sorafenib versus placebo	1	1420	June 2007	December 2012	DFS	No	Eligibility: Intermediate– or high–risk RCC (Leibovich score, 3–11)
S-TRAC (Pfizer)	Sunitinib versus placebo	3	720	July 2007	November 2015	DFS	Yes	Eligibility: High-risk RCC (modified UISS criteria) pT3–4N0M0 or pTxN1M0 RCC

DFS = disease-free survival; ECOG = Eastern Cooperative Oncology Group; 5-FU = 5-fluorouracil; GSK = GlaxoSmithKline; M = metastasis; MRC = Medical Research Council; N = regional lymph nodes; OS = overall survival; RCC = renal cell carcinoma; T = primary tumor; UISS = UCLA Integrated Staging System.

[a] Study completion date reflects estimated primary completion date cited at http://www.clinicaltrials.gov or actual date of complete enrollment.

Source: Pal and Haas 2014.

1.2 TREATMENT FOR EARLY–STAGE RENAL CELL CARCINOMA

For patients who present with early–stage RCC, nephrectomy is the standard of care (Ljungberg et al. 2015). Among patients with localized RCC who undergo nephrectomy, 78% of surgeries are open radical nephrectomy and 16% are open partial nephrectomy (Bianchi et al. 2013). After surgery, whereas patients with Stage I RCC have a 5–year survival of >90%, patients with stage II or III RCC disease have a 5–year relapse rate of 30%–40%, representing a critical unmet need (Escudier et al. 2014). Risk reduction strategies for this population remain an important goal. Currently, sunitinib has been approved in the United States as adjuvant treatment after nephrectomy in high–risk patients who have undergone complete resection of their tumor (National Comprehensive Cancer Network [NCCN] Guidelines 2018). Observation remains as one standard of care after nephrectomy, and eligible patients should be offered enrollment in randomized clinical studies (NCCN 2018; European Society for Medical Oncology [ESMO] guidelines 2014).

1.2.1 Treatment for Patients with Oligometastatic Disease

Definitive therapy for oligometastatic disease may be considered and performed in selected patients with limited metastatic disease for whom complete surgical resection (R0) is an option. These patients may include those with resectable pulmonary metastases, solitary abdominal metastases, or nodal disease. Retrospective studies suggest metachronous metastasectomy may provide a survival benefit and/or delay in systemic therapy in selected patients with limited metastatic disease and, in particular, those with a long disease–free interval or solitary metastasis after nephrectomy (Karam et al. 2011; Dabestani et al. 2014). Patients may also be candidates for synchronous metastasectomy (typically synchronous adrenal or pulmonary metastasis) at the time of nephrectomy. Whereas some patients experience long–term survival, most patients with synchronous metastasis who undergo nephrectomy and metastasectomy remain at high risk of disease recurrence (Eggener et al. 2008; Dabestani et al. 2014).

For these patients, systemic treatment after metastasectomy is not recommended in the ESMO guidelines (Escudier et al. 2014), and the most recent NCCN or EAU guidelines do not have specific comments for this unique population. This underscores the lack of effective therapies and dearth of studies in this at–risk population.

1.2.2 Anti–VEGF Adjuvant Strategies in Renal Cell Carcinoma

Clear–cell RCC is associated with an overproduction of VEGF due to the mutation/inactivation of the VHL tumor–suppressor gene (George and Kaelin 2003; Kaelin et al. 2003). Several agents that target the VEGF pathway (sunitinib, pazopanib, bevacizumab, axitinib, sorafenib) are approved for the treatment of metastatic RCC. These studies have demonstrated significant anti-tumor activity (e.g., by objective responses and prolonged progression–free survival [PFS]) in the metastatic setting but thus far have demonstrated limited benefit in the adjuvant setting.

Recent adjuvant studies of RCC employ vascular endothelial growth factor receptor (VEGFR) –directed therapies as an extrapolation from metastatic studies. The recent ASSURE (ECOG 2805) study of 1,943 patients with T1bNx (Fuhrman 3–4) or greater disease randomized subjects to sunitinib, sorafenib, or placebo for one year (Haas et al. 2015); median disease–free survival (DFS) was unchanged at 5.6 years (HR 1.0) versus 5.6 years (HR 0.97) versus 5.7 years, respectively (Haas et al. 2016). In addition, these treatments did not improve median DFS in high–risk patients (pT3 or higher or node-positive) in this study with a median DFS of approximately 48 months (see Table 2; Haas et al. 2017).

The PROTECT trial evaluated the efficacy of pazopanib to placebo in 1538 patients with high–risk clear cell renal cell carcinoma. The study was modified to lower the pazopanib dose from 800 mg to 600 mg due to toxicity; ITT analysis was performed for patients who received 600 mg once daily. The median DFS was not reached in both treatment groups (HR = 0.862, 95% CI: 0.699 to 1.063, p = 0.1649; Motzer et al. 2017).

The STRAC study enrolled 615 patients with T3 or higher or node–positive disease to compare 1–year treatment with sunitinib to placebo. The median DFS was 6.8 years in the sunitinib group and 5.6 years in the placebo group, with a HR of 0.76 (95% CI, 0.59 to 0.98) and $p < 0.03$. Overall survival was immature at the time of DFS analysis (Ravaud et al. 2016). The median DFS for UISS high–risk patients was 6.2 years in the sunitinib group and 4.0 years in the placebo group (see Table 2) (Motzer et al. 2018).

The three recent studies described above, which all employ VEGFR–directed therapies in the adjuvant RCC setting (ASSURE, PROTECT, and STRAC), are consistent in their estimation of median DFS for high–risk patients in the control placebo arms with approximately 47 months, 48 months, and 48 months, respectively (see Table 2 below). Therefore, median control arm DFS assumption has been updated for this trial from 36 months to 47 months. See Section 6.1 for a full description of sample size calculation.

Table 2 Adjuvant Renal Cell Carcinoma Studies: Control Arm Median Disease-Free Survival

Study	High–Risk Population	Control Arm Treatment	Median DFS	N
STRAC [a]	T3/≥G2/PS≥1, T4, any T/N+	Placebo	48 mo	388 (sunitinib n=194; placebo n=194)
ASSURE [b]	≥T3/any G, any T/N+	Placebo	~ 47 mo	1069 (sunitinib n=358; sorafenib n=355; placebo n=356)
PROTECT [c] (800 mg only)	T2≥G3, ≥T3/any G, any T/N+	Placebo	~ 48 mo	403 (pazopanib n=198; placebo n=205)

DFS=disease–free survival; mo=months; PS=performance status.

[a] Motzer et al. 2018.

[b] Haas et al. 2017.

[c] Motzer et al. 2017.

Based on the results from the STRAC study, sunitinib was approved as an adjuvant treatment for high–risk RCC patients in the United States. The use of sunitinib was not approved by the European Medicines Agency because the benefits were regarded as not outweighing the safety risks. Therefore, there remains significant unmet medical need for reducing the risk of recurrence with an efficacious, well-tolerated treatment for patients with RCC in the adjuvant setting.

1.2.2.1 Immune–Based Adjuvant Strategies in Renal Cell Carcinoma

Immunotherapy has historically played a significant role in the management of metastatic RCC. Treatment using interferon (IFN)–α results in objective responses in approximately 5% of patients with RCC. Immunotherapy with high dose interleukin (IL)-2 is associated with an infrequent, yet durable long–term benefit (approximately 10% durable response rate [Yang et al. 2006]). Numerous efforts with immune based therapies such as IL–2 and IFN–α have been made in the adjuvant setting in varying countries and cooperative settings, but each of these studies was negative (Pizzocaro et al. 2001; Messing et al. 2003; Clark et al. 2003; Atzpodien et al. 2005).

One positive adjuvant immunotherapy study involved an autologous tumor vaccine that was injected intradermally (Joacham et al. 2004). The hazard ratio (HR) for progression (1.58, CI: 1.05 to 2.37) and 5-year DFS follow–up favored the vaccine (67.8% in observation vs. 77.4% in the vaccine arm). However, imbalances in patient characteristics, high post-randomization dropout, and the open-label design limit the interpretability of these results. Girentuximab, an antibody to carbonic anhydrase IX,

was studied in the Phase III ARISER study (Belldegrun et al. 2013). Intermediate and high-risk patients were randomized to receive IV girentuximab weekly for 24 weeks versus IV placebo. No difference in DFS or OS was observed (5 year DFS was 53.9% for girentuximab vs. 51.6% for placebo). However, an unplanned analysis in patients with high expression of carbonic anhydrase IX did indicate a DFS advantage for patients receiving girentuximab.

In Keynote-564 study, a randomized phase III trial evaluating pembrolizumab vs placebo in patients with intermediate-high, or high risk mRCC who had undergone nephrectomy, the primary endpoint of DFS per investigator assessment was met [hazard ratio (HR) 0.68, 95% confidence interval (CI): 0.53-0.87, P =0.001]. The estimated 24 month DFS rate was 77% versus 68% for pembrolizumab and placebo, respectively. Overall survival (OS) showed a non-statistically significant trend towards a benefit in the pembrolizumab arm (HR 0.54, 95% CI 0.30-0.96, P =0.0164). Follow up was short and few OS events occurred [2 year OS rate of 97% (pembrolizumab) versus 94% (placebo)] (Choueiri et al. 2021).

1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets programmed death–ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, programmed death–1 (PD-1) and B7–1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab is expected to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity. Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody–mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer, small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

1.3.1 Nonclinical Studies with Atezolizumab

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration. Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab provided adequate safety factors for clinical development in oncology patients. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1 pathway.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical studies.

1.3.2 Clinical Studies with Atezolizumab

Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti–cancer therapies. Safety, efficacy, pharmacokinetic (PK), and immunogenicity data are summarized below for patients treated with atezolizumab as a single agent in the Phase Ia Study PCD4989g, a multicenter, first–in–human, open–label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered by IV infusion every 3 weeks (q3w) to patients with locally advanced or metastatic solid or hematologic malignancy. Study PCD4989g represents the largest cohort of patients who have been followed for the longest duration with atezolizumab.

Refer to the Atezolizumab Investigator's Brochure for details on clinical studies.

1.3.2.1 Summary of Clinical Safety of Atezolizumab

Safety data have been derived from patients who received atezolizumab as a single agent in the Phase Ia Study PCD4989g. As of the data cutoff date of 15 December 2015, the clinical database of Study PCD4989g contained safety data from 629 patients who received atezolizumab at doses ranging from 0.01 to 20 mg/kg across multiple tumor types, the most common of which were non–small cell lung cancer (NSCLC), urothelial carcinoma, and RCC. No dose-limiting toxicities or dose-related trends have been observed, and no maximum tolerated dose (MTD) has been determined. All data below are based on the 15 December 2015 cutoff date unless otherwise stated.

Summary of Adverse Events

Adverse events were reported in 619 of the 629 safety–evaluable patients (98.4%) in Study PCD4989g. The following adverse events occurred in ≥10% of patients: fatigue, decreased appetite, nausea, pyrexia, constipation, cough, dyspnea, diarrhea, anemia, vomiting, asthenia, back pain, headache, arthralgia, pruritus, rash, abdominal pain, insomnia, peripheral edema, urinary tract infection, dizziness, and chills. Treatment-related adverse events were reported in 444 patients (70.6%). Grade ≥3 adverse events were reported in 316 of 629 patients (50.2%), with 86 patients (13.7%) experiencing treatment–related Grade ≥3 events. The following Grade ≥3 treatment-related adverse events occurred in ≥0.8% of patients: increased AST, fatigue, asthenia, dyspnea, and hyponatremia.

Serious adverse events were reported in 261 of 629 patients (41.5%), with 57 patients (9.1%) experiencing treatment–related serious adverse events. The following treatment-related serious adverse events occurred in ≥0.3% of patients: pyrexia, malaise, fatigue, colitis, bone pain, dyspnea, hypoxia, and pneumonitis.

Adverse events that led to treatment withdrawal were reported in 5.4% of patients.

Three deaths were assessed by the investigator and/or the Sponsor as related to atezolizumab: death (cause not otherwise specified), death due to pulmonary hypertension, and death due to hepatic failure.

Immune-Mediated Adverse Events

Given the mechanism of action of atezolizumab, immune–mediated adverse events have been closely monitored during the atezolizumab clinical program. On the basis of the cutoff date of 11 May 2015, immune–mediated adverse events occurred in 189 of 588 patients (33.9%) in Study PCD4989g. The most common immune–mediated adverse events (occurring in $>2\%$ of patients) were pneumonitis, neuropathy peripheral, hypothyroidism, increased ALT, increased blood bilirubin, increased AST, rash, and maculopapular rash.

Adverse Events in Patients with Metastatic Renal Cell Carcinoma

Nearly all patients (97.2%) reported at least one adverse event; the most common ($\geq 20\%$ of patients) were fatigue (43.1%), cough (34.7%), arthralgia (30.6%), nausea and decreased appetite (27.8% each), constipation (26.4%), pyrexia (25.0%) back pain (23.6%), diarrhea and dyspnea (22.2% each) and anemia (20.8%). Related adverse events were reported in 83.3% (60 of 72 patients; the most common ($\geq 10\%$ of patients) were fatigue (30.6%), chills (11.1%), influenza–like illness (11.1%), and pyrexia (11.1%); rash (13.9%) and pruritus (13.9%); nausea (12.5%) and diarrhea (13.9%); decreased appetite (16.7%); arthralgia (13.9%); and anemia (11.1%).

Grade 3 adverse events were reported in 45.8% of patients; the most common ($\geq 3\%$ of patients) were anemia (6.9%), dyspnea (9.7%), pleural effusion (4.2%), asthenia (4.2%), pathological fracture (4.2%), and fatigue (4.2%). Four patients experienced a Grade 4 adverse event: hyperuricemia (non-treatment related), hypercalcemia (non–treatment related), increased aspartate aminotransferase (treatment related) and suicide attempt (drug attribution not reported). Treatment-related Grade 3 adverse events were reported in 15.3% of patients; the most common ($\geq 3\%$ of patients) were anemia (4.2%), and fatigue (4.2%). A comprehensive safety profile is described in McDermott et al. 2016. Serious adverse events were reported in 37.5% of patients. Serious adverse events reported in $\geq 2\%$ of patients included pyrexia (5.6%), dyspnea (5.6%), pleural effusion (4.2%), and pathological fracture (4.2%). No deaths were identified in this RCC cohort (note that the fatal event of “sudden death” stated previously did not occur within the adverse event reporting period and was reported as unrelated to study drug). Treatment–related serious adverse events were reported in 11.1% of patients (8 of 72) and included the following events, each in 1 patient: influenza like illness (Grade 3); pyrexia (Grade 1); myasthenia gravis (Grade 2); pyrexia (Grade 2); dyspnea (Grade 3); ataxia (Grade 2); autoimmune hypothyroidism (Grade 2); suicide attempt (Grade 4); and abdominal pain (Grade 2).

Based on the cutoff date of 11 May 2015, immune–mediated adverse events or adverse events of special interest were reported in 30 patients (42.9%). The majority of these patients experienced Grade 1 (27.1%) or Grade 2 (11.4%) adverse events of special interest with the remaining 4.3% of patients experiencing Grade 3 adverse events of special interest. Adverse events of special interest reported in ≥2 patients included rash (20.0%), hypothyroidism (10.0%), pneumonitis (4.3%, 3 of 70), psoriasis (2.9%), and maculopapular rash (2.9%).

Adverse events that led to treatment withdrawal were reported in 4.2% of patients. Events that led to treatment withdrawal included 1 patient with a Grade 4 suicide attempt, 1 patient with Grade 3 fatigue, and 1 patient with a non–serious gaze palsy (Grade 2) event.

Atezolizumab treatment was, in general, well tolerated, and safety data from the RCC cohort of Study PCD4989g were consistent with the safety profile exhibited by the overall population in this study.

1.3.2.2 Summary of Clinical Efficacy of Atezolizumab

Efficacy data have been derived from patients who received atezolizumab as a single agent in Study PCD4989g. Clinical efficacy of atezolizumab monotherapy was observed in a broad range of malignancies, including NSCLC, urothelial carcinoma, RCC, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. Efficacy results based on a data cutoff date of 2 December 2014 are summarized below for the RCC cohort. Refer to the Atezolizumab Investigator's Brochure for information on efficacy in NSCLC, urothelial carcinoma, and other tumor types.

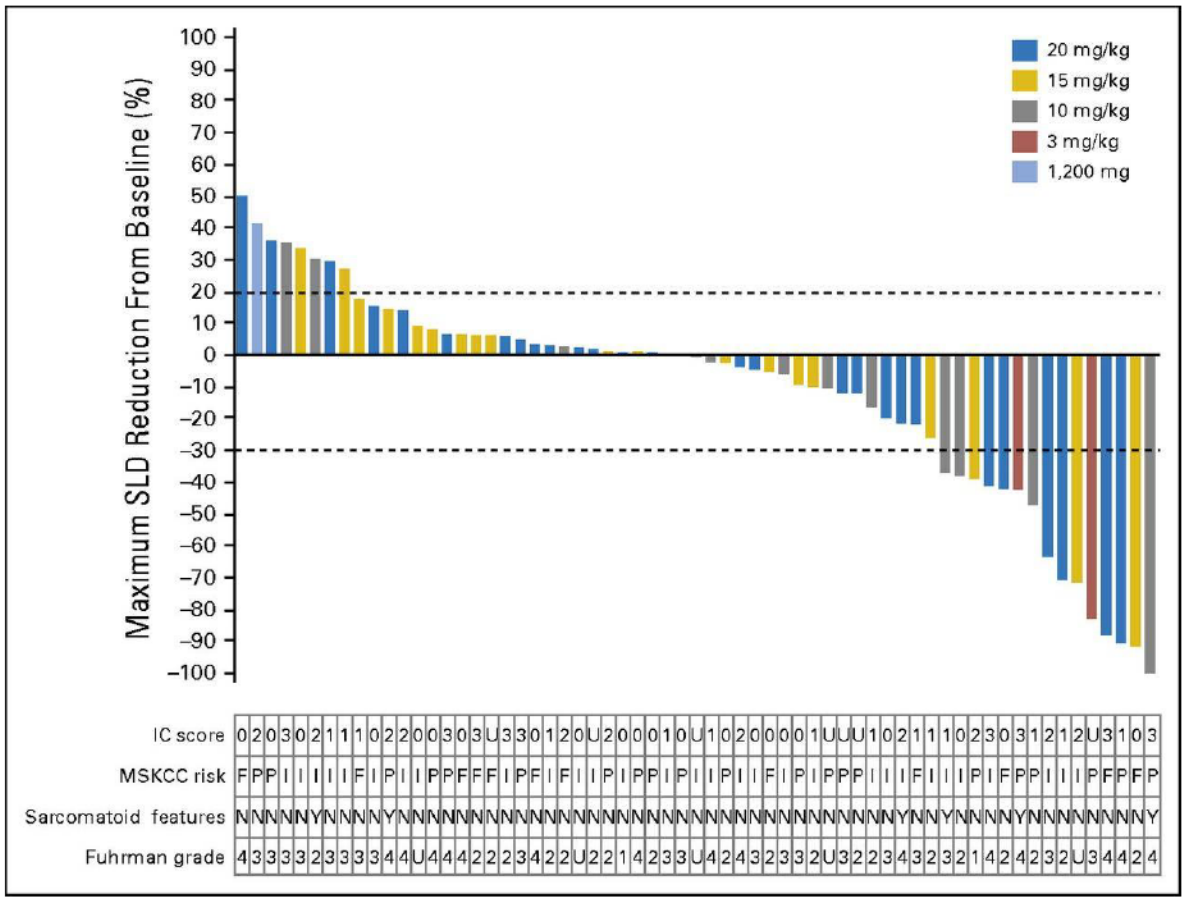
Efficacy in Metastatic Renal Cell Carcinoma

Seventy patients were enrolled in the RCC cohort of Study PCD4989g and represented a heavily pre–treated population, with 87% having received at least one prior systemic therapy and 57% having received two or more prior systemic therapies. The median duration of survival follow–up was 23.9 months (95% CI: 16.1 to 29.2; McDermott et al. 2016).

A total of 63 patients (90%) had clear–cell histology RCC, of which 62 were followed for a minimum of 12 weeks and were evaluable for efficacy. Among 62 efficacy evaluable patients with clear cell histology, the confirmed investigator-assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) was 15% (95% CI: 7% to 26%) with 1 complete and 8 partial responses. Four of 18 patients (22%) with aggressive Fuhrman Grade 4 and/or sarcomatoid histology achieved a confirmed response. In patients with a RECIST response, the median duration of response (DOR) was 17.4 months; 4 of the 9 responders had ongoing responses at the date of the clinical cutoff. When tumor shrinkage was examined overall, 46% of patients with clear cell RCC had a reduction in tumor burden

(see Figure 2). The median PFS was 5.6 months (95% CI: 3.9 to 8.2) and the median OS was 28.9 months (95% CI: 20.0 to not reached).

Figure 2 Atezolizumab Anti-Tumor Activity in Patients with Renal Cell Carcinoma in Study PCD4989g



F = MSKCC favorable risk; I = MSKCC intermediate risk; IC = tumor–infiltrating immune cell; MSKCC = Memorial Sloan Kettering Cancer Center; N = no; NE = not evaluable; P = MSKCC poor risk; PD–L1 = programmed death–ligand 1; U = unknown; Y = yes.

Notes: Waterfall plot of patients with clear–cell renal cell carcinoma, measuring the maximum reduction from baseline in the sum of the longest diameter (SLD) for target lesions; +20% and –30% are marked by dashed lines. PD–L1 IC score, MSKCC risk status, sarcomatoid features, and Fuhrman grade are given by patient.

Patients with RCC with ≥ 1% PD–L1 tumor–infiltrating immune cell (IC) expression as determined by IHC scoring (corresponding to IHC score of IC1/2/3) was associated with greater anti-tumor activity with atezolizumab than in patients with IC0 score (IHC PD–L1 staining < 1%). The confirmed ORR for IC1/2/3 patients was 18% versus 9% for IC0 patients. The 2-year OS rate was also higher for IC1/2/3 patients (65%) compared with IC0 patients (51%; see Table 3). Median OS was not reached for IC1/2/3, compared with 28.8 months (16.3 to 28.9) for patients with IC0 PD–L1 expression.

Table 3 Efficacy in Patients with Renal Cell Carcinoma (Clear Cell) by PD-L1 Status in Study PCD4989g (n=62)

PD–L1 Status	ORR by Investigator-Assessed RECIST v1.1 (95% CI)	Median DOR, months (range)	Median PFS, months (95% CI)	Median OS, months (95% CI)	2–Year OS (95% CI)
All patients (n=62)	15% (9) (7 to 26)	17.4 (7.6 to ≥27)	5.6 (3.9 to 8.2)	28.9 (20.0 to NR)	58% (43 to 73)
IC1/2/3 (n=33)	18% (6) (7 to 35)	14.9 (7.6 to ≥ 20.2)	5.6 (2.8- to, 9.0)	NR (20.0 to NR)	65% (45 to 86)
IC0 (n=22)	9% (2) (1 to 29)	NR (≥16.6 to ≥ 26.9)	4.5 (1.3 to 8.1)	28.8 (16.3 to 28.9)	51% (27 to 74)
IC Unknown (n=7)	14% (1) (0 to 58)	8.3 (8.3 to 8.3)	11.1 (4.3 to NR)	NR (11.7 to NR)	53% (5 to100)
Fuhrman Grade 4 and/or sarcomatoid (n=18)	22% (4) (6 to 48)	NA	4.2 (1.4 to 8.4)	NA	57% (31 to 83)

DOR=duration of response; IC=tumor–infiltrating immune cell; NR=not reached; ORR=objective response rate; OS=overall survival; PD–L1=programmed death-ligand 1; PFS= progression-free survival; RECIST v1.1=Response Evaluation Criteria in Solid Tumors Version 1.1.

Note: This table is based on a data cutoff of 2 Dec 2014. Patients with RCC were dosed by 4 October 2014.

The results from Study PCD4989g suggest that atezolizumab monotherapy has clinical activity in the heavily pre-treated metastatic RCC setting. The DOR suggests clinically meaningful benefit in those who respond to atezolizumab.

1.3.2.3 Clinical Pharmacokinetics and Immunogenicity

On the basis of available preliminary PK data from Study PCD4989g (for doses ranging 0.03–20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥1 mg/kg. On the basis of a population pharmacokinetic analysis that included 472 patients in the dose range of 1–20 mg/kg, the typical population clearance was 0.20 L/day, the volume of distribution at steady state was 6.9 L, and the terminal half-life was 27 days (see the Atezolizumab Investigator's Brochure for additional details).

The development of anti–drug antibodies (ADAs) has been observed in patients in all dose cohorts in Study PCD4989g and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). *Treatment-emergent ADA status appeared to have no clinically meaningful* impact on pharmacokinetics for

doses ranging 10–20 mg/kg. To date, no *clinically relevant* relationship between the ADA *status* and safety or efficacy has been observed. Patients who were dosed at the 10–, 15–, and 20 mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ADAs, and likely for this reason clinical efficacy does not appear to be affected.

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Encouraging clinical data that are emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors PD–1 and B7.1. Many human tumors have been found to overexpress PD–L1, which acts to suppress anti-tumor immunity. PD–1 is an inhibitory receptor that is expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer (Blank et al. 2005; Keir et al. 2008). Ligation of PD–L1 with PD–1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. PD–L1 binding to B7.1 on T cells and antigen-presenting cells can mediate downregulation of immune responses, including inhibition of T–cell activation and cytokine production (Butte et al. 2007; Yang et al. 2011).

Overexpression of PD–L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD–1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity. Tumor cell expression of PD–L1 in metastatic clear cell RCC is associated with poorer outcomes, including worse PFS as well as OS, even in the presence of active therapy with anti–VEGF inhibitors (Thompson et al. 2007; Choueiri et al. 2015; Iacovelli et al. 2016).

Targeting the PD–L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies whose disease has failed standard-of-care therapies or who have refused standard-of-care therapies. In Study PCD4989g, a Phase Ia dose-escalation and expansion study, objective responses with atezolizumab monotherapy were observed in a broad range of malignancies (see Section 1.3.2.2). In the RCC cohort, patients who had a PD-L1 expression of IC1/2/3 had a numerically better response rate and survival with atezolizumab than those with IC0 (McDermott et al. 2016). Nevertheless, atezolizumab appears to confer activity in patients with RCC tumors with a PD–L1 IHC of IC0 as well (see Section 1.3.2.2 and Section 3.3.3). In other atezolizumab studies in non–small cell lung cancer and urothelial cancer, although there is some association of PD–L1 expression with efficacy,

atezolizumab remains active in patients with low or no expression of PD-L1, particularly with regard to OS (Balar et al. 2016; Smith et al. 2016; Rosenberg et al. 2016). Given the broad activity of atezolizumab in patients with IC0 in the metastatic setting across diverse tumor types, atezolizumab may benefit patients with RCC in the adjuvant setting regardless of PD–L1 expression.

The safety profile of atezolizumab is well established, is consistent across indications, and has been generally well tolerated (see Section 1.3.2.1). Adverse events with potentially immune–mediated causes consistent with an immunotherapeutic agent, including hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain–Barré syndrome, myasthenic syndrome/myasthenia gravis, meningoencephalitis, and infusion–related reactions (IRRs) have been observed in clinical studies to date. To date, these events have been manageable with appropriate treatment and/or withholding of atezolizumab dose as needed.

Given the evidence of the clinical activity that includes durable response with atezolizumab in advanced and metastatic RCC, atezolizumab offers the potential for clinical benefit in patients with RCC in the adjuvant setting. This study will enroll patients who are classified as high risk in order to select a population that is at greatest risk of recurrence and death from RCC who are most likely to benefit from adjuvant atezolizumab therapy. Because most atezolizumab-related toxicities observed to date have been mild and transient in nature, it is anticipated that adjuvant treatment with atezolizumab will have a manageable safety profile and has an acceptable benefit–risk assessment for the conduct of the study.

Covid-19 Benefit–Risk Assessment

In the setting of the *coronavirus disease 2019 (*COVID-19*)* pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from *severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection*. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of *SARS-CoV-2 infection*.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from *SARS-CoV-2 infection* is altered by cancer immunotherapy.

Severe *SARS-CoV-2 infection* appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines IL-6, IL-10, IL-2, and interferon-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops acute SARS CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from COVID-19.

There may be potential synergy or overlap in clinical and radiologic features for immune mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for *SARS-CoV-2*–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and SARS-CoV-2 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of SARS-CoV-2 vaccination (Society for Immunotherapy of *Cancer [SITC] 2020).*

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering SARS-CoV-2 vaccines. When administered, SARS-CoV-2 vaccines must be given in accordance with the approved or authorized vaccine label.

2. OBJECTIVES AND ENDPOINTS

This is a Phase III, multicenter, randomized, placebo–controlled, double–blind study (IMmotion010) to evaluate the efficacy and safety of atezolizumab versus placebo in patients with RCC who are at high risk of disease recurrence following resection. Specific objectives and corresponding endpoints for the study are outlined in Table 4.

Table 4 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective	
• To evaluate the efficacy of adjuvant treatment with atezolizumab	• *Investigator*-assessed DFS, defined as the time from randomization to death from any cause or the first documented recurrence assessed by *investigator, whichever occurs first. Recurrence is* defined as any of the following: Local recurrence of RCC New primary RCC Distant metastasis of RCC
Secondary Efficacy Objective	
• To evaluate the efficacy of adjuvant treatment with atezolizumab	• Overall survival, defined as the time from randomization to death from any cause • Investigator-assessed DFS *in patients with PD-L1 expression status IC1/2/3** • *IRF-assessed DFS, defined as the time from randomization to death from any cause or the first documented recurrence assessed by IRF, whichever occurs first.* • IRF-assessed DFS in patients with *PD-L1 expression status* IC1/2/3* • *IRF-assessed event-free survival (EFS), defined as the time from randomization to death from any cause, or the first documented recurrence in patients without baseline disease by IRF or the first documented disease progression in patients identified as having baseline disease by IRF, whichever occurs first. Disease progression is defined as either unequivocal progression of baseline disease or new unequivocal lesions.* • Disease-specific survival, defined as the time from randomization to death from RCC • Distant metastasis–free survival, defined as the time from randomization to *death from any cause or* the date of diagnosis of distant (i.e., non-locoregional) metastases assessed by investigator*, whichever occurs first.* • 1–, 2–, and 3–year investigator-assessed DFS rate, defined as the probability of patients being alive and free of recurrence assessed by investigator *at* Year 1, 2, and 3 after randomization

• Secondary Efficacy Objective (cont.)	
	• *1–, 2–, and 3–year IRF-assessed DFS rate, defined as the probability of patients being alive and free of recurrence assessed by IRF at Year 1, 2, and 3 after randomization*
Safety Objective	
• To evaluate the safety and tolerability of atezolizumab in the adjuvant setting	• Incidence, nature, and severity of adverse events graded according to NCI CTCAE v4.0 • Changes in vital signs and clinical laboratory results
Pharmacokinetic Objective	
• To characterize the PK profile of atezolizumab	• Serum concentration of atezolizumab at specified timepoints
Immunogenicity Objectives	
• To evaluate the immune response to atezolizumab	• Prevalence of anti-drug antibodies (ADAs) to atezolizumab at baseline *and incidence of ADAs to atezolizumab after treatment*
• To explore the potential relationship of the immunogenic response	• Relationship between ADA *status* and PK (i.e., minimum serum concentration), safety, and efficacy *endpoints*
Exploratory Objectives	
• To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease recurrence *and overall survival*	• Tumor *and circulating* biomarkers (including, but not limited to PD-L1, PD-1, *prevalence of immune subsets, circulating factors, genomic mutations, gene expression, gene expression signatures of tumor and immune biology, and molecular subtypes),* as defined by IHC or qRT-PCR, NGS, and/or other methods will be correlated with efficacy measures.
• To document patients' perspective regarding treatment tolerability and health–related quality of life	• The Functional Assessment of Cancer Therapy Kidney Symptom Index 19 (FKSI-19)
• To measure health status for health economic modeling	• EQ–5D–5L questionnaire as a measure of patient reported health status to derive utilities
• To evaluate the efficacy of adjuvant treatment with atezolizumab among patients with tumor Fuhrman Grade 4 or sarcomatoid histology (defined by investigator-assessed conventional histopathology)	• *Investigator*-assessed DFS in patients with tumor Fuhrman Grade 4 or sarcomatoid histology (defined by the investigator-assessed conventional histopathology).

ADA=anti-drug antibody; DFS=disease free-survival; *EFS =event free survival,* EQ-5D-5L=EuroQoL 5-Dimension, 5-level version; IC=tumor-infiltrating immune cell; IHC=immunohistochemistry; IRF=Independent Review Facility; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0; NGS=next generation sequencing; PD-1=programmed death-1; PD-L1=programmed death ligand-1; PK=pharmacokinetic; qRT-PCR=quantitative reverse transcriptase=polymerase chain reaction; RCC=renal cell carcinoma

**PD-L1 IC0 is defined as <1% and IC1/2/3 is defined as ≥1% of tumor-infiltrating immune cells (IC) expressing PD-L1 as assessed by immunohistochemistry using SP142 assay.*

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, multicenter, randomized, placebo–controlled, double–blind study designed to evaluate the efficacy and safety of adjuvant treatment with atezolizumab versus placebo in patients with RCC who are at high risk for disease recurrence following resection.

Male and female patients aged ≥18 years of age who have histologically confirmed RCC and who have undergone nephrectomy and are classified as being at high risk of RCC recurrence are eligible for study participation. Patients who have not developed RCC metastases but are at high risk of recurrence are eligible on the basis of the following TNM/grading criteria as determined by the investigator: T2 Grade 4, T3a Grade 3–4, T3b/c any Grade, T4 any Grade, or TxN+ any Grade. Patients with metachronous recurrence no less than 12 months following nephrectomy who have undergone metastasectomy with a complete resection (R0 resection) of all sites of disease (restricted to lung, soft tissue, and lymph node) and have no evidence of disease recurrence are also eligible. Patients with synchronous metastases who have undergone complete resection of residual disease are eligible in the following circumstances: isolated solitary ipsilateral or contralateral adrenal metastasis treated with adrenalectomy and lung metastasis resected with a sublobar or lobar resection within 12 weeks of nephrectomy. The TNM/grading eligibility requirements do not apply to patients who enroll on the basis of resected metachronous or synchronous metastasis.

Patients who have received prior neoadjuvant or adjuvant therapy are not eligible for study participation.

Nephrectomy and/or metastasectomy tumor specimens from patients who meet eligibility criteria will be evaluated for PD–L1 expression. Patients must have sufficient amounts of viable tumor for IHC scoring of PD–L1 by the central pathology laboratory in order to be eligible. When tissue from both nephrectomy and metastatic specimens are available, submission of both specimens is recommended. The highest PD-L1 staining

score will be used for patients who provide both nephrectomy and metastasectomy specimens.

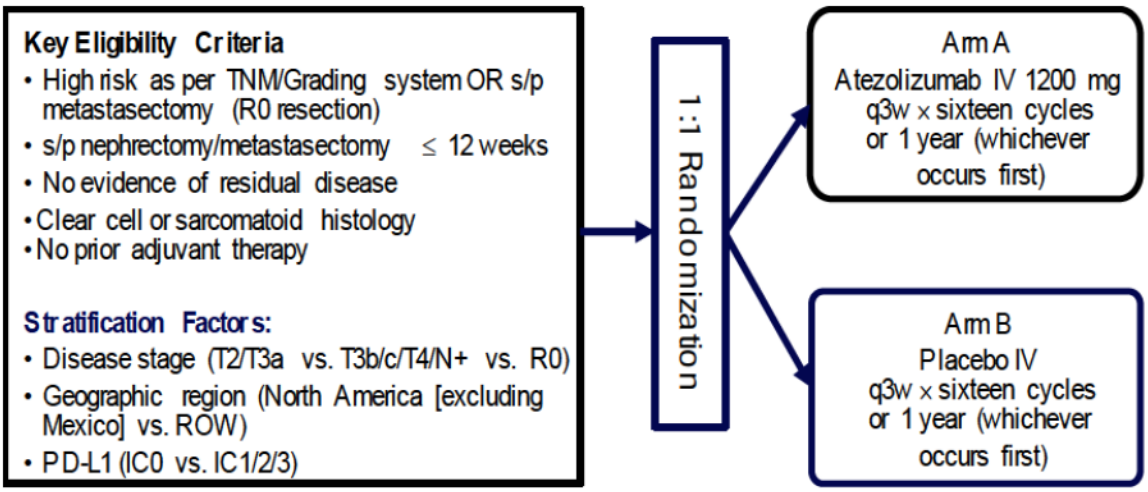
Approximately 764 patients at high risk for RCC recurrence [see below for high-risk definition]) will be randomized to one of the following arms in a 1:1 ratio:

- Arm A (experimental arm): Atezolizumab 1200 mg q3w for 16 cycles or 1 year (whichever occurs first)
- Arm B (control arm): Placebo q3w for 16 cycles or 1 year (whichever occurs first)

High–risk patients are defined as patients with any of the following:

- T2 Grade 4, T3a Grade 3–4, T3b/c any Grade, T4 any Grade, TxN+ any Grade
- Limited metachronous/synchronous recurrence in patients who undergo complete R0 resection of all sites of disease. These patients will be eligible regardless of their original TNM/grade.

Figure 3 Study Schema



IC=tumor–infiltrating immune cell; IV=intravenous; PD-L1=programmed death ligand–1; q3w=every 3 weeks; s/p=status post; ROW=rest of world.

Note: TNM/grading: High risk=T2 Grade 4, T3a Grade 3=4, T3b/c any Grade, T4 any Grade, TxN+= any Grade.

PD-L1 IC0 is defined as <1% and IC1/2/3 is defined as ≥1% of IC) expressing PD-L1 as assessed by immunohistochemistry using SP142 assay.

Randomization will be conducted with the aid of an interactive voice/Web response system (IxRS).

Randomization will be stratified by the following factors:

- Disease stage (T2/T3a vs. T3b/c/T4/N+ vs. patients with resected synchronous/metachronous metastasis [R0])
- Geographic region (North America [excluding Mexico] vs. rest of world)
- *PD–L1 IC0 vs IC1/2/3 (< 1% vs ≥ 1% of tumour-infiltrating immune cells (IC) expressing PD-L1 as assessed by immunohistochemistry using SP142 assay)*

Randomization should occur within 12 weeks after nephrectomy or metastasectomy, and study drug administration should begin within 5 calendar days after randomization.

3.1.1 Study Treatment

Patients in both treatment arms will receive up to 1 year of treatment with either atezolizumab or placebo. Treatment will be administered intravenously on Day 1 of each 21-day cycle. Treatment will be discontinued in the event of disease recurrence, unacceptable toxicity, consent withdrawal, or study termination by the Sponsor.

3.1.2 Study Assessments

Surveillance for tumor recurrence will be performed every 3 months +/– 2 weeks for 3 years after randomization. After 3 years, patients will undergo tumor assessment every 6 months ± 4 weeks thereafter until independent review facility (IRF)–assessed disease recurrence, death, consent withdrawal, or study termination by the Sponsor, whichever occurs first. Results of fluorodeoxyglucose positron emission tomography (FDG–PET) scans alone will not be sufficient for purposes of documenting disease recurrence. Disease recurrence will be as determined on the basis of radiographic evidence and whenever possible, supported/confirmed by biopsy results. Recommended guidelines for assessment of RCC disease recurrence are provided in Appendix 9 for the investigator. In the absence of IRF-assessed disease recurrence, tumor assessments should continue, regardless of whether patients start new anti-cancer therapy, until death, loss of follow–up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. Follow-up data capture, including subsequent anti–cancer therapies (including targeted therapies and immunotherapies) and subsequent disease progression, will continue for each patient until death, loss of follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patients will undergo a mandatory tumor biopsy sample collection, if clinically feasible as assessed by investigators, at the first evidence of suspected disease recurrence. These data will be used to confirm whether radiographic and clinical findings are consistent with the presence of tumor. In addition, these data will be analyzed for the association between changes in tumor biomarkers and clinical outcome and to further understand the potential mechanisms of resistance to atezolizumab.

Safety assessments will include the incidence, nature, and severity of adverse events; vital signs; and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Laboratory safety assessments will include the regular monitoring of hematology, blood chemistry, and urinalysis. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab. Patient samples, including archival tumor tissues as well as serum, plasma, and whole blood, will be collected for future exploratory biomarker assessments.

An external independent Data Monitoring Committee (iDMC) will evaluate safety data according to policies and procedures detailed in a separate iDMC Charter (see Section 3.1.4).

3.1.3 Number of Patients

A total of approximately 764 patients will be enrolled at approximately 215 centers globally.

3.1.4 Independent Data Monitoring Committee

An iDMC will be convened to evaluate safety data during the study. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. The iDMC will evaluate study safety data on a periodic basis, approximately every 6 months, until the time of the analysis of the primary efficacy endpoint. The Sponsor will remain blinded to treatment assignment information until the primary analysis has occurred.

All summaries and analyses by treatment arm for the iDMC review will be prepared by an external independent Data Coordinating Center. The safety data will include demographic data, adverse events, serious adverse events, and relevant laboratory data.

Following their data review, the iDMC will provide a recommendation to the Sponsor in accordance with the iDMC Charter. The final decision will rest with the Sponsor.

Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to Health Authorities and to investigators for notification to their Institutional Review Boards/Ethics Committees.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as when the required numbers of deaths have been observed for the final analysis of OS in the intent–to–treat (ITT) population (see Section 6). Additionally, the Sponsor may decide to terminate the study at any time.

The total length of the study, from randomization of the first patient to the end of the study, is projected to be approximately 88 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Dose and Schedule

The fixed dose of 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) q3w was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g, as described below.

The target exposure for atezolizumab was projected on the basis of nonclinical tissue distribution data in tumor–bearing mice, target–receptor occupancy in the tumor, the observed atezolizumab interim pharmacokinetics in humans, and other factors. The target trough concentration (C_{trough}) was projected to be 6 μg/mL, on the basis of several assumptions, including: 1) 95% tumor-receptor saturation is needed for efficacy and 2) the tumor-interstitial concentration to plasma ratio is 0.30 based on tissue distribution data in tumor-bearing mice.

The atezolizumab dose is also informed by available clinical activity, safety, PK, and immunogenicity data. Anti-tumor activity has been observed across doses ranging 1–20 mg/kg administered q3w. The MTD of atezolizumab was not reached, and no dose limiting toxicities have been observed at any dose in Study PCD4989g. Available preliminary PK data (0.03–20 mg/kg) from Study PCD4989g suggest that for doses ≥ 1 mg/kg q3w, overall, atezolizumab exhibits pharmacokinetics that are both linear and consistent with typical IgG1 antibodies.

Detectable ADAs were observed in patients at all dose levels but were associated with changes in pharmacokinetics for some patients in only the lower dose cohorts (0.3, 1, and 3 mg/kg). It is unclear from currently available data in these lower dose cohorts whether administration of higher doses to patients with both detectable ADAs and reduced exposure would necessarily restore exposure to expected levels. No clear relationship between the development of measurable ADAs and safety or efficacy has been observed. Available data suggest that the development of detectable ADAs does not appear to have a significant impact on pharmacokinetics for doses from 10 to 20 mg/kg administered q3w in most patients. Correspondingly, patients who were dosed at the 10–, 15–, and 20–mg/kg q3w dose levels have maintained target trough levels of drug despite the detection of ADAs.

Currently available PK and ADA data suggest that the 15 mg/kg atezolizumab q3w regimen (or fixed–dose equivalent) for Phase II and Phase III studies would be sufficient to both maintain $C_{trough} \geq 6$ μg/mL and further safeguard against both interpatient variability and the potential effect of ADAs that could lead to sub-therapeutic levels of atezolizumab. From inspection of available observed C_{trough} data, moving further to the 20 mg/kg atezolizumab q3w regimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15 mg/kg atezolizumab q3w level.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following fixed dose or dose adjusted for weight. On the basis of this analysis, a fixed dose of 1200 mg q3w is selected (equivalent to a body–weight–based dose of 15 mg/kg q3w).

The duration of time required to elicit an effective anti-tumor response in the adjuvant setting through PD–L1 inhibition is unclear. However, given the risk of recurrence in this RCC population and the existing safety profile of atezolizumab, it was felt that 1 year of adjuvant therapy balances the benefit–risk profile. Other adjuvant RCC studies commonly employ 1 or 3 years of adjuvant therapy (see Section 1.2.2).

3.3.2 Rationale for Patient Population

This study will enroll patients with RCC who are at high risk for disease recurrence following resection. The study will enroll patients irrespective of PD–L1 expression, (i.e., IC score of 0, 1, 2, or 3) as determined by IHC.

There is currently no widely accepted, effective adjuvant treatment for RCC, despite the recent approval of sunitinib in the United States. Advanced or metastatic RCC can be treated successfully with immune therapy and targeted therapy; however, such treatments have either not yet demonstrated efficacy or demonstrated limited efficacy in the adjuvant setting, and such approved therapies are associated with significant toxicities (e.g., diarrhea, rash, fatigue, hand–foot syndrome) that negatively affect quality of life. Further, the 5-year relapse rate for high–risk early–stage RCC is 30%–40% (Escudier et al. 2014). Therefore, there is a need for an efficacious, well-tolerated treatment for patients with RCC in the adjuvant setting.

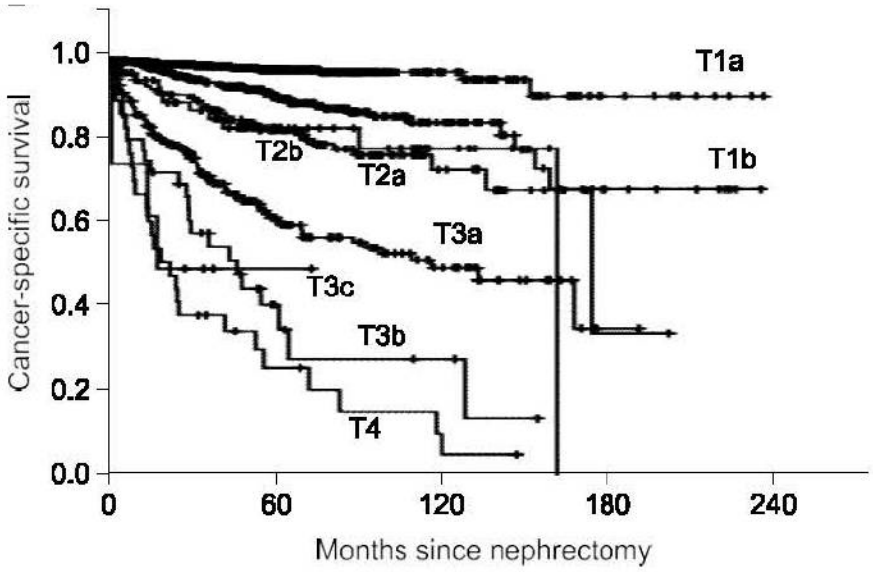
3.3.2.1 Inclusion of Patients Who are at High Risk of Renal Cell Carcinoma Recurrence

This study will enroll patients who are classified as being at high risk of RCC recurrence with use of a TNM/grading system whereby high risk is defined as T2 Grade 4, T3a Grade 3–4, T3b/c any Grade, T4 any Grade, or TxN+ any Grade in order to define a population that is at the greatest risk of recurrence and most likely to benefit from adjuvant atezolizumab therapy.

Both tumor grade and stage are associated with RCC survival and recurrence (Zisman et al. 2001, 2002; Lam et al. 2005). In an Italian study of 338 patients with T3 and T4 tumors, grade was strongly associated with RCC–specific survival. Five-year RCC survival was 69.9%, 73%, 43%, and 31% for Grades 1, 2, 3, and 4 respectively (Ficarra et al 2007). Grade was also strongly associated with RCC-specific survival for patients with T2 tumors. In a small study of 39 patients with T2 disease, those with Grade 3–4 tumors performed substantially worse than those with Grade 1–2 tumors (Minervini et al. 2002). Furthermore, a review of 706 patients with T2 tumors suggested grade was strongly associated with RCC-specific survival after multivariate analysis (HR 2.27 for Grade 3 and HR 3.76 for Grade 4) (Klatte et al 2007).

Higher stage, such as T3b, T3c, and T4, also had a poorer prognosis compared with T3a in large Korean study of 1691 patients with post-nephrectomy RCC (Lee et al. 2009). Five-year RCC–specific survival was 62.6% for T3a compared with 41.1%, 50%, and 26% for T3b, T3c, and T4, respectively (see Figure 4). Regional node involvement was also a strong predictor for RCC–specific mortality in this study with a 5–year RCC-specific survival of approximately 33% with nodal involvement.

Figure 4 Renal Cell Carcinoma–Specific Survival According to the 2009 Tumor Node Metastasis Classification



Source: Lee et al. 2009.

Specifically within the T3a stage, in an MD Anderson study of 365 patients with T3a disease, only grade (HR 1.5) and sarcomatoid status (HR 1.8) predicted RCC-specific mortality in a multifactorial analysis (Margulis et al. 2007). Patients who had regional lymph node involvement (HR=2.7 in a unifactorial analysis) also had a poorer prognosis.

Given the potential discrepancies in Fuhrman grading that have been described between local sites and a central review (Aydin et al. 2010) and the importance of grading for eligibility, monitoring of tumor samples for Fuhrman grading will be performed by a central laboratory.

3.3.2.2 Inclusion of Patients Who Have Undergone Metastasectomy

This study will include patients who have undergone complete metastasectomy to NED (no evidence of disease; R0 resection) status because this population is at very high risk of disease recurrence and therefore represents a high unmet medical need.

Most patients who undergo metastasectomy experience a recurrence, but there is a subset of patients that experiences long–term survival (Eggener et al. 2008;

Dabestani et al. 2014). In a study of 44 patients who underwent complete metastasectomy across diverse sites of metastasis, the 5–year survival rate was 49% (95% CI: 32% to 64%) for all patients and 71% (95% CI: 43 to 87) in the favorable risk group (Eggener et al. 2008). In a recent series of 138 patients who underwent metastasectomy, the most common sites for resection were lung (57%) followed by adrenal gland (20%) (Untch et al. 2016).

Five–year survival rates in patients with RCC with pulmonary metastases range from 21% to 60% following complete metastasectomy (Meimarakis et al. 2011; Dabestani et al. 2014). The lung is the most common site of recurrence, occurring in about 50% of RCC patients with metastatic disease (Meimarakis et al. 2011). These patients remain at high risk for disease recurrence and death with a 5–year DFS and OS of approximately 33% and 40% in one series that examined patients who underwent complete synchronous or metachronous pulmonary metastasectomy (Hofmann et al. 2005). In the study, patients with synchronous lung lesions who underwent complete resection had a 5–year OS of 0% (n = 5), compared with patients with metachronous resected lung lesions who had a 5-year OS of 43.7% (n = 49). In one of the largest studies of pulmonary metastasectomy (n = 202), the 5-year OS was 45% following complete (R0) metastasectomy (Meimarakis et al. 2011). Synchronous metastasis was again associated with a worse survival than metachronous metastasis (HR 1.9 [95% CI: 1.2 to 3.0]).

Lung, soft tissue, and lymph nodes are common sites of RCC metastases amenable to complete surgical resection; hence, these patients are included within the metachronous metastasectomy eligibility criteria. Time from nephrectomy to recurrence of < 12 months has been incorporated into prognostic models for survival after metastasectomy (Eggener et al 2008). Hence, in order to mimic an adjuvant population, the eligibility criteria for metachronous resections includes patients who have undergone metastasectomy more than 12 months after nephrectomy. Eligibility will also include patients with limited synchronous metastases (isolated solitary ipsilateral or contralateral adrenal metastasis treated with adrenalectomy and lung metastasis treated with a sub-lobar or lobar resection within 12 weeks of nephrectomy) who have undergone complete resection of residual disease. This population is expected to be a small but clinically relevant group that is in need of adjuvant treatment options. The incidence of ipsilateral synchronous metastasis to the ipsilateral adrenal gland was approximately 5% (Peters et al. 2013).

In patients who undergo metastasectomy, there are no recommended systemic treatments after surgery (ESMO guidelines 2014 [Escudier et al. 2014]). NCCN and EAU guidelines have no specific comments for this unique population. This underscores the lack of effective therapies and dearth of historical studies in this at–risk population.

3.3.3 Rationale for PD–L1 All-Comer Population

This study will enroll patients with RCC whose nephrectomy or metastasectomy specimens have a PD–L1 IHC score of IC0/1/2/3 as determined by a central laboratory.

Although data from the Phase Ia Study PCD4989g suggest that PD-L1 status as determined by IC score correlates with response and survival in patients with metastatic RCC treated with atezolizumab (see Section 1.3.2 and Table 1), atezolizumab appears to be active in patients with RCC whose tumors express IC0. For example, in this heavily pre-treated and metastatic population, the 2–year OS was 58% (95% CI: 43 to 73), ORR was 15%, and median OS was 28.9 months (20, not reached) in the overall RCC population, compared with a 2–year OS of 51% (27 to 74), ORR of 9%, and median OS of 28.8 months (16.3 to 28.9) in the IC0 population, respectively. In other studies with non-small cell lung cancer and urothelial cancer, although there is some correlation of PD–L1 expression with efficacy, atezolizumab remains active in patients with low or no expression of PD–L1, particularly with regard to OS (Balar et al. 2016; Rosenberg et al. 2016; Smith et al. 2016).

However, considering that there may be some correlation between PD–L1 expression and efficacy as described above and in Section 1.3.2, this study will stratify enrollment by patients with IC0 versus IC1/2/3 in order to ensure balance across the two study arms for this potentially predictive factor.

3.3.4 Rationale for Stratification Factors

The stratification factors are as follows:

- Disease stage as defined by T2/T3a versus T3b/c/T4/N+ versus patients with resected synchronous/metachronous metastasis[R0])
- Geographic region (North America [excluding Mexico] vs. rest of world)
- PD–L1 IHC IC0 versus IC1/2/3

The TNM/Grading system is a scoring system that uses pathologic tumor stage, regional lymph node status (N stage), and Fuhrman nuclear grade to predict the risk of progression to metastatic RCC in patients who have undergone radical nephrectomy for clinically localized clear cell RCC. Only patients who are categorized as being at high risk for RCC recurrence as per this system will be eligible. Even within this overall high-risk population, there may be potential differences in the rates of RCC recurrence between subpopulations of patients. As described in Section 3.3.2.1, patients with T2 and or T3a tumors may have a different prognosis than those with T3b or T4 tumors or nodal disease (Lee et al 2009). Patients who have undergone complete metastasectomy are at very high risk of disease recurrence (see Section 3.3.2.2) and may perform differently than those who have not developed metastatic disease.

Differences in the standard of care and access to treatment in different geographic regions have the potential to impact survival outcome. Geographic region is considered

to be a potential prognostic factor given regional variability in diagnosis and treatment patterns after diagnosis. Variations by geographic region in surgical practice (Hollenbeck et al. 2006; Kim et al. 2011) and the threshold for symptom–directed clinical imaging may occur, which may affect DFS and OS. Treatment practices that occur after diagnosis, including access to therapies which may affect overall survival, may also differ by geographic region (Znaor et al. 2015). Accordingly, geographic region will be used as a stratification factor.

As stated in Section 3.3.3, patients whose tumors express PD–L1 may be more likely to benefit from atezolizumab treatment. Therefore, the study will stratify patients by their IC score (IC0 vs. IC1/2/3).

3.3.5 Rationale for Placebo–Control Arm and Blinded Design

Observation is the standard of care after nephrectomy or metastasectomy for patients after complete resection of their RCC to NED status. According to NCCN and EAU guidelines (2014), there are no standard adjuvant therapies, and clinical study participation should be encouraged.

The Sponsor has chosen a double–blind placebo control rather than observation for the control arm primarily because of the advantages that double–blind control studies provide in reducing potential bias in the assessment of disease recurrence and safety. Additional advantages include reduced chances of drop–out (attrition)/improved study retention for follow up for the control arm as well as the potential to minimize the risk of off-label use of currently approved metastatic therapies. Despite of the lack of demonstrable adjuvant benefit, up to 20% of patients with high–risk, resected RCC are exposed to adjuvant anti–VEGF based therapies, on the basis of real–world surveys (Kantar Health 2014). Maintaining optimal study follow up may be a considerable concern with an observation–only arm, and this may also introduce unforeseen potential biases in investigator assessments. The Sponsor has chosen to utilize a placebo arm in this study in order to maintain optimal scientific integrity and rigor.

To minimize bias in the timing of key assessments of safety and efficacy, patients in the placebo arm will receive placebo and will undergo assessments conducted on the same schedule as patients in the atezolizumab arm.

3.3.6 Rationale for Efficacy Endpoints

The treatment benefit in this study will be measured using DFS as the primary efficacy endpoint and OS, DFS in IC1/2/3 patients, distant metastasis–free survival (DMFS), 1-, 2-, and 3-year DFS, and disease specific-survival (DSS) as secondary efficacy endpoints.

Improvement in DFS and the ability to delay surgery or the initiation of metastatic treatment such as tyrosine kinase inhibitors ([TKIs]; e.g., sunitinib, pazopanib) represents clinically meaningful benefit to patients with RCC. Given that the current

standard regimens for metastatic disease, such as TKIs, are associated with significant chronic toxicities such as fatigue, diarrhea, mucositis, and hand–foot syndrome (Motzer et al. 2014), improvement in DFS delays the initiation of these adverse events associated with first-line therapy and therefore reflects direct benefit to patients. Also, interpretation of DFS is not confounded by the use of subsequent therapies. Given the availability and ongoing development of multiple agents in the relapsed and metastatic settings, interpretation of OS may be confounded by the use of subsequent therapies in this patient population. Current studies in adjuvant RCC (S–TRAC, SORCE, PROTECT, ATLAS, EVEREST) employ a DFS endpoint.

The primary efficacy objective endpoint of investigator-assessed DFS is considered an adequate clinical endpoint for an adjuvant clinical trial in RCC that better approximates treatment benefit in real world clinical practice and has been employed in several pivotal Phase III adjuvant RCC studies (Haas et al. 2016; Choueiri et al. 2021). Moreover, investigator-assessed DFS has been accepted as a surrogate endpoint for OS to support drug approval in the adjuvant setting in other malignancies, including NSCLC (Wu et al. 2021), breast cancer (Masuda et al. 2017), urothelial cancer (Bajorin et al. 2021), and colon cancer (Andre et al. 2004). Given the blinded trial design, investigator assessment is acceptable for the determination of recurrence in this setting and better approximates clinical practice (McKay et al. 2021).

DFS, as assessed by an independent central radiological review, will be included as a secondary endpoint. The S–TRAC study comparing sunitinib versus placebo in the adjuvant setting of RCC reported a disagreement rate between IRF-assessed and investigator-assessed DFS events of 11.3% in the sunitinib group and 8.5 % in the placebo group. Investigators called relapse earlier than the blinded independent central review more often for sunitinib than for placebo. This lead to a statistically significant DFS benefit for the IRF-assessed DFS analysis but not the investigator-assessed DFS analysis (Ravaud et al. 2016). In addition, a recent Phase III trial investigating girentuximab versus placebo compared investigator assessment to independent radiologic review at baseline. Eleven percent of patients determined disease–free at baseline by the investigator were diagnosed with metastatic disease by independent radiologic review, supporting the need to confirm disease–free status by independent central radiologic review at baseline and radiographic disease recurrence throughout the trial (Chamie et al. 2016).

IRF-assessed EFS has been added as a secondary efficacy objective endpoint because retrospective IRF review may identify patients with disease at baseline, who had already been enrolled onto the study, and received study treatment. IRF-assessed EFS allows the assessment of treatment benefit in both patients with and without identified baseline disease.

OS is included as an important secondary endpoint. Because subsequent treatments after disease recurrence are evolving, the impact of adjuvant treatment on OS may be

confounded by the use of subsequent therapies. DMFS is also included as a secondary endpoint because distant recurrence is considered to be a major threat to patient survival. This endpoint will be informative as to how atezolizumab adjuvant treatment might affect patterns of recurrence. Additionally, DSS (also known as cancer–specific survival) is a secondary endpoint because non–RCC cancer mortality in this frail and elderly population can be quite significant and may be a competing cause of mortality. Comorbidities that result in death from non–RCC causes are an independent prognostic factor for OS in patients with RCC (Berger et al. 2008). Hence, improvement in DSS in this population may not be reflected in an analysis of OS.

DFS in the IC1/2/3 patients is included, considering there may be some association between PD–L1 expression and efficacy as described in Section 1.3.2 and Section 3.3.3.

Three–year DFS analysis is included as a secondary endpoint to assess the potential predictive value of this endpoint on OS, because recurrence of patients' RCC commonly occurs within the first 2–3 years after nephrectomy (Eggener et al. 2008).

3.3.7 Rationale for Collection of Archival and/or Pre-Treatment Tumor Specimens

In this study, surgical resection tumor specimens from patients will be prospectively tested for PD–L1 expression and pathologic evaluation by a central laboratory during the screening period. PD–L1 status may be associated with prognosis. In addition to the assessment of PD–L1 status, other exploratory markers, such as potential predictive and prognostic markers related to the clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may also be analyzed. Pathologic evaluation is important as a monitoring tool to review the local eligibility.

Patients with additional pre–study tumor tissue samples (i.e., beyond those required to meet eligibility requirements) from procedures performed at different times during the course of their RCC will be requested (but not required) to also submit these samples for central testing. Tissue samples obtained at multiple timepoints from individual patients will contribute to an improved understanding of the dynamics of PD–L1 expression and relationship with intervening anti-cancer therapy.

3.3.8 Rationale for Blood Sampling for Biomarkers and for Collection of Tumor Specimens

Changes in different blood biomarkers may provide evidence for biologic activity of atezolizumab in humans and may allow for the development of a blood–based biomarker to help predict which patients may benefit from atezolizumab. An exploratory objective of this study is to evaluate changes in surrogate biomarkers in blood samples.

In addition, potential correlations of these pharmacodynamic markers with the dose, safety, and anti-tumor activity of atezolizumab will be explored.

For this study, a confirmatory tumor biopsy is mandatory at the time of disease recurrence. Analysis of biomarkers in the tumor samples may explain why RCC recurs and help develop further treatment. However, it is optional for patients to agree for their biopsy samples to be placed in the Research Biosample Repository ([RBR]; see Section 4.5.9).

3.3.9 Rationale for Patient-Reported Outcome Assessments

Treatment tolerability is a key issue in the treatment of RCC. In a context of patient-centered drug development, it is important to understand patients' experience with the treatment and document whether an increase in survival is associated with deleterious adverse events. Therefore, the patients' rating of occurrence of commonly reported treatment-related symptoms and the impact of the symptoms on patient quality of life will be captured through a self-completed questionnaire, the NCCN Functional Assessment of Cancer Therapy Kidney Symptom Index 19 (FKSI–19) questionnaire.

In addition, health status will be collected by use of the EuroQoL 5 Dimensions 5–Level (EQ-5D-5L) questionnaire to derive utilities for health economic modeling.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 764 patients with RCC who are at high risk for disease recurrence following resection will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- ECOG performance status of ≤ 1
- Able to comply with the study protocol, in the investigator's judgment
- Pathologically confirmed RCC with a component of either clear cell histology or sarcomatoid histology (sarcomatoid differentiation regardless of the primary epithelial subtype) that has not been previously treated in the adjuvant or neoadjuvant setting (See Appendix 10 for further guidelines regarding the definition of sarcomatoid histology.)

  Patients with localized disease with T2 Grade 4, T3a Grade 3 – 4, T3b/c any grade, T4 any grade and TxN+ any grade are eligible (see Appendix 3 and Appendix 4).

  Patients with pulmonary (treated with sub–lobar or lobar resection), lymph node, or soft–tissue metachronous recurrence of disease occurring greater than 12 months following nephrectomy who undergo complete resection (R0; microscopically margin-negative resection in which no gross of microscopic disease remains) and have no evidence of disease following metastasectomy

are eligible. Patients with resected CNS, bone or adrenal metastasis are not eligible.

Patients with synchronous metastases who have undergone complete resection of residual disease are eligible in the following circumstances: isolated solitary ipsilateral or contralateral adrenal metastasis treated with adrenalectomy and lung metastases treatable with a sub–lobar or lobar resection within 12 weeks of nephrectomy. Patients with resected CNS, bone or other soft-tissue metastasis are not eligible.

Medical Monitor approval is necessary for patients with resected metachronous and synchronous metastasis.

A TNM/grading high risk classification is not required for patients with metachronous/synchronous recurrence.

- Radical or partial nephrectomy with lymphadenectomy in select patients

  Surgeries may be performed by the open, laparoscopic, or robotic approach.

  Nephrectomy should include a lymph node dissection in patients with suspected nodal metastases on preoperative imaging (e.g., 2 cm) rendering the patient surgically NED (no evidence of disease). For patients with clinical venous involvement or whose tumors are clinically $>$10 cm, a lymph node dissection is recommended but not required. The extent of the lymph node dissection will be at the discretion of the treating surgeon.

  For patients with no preoperative evidence of abdominal node involvement and those not at increased risk of nodal metastases, a lymph node dissection is not required.

  Patients must have a negative surgical margin. Positive surgical margin is defined as tumor identified at the inked perinephric fat margin surrounding the nephrectomy specimen (R2), evidence of microscopic disease at the tumor margin (R1), or evidence of tumor histologically invading or adherent to the renal vein wall at the margin. Luminal thrombus without venous wall invasion is not considered a positive margin. The final surgical margin must be free of disease. Contact the Medical Monitor if clarification is required.

  For patients with evidence of thrombus involving the inferior vena cava and/or right atrium (i.e., cavoatrial involvement), a thrombectomy should be performed at the time of the radical nephrectomy.

- Representative formalin–fixed paraffin–embedded (FFPE) resected tumor specimens in paraffin blocks (blocks preferred) or at least 15 unstained slides, with an associated pathology report, for central testing and determined to be evaluable for tumor PD-L1 expression prior to study enrollment

  Up to 5 unstained slides will be used to determine tumor PD–L1 expression. The remaining unstained slides will support exploratory biomarker analysis and objectives

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

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

The tumor specimen must contain adequate viable tumor tissue to establish PD-L1 expression status.

Patients who have additional tissue samples from procedures performed at different times (e.g., nephrectomy and metastasectomy) during the course of their RCC will be requested (but not required) to also submit these samples for central testing.

In situations in which multiple specimens were received from different sites or at different times, the highest score will be used for eligibility.

- Absence of residual disease and absence of metastasis, as confirmed by a negative baseline computed tomography (CT) of the pelvis, abdomen, and chest no more than 4 weeks prior to randomization (for patients with a contraindication to CT with contrast, see Section 4.5.5). Confirmation of disease–free status will be assessed by an independent central radiologic review of imaging data (see Appendix 9 for details on criteria for assessment of disease-free status by imaging).
- Absence of brain metastasis, as confirmed by a negative CT with contrast or MRI scan of the brain, no more than 4 weeks prior to randomization

  Applicable only to patients who are eligible based upon completely resected metachronous lung, soft tissue or lymph node metastasis, or synchronous lung or adrenal metastasis
- Full recovery from nephrectomy or metastasectomy within 12 weeks from randomization following surgery.

  Randomization should occur within 12 weeks after nephrectomy or metastasectomy.
- Adequate hematologic and end–organ function, defined by the following laboratory results obtained within 28 days prior to randomization:

  ANC $\geq$ 1500 cells/μL (without granulocyte colony-stimulating factor support within 2 weeks prior to Cycle 1, Day 1)

  WBC counts $>$ 2500/μL

  Lymphocyte count $\geq$ 300/μL

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

  Hemoglobin $\geq$ 9.0 g/dL

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

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

  Serum bilirubin $\leq$ 1.5 $\times$ ULN

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

INR and aPTT $\leq 1.5 \times$ ULN

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

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

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period for at least 5 months after the last dose of study drug, and agreement to refrain from donating eggs during this same period

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

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

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

4.1.2 Exclusion Criteria

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

- Bilateral synchronous tumors with inheritable forms of RCC including von Hippel-Lindau
- Any approved anti-cancer therapy, including chemotherapy or hormonal therapy, within 3 weeks prior to initiation of study treatment

  Hormone–replacement therapy or oral contraceptives are allowed.
- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days or five half-lives of the investigational agent, whichever is longer, prior to enrollment
- CNS metastases or leptomeningeal disease
- Malignancies other than RCC within 5 years prior to Cycle 1, Day 1

  Patients with low–risk prostate cancer (defined as Stage cT1/T2a, Gleason score ≤ 6 and PSA ≤ 10 ng/mL) who are treatment–naive or who have been treated definitively with surgery or radiation and who are currently undergoing 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 (e.g., adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ of the breast treated surgically with curative intent)

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

- Life expectancy of <24 weeks
- Pregnancy or lactation, or intending to become pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
- Serum albumin <2.5 g/dL
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain–Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 7)

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

  Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only are permitted provided that they meet the following conditions:

  Rash must cover less than 10% of body surface area (BSA)

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

  No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
- Patients with prior allogeneic stem cell or solid organ transplantation

- 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 CT scan

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

- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class III or greater), myocardial infarction within 3 months prior to initiation of study treatment, unstable arrhythmias, or unstable angina
- Patients with a known left ventricular ejection fraction (LVEF) $<$40%.

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

- Positive test for HIV

  Documentation of HIV testing is required. The most recent testing must have occurred within 3 months prior to randomization. If such testing has not been done, it must be performed during screening.

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

  Documentation of HBsAg, hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), and hepatitis C virus (HCV) antibody testing is required. The most recent testing must have occurred within 3 months prior to randomization. If such testing has not been done, it must be performed during screening

  Patients with a positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening are eligible. The HBV DNA test will be performed only for patients who have a positive total HBcAb test.

  Patients with a positive HCV antibody test followed by a negative HCV RNA test at screening are eligible. The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

- Active tuberculosis
- Severe infections within 4 weeks prior to initiation of study treatment including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Receipt of therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

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

- Major surgical procedure within 4 weeks prior to initiation of study treatment or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis

- Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment

  Patients must agree not to receive live, attenuated influenza vaccine, or any other live, attenuated vaccine, within 28 days prior to initiation of study treatment, during treatment, or within 5 months after the last dose of study drug.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- Prior treatment with CD137 agonists, anti–CTLA–-4, anti–PD–1, or anti–PD–L1 therapeutic antibody or pathway-targeting agents
- Treatment with systemic immuno-stimulatory agents (including, but not limited to, interferons or interleukin–2) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to initiation of study treatment
- Treatment with systemic immunosuppressive medications (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to initiation of study treatment or anticipated need for systemic immunosuppressive medications during the study
  - Patients who have received acute, low-dose (≤ 10 mg/day oral prednisone or equivalent), systemic immunosuppressant medications (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.
  - The use of corticosteroids (≤ 10 mg oral prednisone or equivalent), physiologic replacement doses of glucocorticoids, and mineralocorticoids (e.g., fludrocortisone for non-autoimmune adrenal insufficiency) is allowed.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, placebo–controlled, double–blind study. The investigator, patient, and Sponsor will be blinded to treatment assignment.

After written informed consent has been obtained and eligibility has been established (including determination of tumor PD–L1 expression status by central testing), the study site will enter demographic and baseline characteristics into the IxRS. For those patients who are eligible for enrollment, the study site will obtain the patient's identification number and treatment assignment from the IxRS.

Patients will be randomized to one of the following treatment arms in a 1:1 ratio (experimental to control arm):

- Arm A (experimental arm): atezolizumab
- Arm B (control arm): placebo

Randomization will be stratified by the following factors:

- Disease stage (T2/T3a vs. T3b/c/T4/N+ vs. patients with resected synchronous/metachronous metastasis[R0])
- Geographic region (North America [excluding Mexico] vs. rest of world)
- PD–L1 IHC IC0 versus IC1/2/3

A stratified, permuted–block randomization will be implemented to balance assignment to each treatment within levels of the stratification factors.

4.2.2 Blinding

Study site personnel (with the exception of unblinded pharmacist and injecting physician) and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and iDMC members.

Whereas PK and ADA samples must be collected from patients assigned to the control arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of this study. Laboratory personnel responsible for performing PK and ADA assays will be unblinded to patients' treatment assignments to identify appropriate PK and ADA samples to be analyzed. Samples from patients who are assigned to the control arm will not be analyzed except by request (e.g., to evaluate a possible error in dosing).

The Sponsor, investigators, and patients will remain blinded to treatment assignment until the primary analysis has occurred.

4.2.2.1 Unblinding in the Event of Medical Emergency

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code. *However, the investigator should inform the Medical Monitor that the treatment code has been broken.*

After a patient is unblinded by the investigator for safety reasons, the patient may continue treatment with the study drug *upon investigator decision.*

The person responsible for this newly introduced role of Unblinded Medical Monitor will not be directly involved in the conduct of the clinical study.

4.2.2.2 Unblinding in Non–Emergency Situations

Single patient unblinding in non–emergency situations will be allowed at the time of disease recurrence to help guide decisions on subsequent treatment. The investigator will be able to break the treatment code by contacting the IxRS.

Prior to breaking the treatment code, the investigator should provide *the following information* to the Medical Monitor:

- A new lesion has appeared that was not seen in previous scans. Lesion characteristics meet guidelines for disease recurrence as outlined in Appendix 9
- A biopsy has been taken for the suspicious lesion, if applicable
- A plan is in place to treat the patient with next line of therapy and knowledge of previous treatment is required to inform treatment decision
- All scans have been submitted to the IRF
- The location of lesion is captured in the eCRF, if applicable
- Study drug discontinuation has occurred and is recorded in the eCRF

Unblinding for reasons other than to inform subsequent treatment preference following disease recurrence or manage an adverse event *will be managed by the investigator.*

4.2.2.3 Unblinding to Meet Health Authority Requirements

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT

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

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab

Atezolizumab will be supplied by the Sponsor as sterile liquid in 20 mL glass vials. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. For information on the formulation and handling of atezolizumab, refer to the Atezolizumab Investigator's Brochure and Pharmacy Manual.

4.3.1.2 Placebo

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

Placebo will be supplied by the Sponsor.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Atezolizumab and Placebo

Administration of atezolizumab/placebo 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 regarding administration, refer to the Atezolizumab Investigator's Brochure and Pharmacy Manual. For anaphylaxis precautions, see Appendix 8. Atezolizumab/placebo infusions will be administered per the instructions outlined in Table 5.

Table 5 Administration of First and Subsequent Atezolizumab/Placebo Infusions

First Infusion	Subsequent Infusions
• Premedication is not routinely recommended prior to the atezolizumab/placebo infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post–infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab/placebo should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion–related reaction, or 60 (±15) minutes if the patient experienced an infusion–related reaction with the previous infusion. • If the patient experienced an infusion–related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion.

Guidelines for medical management of IRRs are provided in Appendix 11.

No dose modification for atezolizumab/placebo is allowed. Guidelines for treatment interruption or discontinuation are provided in Section 5.1.2 and in Appendix 11.

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

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post–Study Access to Atezolizumab

Currently, the Sponsor does not have any plans to provide atezolizumab or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing atezolizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over–the–counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol–mandated study treatment from 7 days prior to the screening visit to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF). In addition, any medication given as treatment for an adverse event should be reported even if it is after the Treatment Discontinuation Visit on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Premedication with antihistamines may be administered for the second and subsequent atezolizumab infusions, at the discretion of the investigator.

The following therapies should continue while patients are in the study:

- Oral contraceptives
- Hormone–replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low–molecular–weight heparin)
- *Vaccinations (such as influenza, SARS-CoV-2)*

  Live, attenuated vaccines are not permitted (see Section 4.4.3).
- Megestrol administered as an appetite stimulant
- Corticosteroids (e.g., ≤ 10 mg oral prednisone or equivalent, inhaled corticosteroids, low–dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency (prednisone dose or dose equivalent ≤ 10 mg/day)
- Mineralocorticoids (e.g., fludrocortisone)

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2–receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard 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 β_2–adrenergic agonists; see Appendix 8).

4.4.2 Cautionary Therapy for Atezolizumab–Treated Patients

Systemic corticosteroids and tumor necrosis factor (TNF) –α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF–α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF–α inhibitors may be administered at the discretion of the investigator, including the use of corticosteroids as premedication to patients for whom CT scans with contrast are contraindicated (see Section 4.4.3).

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (see Section 5.1.2 and Appendix 11 for details).

4.4.3 Prohibited Therapy

Any concomitant therapy intended for the treatment of *cancer*, whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment (depending on the anti–cancer agent; see Section 4.1.2) and during study treatment until disease recurrence is documented and the patient has discontinued study treatment. This includes but is not limited to chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (unless otherwise noted).

The following medications are prohibited during the study treatment, unless otherwise noted:

- Any live, attenuated vaccine (e.g., FluMist®) within 28 days prior to randomization, during treatment, or within 5 months following the last dose of study drug
- Immunomodulatory agents (during the treatment period and for 10 weeks after the last dose of study drug), including, but not limited to, interferons or IL–2, during study treatment; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab
- Immunosuppressive medications (during the treatment period and for 10 weeks after the last dose of study drug), including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab

The concomitant use of herbal therapies is not recommended, because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, their use for patients in the study is allowed at the discretion of the investigator, provided that there are no known interactions with any study treatment. As noted above, herbal therapies that are intended for the treatment of cancer are prohibited.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

If the timing of a protocol–mandated study visit coincides with a holiday or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study–related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Prior to signing the main consent form for the study, patients may specifically allow for the collection and testing of archival or fresh tumor tissue by signing the Prescreening Informed Consent Form.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to screening. At the time of each follow–up physical examination, an interval medical history should be obtained, and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and at treatment discontinuation, 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.

4.5.4 Vital Signs

Vital signs will include the measurements of respiratory rate, heart rate, systolic and diastolic blood pressures, and temperature while the patient is in a seated position.

Vital signs are to be measured within 60 minutes prior to each infusion and, if clinically indicated, during or after infusions as outlined in Table 6, and at other specified timepoints as outlined in the Schedule of Assessments (see Appendix 1).

Table 6 Timing for Vital Sign Measurements for First and Subsequent Infusions

Timing for Vital Sign Measurements	
First Infusion	Subsequent Infusions
• Within 60 minutes prior to the study drug infusion • Record patient's vital signs during or after the infusion, if clinically indicated	• Within 60 minutes prior to the study drug infusion • Record patient's vital signs during or after the infusion, if clinically indicated or if symptoms occurred during the previous infusion

4.5.5 Surveillance for Renal Cell Carcinoma Recurrence

Patients will be assessed for tumor recurrence every 3 months (±2 weeks) for Years 1–3 and every 6 months (±4 weeks) thereafter until occurrence of an IRF-assessed DFS event, death, loss to follow–up, withdrawal of consent, or study termination, whichever occurs first, regardless of length of treatment/observation (See Appendix 9 for details regarding assessment of RCC recurrence). Tumor recurrence will be assessed by an independent central radiologic review and investigator assessment.

Surveillance for tumor recurrence will include clinical history, physical examination, (as clinically indicated), laboratory evaluation, (as clinically indicated or per local surveillance guideline for RCC recurrence), and imaging studies of the chest, abdomen, and pelvis.

All eligible patients will undergo a contrast–enhanced CT of the chest, abdomen, and pelvis at screening no more than 4 weeks prior to randomization. MRI of the abdomen and pelvis with a non-contrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). Eligibility will be confirmed by an independent central radiologic review of imaging data, supported/confirmed by biopsy results (from biopsies performed before or during the screening period), as well as any historical scans which may support the interpretation of benign radiographic objects.

If a CT scan for tumor assessment is performed in a positron emission tomography PET/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

Surveillance imaging studies should use the same imaging modality that was used at screening and must be performed at the timepoints specified in Appendix 1, regardless of drug delays or interruptions. Other examinations such as bone scan should be performed as clinically indicated.

If recurrent disease or occurrence of a new primary tumor is suspected on clinical grounds, imaging studies must be performed expeditiously, even if not mandated in the Schedule of Assessments.

All patients who present with findings suspicious for disease recurrence must undergo a confirmatory biopsy for histopathologic confirmation, if clinically feasible. Biopsy can only be waived for patients who have no lesions amenable for biopsy at disease recurrence or if clinically infeasible, following discussion with the Medical Monitor.

Disease recurrence will be determined on the basis of radiographic evidence and whenever possible supported/confirmed by biopsy results. Cases for which biopsy results definitively rule out recurrence of RCC will not be considered as disease recurrence for this study.

All scans, as outlined above, should be submitted to the central review facility for independent review. It is important to the integrity of the study that all imaging studies, clinical information (including photographs) and pathology reports for on study biopsies are forwarded to the independent review facility before each patient enrolls and as each patient progresses through the study.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for hematology, serum chemistries, coagulation, urinalysis, and the pregnancy test will be analyzed at the study site's local laboratory. Central laboratories will coordinate the collection of archival tumor, fresh tumor, and leftover tumor tissue and blood samples for the assessment of atezolizumab pharmacokinetics and biomarkers, ADA assays, and autoantibody testing. Instruction manuals and supply kits will be provided for all central laboratory assessments.

Local laboratory assessments will include the following:

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)

  Serum bicarbonate is not required as a laboratory assessment in the screening or on–study serum measurements in countries where it is not considered a standard chemistry measurement (e.g., Japan).
- Coagulation (aPTT and INR)
- Serum pregnancy test during screening and serum or urine pregnancy tests during the study (for women of childbearing potential, including women who have had a tubal ligation)

- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood); dipstick is permitted
- Thyroid function testing (thyroid–stimulating hormone [TSH], free triiodothyronine [T3] [or total T3 for sites where free T3 is not performed], free thyroxine [T4])
- All patients will be tested for HIV prior to the inclusion into the study, and patients with a positive HIV test result will be excluded from the clinical study.
- HBV serology (HBsAg, antibody to HBsAg [anti–HBs], anti–HBc)

  HBV DNA is required for patients with negative serology for HBsAg and positive serology for anti–HBc.
- HCV serology (anti–HCV) and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

Instruction manuals and supply kits will be provided for all central laboratory assessments. The following assessments will be performed at a central laboratory or by the Sponsor:

- ADA assays (patients assigned to atezolizumab only)

  Serum samples will be assayed for the detection and characterization of ADAs to atezolizumab with use of validated immunoassays.
- PK assays (patients assigned to atezolizumab only)

  Serum samples will be assayed for atezolizumab concentration with use of a validated immunoassay.

  Residual PK and ADA samples will be retained for further method development, validation and characterization. Samples will be stored for up to 5 years after the completion of the Clinical Study Report or until they are used up.
- Auto–antibody testing; baseline sample to be collected on Cycle 1, Day 1 prior to the first dose of study drug. For patients who show evidence of immune-related toxicity, additional samples may be collected, and all samples will be analyzed centrally.

  Anti–nuclear antibody

  Anti–double–stranded DNA

  Circulating anti–neutrophil cytoplasmic antibody

  Perinuclear anti–neutrophil cytoplasmic antibody
- C-reactive protein
- Biomarker assays

  Blood and tumor samples will be obtained for biomarker evaluation (including, but not limited to, biomarkers that are related to RCC or tumor immune biology) from all eligible patients according to the schedule in Appendix 2. Samples will be processed to obtain EDTA plasma and serum for the determination of

changes in blood–based biomarkers. Whole blood samples may be processed to obtain peripheral blood mononuclear cells (PBMCs) and their derivatives (e.g., RNA and DNA) and evaluated for immune–related, tumor–type related, and other exploratory biomarkers (e.g. alterations in gene expression or non-germline variants related to RCC biology, including genes such as VHL or PBRM1 [Polybromo 1]).

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.9), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exception{s}:

- Residual PK and ADA samples will be stored for up to 5 years after the completion of the Clinical Study Report or until they are used up.
- Leftover Plasma, Serum, tumor samples collected during the study will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.6.1 Resected Tumor Tissue

A central laboratory will coordinate the sample collection of resected tumor tissue samples for research–related testing at central laboratories or by the Sponsor. Instruction manuals and supply kits will be provided for all central laboratory assessments.

See the Laboratory Manual for additional details on tissue sample handling.

Resected Tumor Tissue during Screening

Representative FFPE tumor specimens in paraffin blocks (blocks preferred) or at least 15 unstained slides of the highest tumor grade portion of the RCC tumor (consistent with the highest Fuhrman grade slides or block read by the local pathologist), with an associated pathology report (including tumor size, stage [e.g., T3a], nodal status [e.g., N2], Fuhrman grade, and presence or absence of tumor necrosis), must be submitted for central testing for determination of sufficient viable tumor content prior to study enrollment. Tumor specimens will be evaluated for PD–L1 expression. PD-L1–expression status (e.g., IHC IC0, IC1/2/3) is required for eligibility. Review of Fuhrman grade will be assessed by a central laboratory with expert pathologists. This serves to ensure careful monitoring of local sites for Fuhrman grading, given its importance for eligibility. Eligibility will be determined locally by investigators.

Tumor tissue should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD–L1 status). Fine–needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core–needle biopsy specimens, at least three cores should be submitted for evaluation.

Patients having additional tissue samples from procedures performed at different times during the course of their RCC will be requested (but not required) to also submit these samples for central testing. Tissue samples obtained at multiple timepoints for individual patients will greatly contribute to an improved understanding of the dynamics of PD–L1 expression and relationship with intervening anti-cancer therapy.

The status of immune–related, tumor type–related, and other exploratory biomarkers (including, but not limited to, T–cell markers and tumor mutation status, as defined by IHC, qRT–PCR, NGS, and/or other methods, in archival and fresh tumor tissue samples of enrolled patients) may be evaluated and correlated with efficacy measures. Gene expression-based signatures of functional T–cell responses (T–effector signature) in archival and fresh tumor tissues may be correlated with efficacy.

For archival samples, the remaining tumor tissue block for all patients enrolled will be returned to the site upon request or 18 months after final closure of the study database, whichever is sooner. Tissue samples from patients who are not eligible to enroll in the study will be returned no later than 6 weeks after eligibility determination.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

4.5.6.2 Tumor Biopsy at the Time of Disease Recurrence

Biopsy at the time of first radiographic confirmation of disease recurrence is mandatory for all randomized patients. Biopsy can only be waived for patients who have no lesions amenable for biopsy at disease recurrence or if clinically infeasible, following discussion with the Medical Monitor.

Acceptable samples include resections; core needle biopsies for deep tumor tissue or lymph nodes; or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. For core needle biopsy specimens, at least three cores, embedded into a single paraffin block, should be submitted for evaluation.

The status of immune–related, tumor type–related, and other exploratory biomarkers (including, but not limited to, T–cell markers and tumor mutation status) in tumor tissue samples of enrolled patients may be evaluated.

Next–generation sequencing (NGS) may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator can obtain results from the samples

collected at the time of disease recurrence in the form of an NGS report, which is available upon request directly from Foundation Medicine. The investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions.

4.5.7 Electrocardiograms

A twelve–lead ECG is required at screening, at timepoints specified in Appendix 1, and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the study site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.8 Patient–Reported Outcomes

Patient–reported outcome (PRO) data will be collected to document patients' perspective regarding the treatment burden. The questionnaires will be translated as required in the local language.

To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient before the patient receives any information on disease status that might bias the patient's answers and prior to the performance of non-PRO assessments and the administration of study treatment. Study site staff will ensure that PRO questionnaires are provided to the patients for completion per the Schedule of Assessments (see Appendix 1), and before the patients complete the visit the site staff will confirm completion or alternatively document any reasons for not completing the questionnaires.

All patients should complete the FKSI–19 and the EQ–5D–5L questionnaires at baseline (Cycle 1, Day 1) and at the beginning of each odd–numbered cycle (i.e., Cycles 3, 5, 7, 9, 11, 13, and 15).

Patients who discontinue study treatment will continue to complete the questionnaires at the end of treatment visit, the post–treatment visit, any visit for assessment of RCC recurrence, and at two timepoints after disease recurrence during survival follow–up.

Patients will complete PRO questionnaires at the clinic during the visits; data will be entered in the eCRF. If patients are no longer receiving treatment, it is expected that patients will not come to the clinic and therefore, the questionnaires will be administered

by the site staff over the phone and recorded in the eCRF. The instructions for completing the PRO questionnaires will be provided by site staff. The data will be subsequently captured electronically and included in the study centralized database maintained by the Sponsor. The data will be available for access by appropriate study personnel.

4.5.8.1 EuroQol 5–Dimension 5–Level Questionnaire

The EQ–5D–5L is generic preference-based health utility questionnaire that provides a single index value for health status (see Appendix 6). The EQ–5D–5L comprises questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the patient's health status. In addition, the EQ-5D-5L includes a visual analog scale for the patient to rate his or her current health status. The EQ-5D-5L will be utilized in this study for the purpose of deriving utilities for economic modeling, not to document treatment benefit. The EQ-5D-5L questionnaire takes 5 minutes or less to complete.

4.5.8.2 National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI-19)

The FKSI–19 is a 19-item tool designed to assess the most important symptoms and concerns related to evaluating treatment effectiveness in advanced kidney cancer (Butt et al. 2013). The FKSI–19 includes symptoms commonly experienced with cancer or with immunotherapy including, fatigue, shortness of breath, fever, and bone pain. In addition, the questionnaire includes items that capture patients' difficulty with the side effects of treatment, the ability to work, the ability to enjoy life, and contentment. Each item is scored on a five-point scale (0–4) with each level corresponding to: 0 = "Not at all," 1 = "A little bit," 2 = "Somewhat," 3 = "Quite a bit," and 4 = "Very much." The questionnaire takes approximately 5 minutes to complete.

4.5.9 Optional Samples for Research Biosample Repository

4.5.9.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long–term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology

- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.9) will not be applicable at that site.

4.5.9.3 Sample Collection

The following samples will be collected and stored in the RBR for research purposes, including, but not limited to, research on dynamic (non–inherited) biomarkers:

- Remaining blood derivatives (serum, plasma, PBMCs and their derivatives) after study-related tests have been performed
- Remaining FFPE tissue (with the exception of archival FFPE blocks, which will be returned to sites) after study-related tests have been performed
- Optional tissue samples collected for biopsy during the study

The following sample will be collected for research purposes, including, but not limited to, research on genetic (inherited) biomarkers

- Whole blood sample for DNA isolation

  This sample will be collected from patients who have consented to optional RBR sampling at Cycle 1, Day 1 as shown in the schedule of assessments in Appendix 1. If, however, the RBR genetic blood sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study. Collection of whole blood will enable the evaluation of single nucleotide polymorphisms in genes associated with immune biology including, but not restricted to, the target and pathway associated genes such as PD–L1, PD-1, and B7.1 as well as IL–8, IL–6, and related cytokines. The sample may be processed using techniques such as qPCR and DNA sequencing.

The above samples may be sent to one or more laboratories for DNA extraction to enable analysis of germline mutations, somatic mutations via whole genome sequencing (WGS), NGS, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic

approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.9.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses, data derived from RBR specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know–how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.9.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.9.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the study is closed. A patient's withdrawal from Study WO39210 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study WO39210.

If a patient wishes to withdraw consent to the testing of his or her specimens after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr–withdrawal@roche.com

4.5.9.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality–controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.5.10 Post–Treatment Assessments

Refer to Section 4.5.5 and Appendix 1 for details of assessments of surveillance of RCC recurrence, including assessments following study treatment completion. After discontinuation of the study treatment, PRO questionnaires will be administered over the phone or at the site at end of treatment visit, the post–treatment visit, any visit for assessment of RCC recurrence, and at two timepoints after disease recurrence during survival follow–up. Post–study treatment follow-up visits for tumor recurrence

surveillance should also include monitoring for potential late serious adverse events and adverse events of special interest.

Following completion of the last treatment cycle, patients will return for a treatment discontinuation visit within 30 days of the last study dose and a post–treatment visit 3 months after the last dose.

Survival follow–up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow–up, consent withdrawal, or study termination by the Sponsor. All patients (irrespective of the arm to which they are randomized) will be followed for survival and new anti-cancer therapy information (including targeted therapies and immunotherapies) and subsequent progressions, unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If a patient withdraws from *the study,* study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non–compliance

Every effort should be made to obtain information on patients who withdraw from the study. Patients who withdraw their consent to be followed for the primary study endpoint (DFS) will be asked to continue follow–up for OS. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment (atezolizumab/placebo) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment

- Use of another non–protocol anti-cancer therapy
- Pregnancy
- Disease recurrence (local recurrence, new primary RCC, or distant metastasis of RCC) documented by radiographic evidence, as determined by the IRF

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non–compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is on the basis of clinical experience with atezolizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Section 5.1.1).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of study drug (atezolizumab/placebo) will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. After initiation of study treatment, serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or

until initiation of new systemic anti-cancer therapy, whichever occurs first. All other adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. At each subsequent follow-up visit for tumor recurrence surveillance, monitoring for potential late–occurring adverse events should be performed. Guidelines for managing anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Section 5.1.2 and in Appendix 11. Refer to Sections 5.2–5.6 for details on safety reporting during the study.

In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain–Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab). Refer to Appendix 11 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.2 Management of Patients Who Experience Specific Adverse Events

There will be no dose modifications for atezolizumab/placebo in this study.

Study drug (atezolizumab or placebo) may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If study drug is withheld for >42 days from the last dose, the patient will be discontinued from study drug. If the investigator believes the patient is likely to derive clinical benefit and the Medical Monitor is in agreement, study drug can be resumed after being withheld for >42 days. If a patient must be tapered off steroids used to treat adverse events, the study drug may

be withheld for additional time beyond 42 days from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

Dose interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed *per investigator discretion*. The investigator *may consult* the Medical Monitor *to* determine the acceptable length of treatment interruption.

Guidelines for the management of patients who experience specific adverse events associated with atezolizumab are provided in Appendix 11.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol–specified vital signs, and conducting other protocol–specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol–mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)
- Late complications related to surgery (e.g., urinary infection, intestinal obstruction, wound dehiscence, anastomotic leak or stricture)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- 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)

- Suspected transmission of an infectious agent by the study treatment, 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 study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: Diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain–Barré syndrome, myasthenic syndrome, myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine-release syndrome, influenza-like illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study treatment**, only serious adverse events caused by a protocol–mandated intervention (e.g., invasive

procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self–care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (as applicable)
- Known association of the event with study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion–Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion–related reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion–Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion–Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology studies, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as

defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment–emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN
- Treatment–emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to recurrence of RCC should be recorded on the Death Attributed to Disease Relapse eCRF. All other on-study deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Recurrence of Renal Cell Carcinoma

Events that are clearly consistent with the expected pattern of disease recurrence should not be recorded as adverse events. These data will be captured as efficacy assessment data only. However in situations in which there is no confirmation of disease recurrence, the underlying symptoms should be captured as adverse events and assessed accordingly for seriousness, severity, and causality until a diagnosis or cause for such events is established or until confirmation of RCC recurrence. If the symptoms are later confirmed to be due to recurrence of disease, then symptoms reported as adverse events should be retracted.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to recurrence/progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.13 Patient–Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow–up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted], M.D.

Email: [redacted]

Telephone No.:

Mobile Telephone No.: [redacted]

Back–up Medical Monitor Contact Information

Medical Monitor: [redacted], M.D.

Email: [redacted]

Telephone No.:

Mobile Telephone No.: [redacted]

Medical Monitor: [redacted], *M.D.*

Email: [redacted]

Telephone No.:

Mobile Telephone No.: [redacted]

Unblinded Medical Monitor Contact Information

Medical Monitor: [redacted], M.D.

Email: [redacted]

Telephone No.:

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll–free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol–mandated intervention should be reported. The *Clinical Trial Adverse Event/Special Situations Form* provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment or until they receive another systemic anti-cancer therapy, whichever comes first. All other adverse events will be reported until 30 days after the last dose of study treatment or until they receive another systemic anti-cancer therapy, whichever comes first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system for serious adverse events and adverse events of special interest.

In the event that the EDC system is unavailable, the *Clinical Trial Adverse Event/Special Situations Form* provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur >90 days after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 5 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF,

and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW–UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow–Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow–up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or study–related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow–Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 90 days for serious adverse events and adverse events of special interest and 30 days for all adverse

events after the last dose of study treatment), all deaths, regardless of cause, should be reported in the appropriate eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported through use of the Adverse Event eCRF if the eCRF is still available. Otherwise, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the *Clinical Trial Adverse Event/Special Situations Form* using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Atezolizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Approximately 764 patients will be enrolled.

The ITT population is defined as all randomized patients regardless of whether the assigned study treatment was received. For analyses of the ITT population, patients will be grouped according to the treatment assigned at randomization.

6.1 DETERMINATION OF SAMPLE SIZE

6.1.1 Type I Error Control

Type I error rate for this study is 0.05 (two–sided). To control the type I error rate at alpha = 0.05 (two–sided) for the primary endpoint of *investigator*-assessed DFS and the key secondary endpoint of OS, the treatment arms will be compared in a hierarchical fashion. The analysis hierarchy will be *investigator*-assessed DFS followed by OS. One planned final analysis of *investigator*-assessed DFS *and* a total of three *planned*

analyses of OS (two interim analyses and one final analysis; see Section 6.10 for details) *will be performed by the Sponsor*. The analysis hierarchy will be implemented as follows:

Step 1: *Investigator*-assessed DFS will be evaluated at alpha = 0.05 (two–sided). The final analysis will be conducted when approximately 334 DFS events have occurred. The *investigator*-assessed DFS endpoint will be considered positive in the ITT population if statistical significance is achieved at the *DFS* final analysis.

Step 2: If the *investigator*-assessed DFS results are statistically significant at the *DFS* final analysis, alpha = 0.05 will be passed to the analysis of OS. At the *time of the investigator*-assessed DFS final analysis, *the first OS interim analysis will be performed and* it is projected that approximately 190 deaths will have occurred. The second interim and final analyses *of* OS will be conducted when approximately 222 and 254 deaths have occurred, respectively. For control of the familywise error rate at level 0.05, OS will be evaluated on the basis of the generalized Haybittle–Peto boundary (Haybittle 1971) for statistical significance, with *alpha boundaries for the two* interim *and* final analysis specified as the following: 0.036, 0.036, and 0.011. If the *investigator*-assessed DFS results are not statistically significant at the *DFS* final analysis, formal treatment comparison of OS will not be performed.

6.1.2 *Investigator-Assessed* Disease–Free Survival

The final analysis of the primary endpoint of *investigator*-assessed DFS will take place when approximately 334 DFS events have occurred (44% of 764 patients) on the basis of the following assumptions:

- Log–rank test (two–sided)
- Type I error rate (alpha) of 0.05 (two–sided)
- 1:1 randomization ratio
- 5% loss to follow–up over 24 months
- Median DFS for the control (placebo) arm of 47 months and estimated median DFS in the atezolizumab arm of 67 months (corresponding to a HR of 0.70, under the proportional hazard assumption)
- 90% power

Accrual of the planned 764 patients is projected to occur over 33 months, assuming a ramp–up period of 8 months. On the basis of these assumptions, the required number of DFS events for final analysis is projected to occur at Month 67 after the first patient is randomized; minimum follow–up at the time of the *investigator*-assessed DFS *final* analysis will be 34 months. Also on the basis of these assumptions, it is projected that an observed HR of $\leq$ 0.80 at the final analysis will result in a statistically significant difference (i.e., minimally detectable difference) between treatment arms. An HR of 0.80 corresponds to an improvement of 12 months in median DFS, from 47 months in the control (placebo) arm to 59 months in the atezolizumab arm.

6.1.3 Overall Survival

The final analysis of the secondary endpoint of OS will take place when approximately 254 deaths have occurred (33% of 764 patients), on the basis of the following assumptions:

- Log–rank test (two–sided)
- Type I error rate (alpha) of 0.05 (two–sided)
- 1:1 randomization ratio
- 2% loss to follow–up over 24 months for OS
- Two interim analyses for OS will take place when approximately 190 and 222 deaths have occurred, respectively
- Alpha boundary is set to be 0.036, 0.036, and 0.011 for the three analyses of OS
- Median OS for the control (placebo) arm of 100 months and estimated median OS in the atezolizumab arm of 143 months (corresponding to HR of 0.70)
- 75% power

On the basis of these assumptions and projected accrual, the required number of OS events for the final analysis of OS is projected to occur at Month 88 from the time the first patient is randomized. Also on the basis of these assumptions, it is projected that an observed HR of $\leq$0.73 and 0.75 at the first and second interim analyses, and an HR of $\leq$0.72 at the final analysis of OS, respectively, will result in a statistically significant difference (i.e., minimally detectable difference) between treatment arms.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment and reasons for discontinuation from the study will be summarized by treatment arm for the ITT population. Major protocol deviations, including major deviations of inclusion and/or exclusion criteria, will be summarized by treatment arm. Study treatment administration and reasons for discontinuation from study treatment will be summarized for the safety–evaluable population (see Section 6.5 for the definition).

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic characteristics (e.g., age, sex, race/ethnicity), stratification factors (disease stage [T2/T3a vs. T3b/c/T4/N+ vs. patients with resected synchronous/metachronous metastasis], geographic region [North America (excluding Mexico) vs. rest of world], PD-L1 expression [IC0 vs. IC1/2/3]), and baseline disease characteristics (e.g., ECOG performance status) will be summarized by treatment arm for the ITT population.

Continuous variables will be summarized using means, standard deviations, medians, and ranges. Categorical variables will be summarized by frequencies and percentages. Baseline measurements are the last available data obtained prior to the patient receiving the first dose of study treatment.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will be performed for the ITT population including all randomized patients, with patients grouped according to their assigned treatment. To control the type I error rate at alpha=0.05 (two–sided) for the primary endpoint of *investigator*-assessed DFS and the key secondary endpoint of OS, the treatment arms will be compared in a hierarchical fashion. The analysis hierarchy will be *investigator-assessed* DFS followed by OS (see Section 6.1.1).

6.4.1 Primary Efficacy Endpoint: *Investigator-Assessed* Disease–Free Survival

The primary efficacy endpoint is *investigator*-assessed DFS, defined as the time from randomization to *death from any cause or the* first documented recurrence assessed by *investigator, whichever occurs first. Recurrence is defined as any of the following: local recurrence of RCC, new primary RCC and distant metastasis of RCC.*

Data for patients without an *investigator*-assessed DFS event will be censored at the last date the patient was assessed to be alive and *investigator*-assessed recurrence free (or, for patients with no post-baseline disease assessment, at the randomization date).

Appropriate sensitivity analyses will be conducted for *investigator*-assessed DFS.

For U.S. registration purposes, the primary efficacy endpoint of *investigator*-assessed DFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with an *investigator*-assessed DFS event who missed two or more scheduled assessments immediately prior to the *investigator*-assessed DFS event will be censored at the last tumor assessment prior to the missed visits.

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

Kaplan-Meier methodology will be used to estimate for each treatment arm the *investigator-assessed* DFS rate at specific timepoints (e.g., every 6 months or yearly) and to estimate median DFS; Kaplan-Meier curves will be produced. Brookmeyer–Crowley methodology (Brookmeyer and Crowley 1982) will be used to construct the 95% CI for the median DFS for each treatment arm.

6.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include OS, Investigator-assessed DFS in patients with PD-L1 expression status of IC1/2/3, *IRF-assessed DFS, IRF*-assessed DFS in patients with PD-L1 expression status of IC1/2/3, *IRF-assessed EFS,* DSS, DMFS, *investigator*-assessed 1-, 2-, and 3-year DFS rate, and *IRF*-assessed 1-, 2-, and 3-Year DFS rate. *Appropriate sensitivity analyses will be conducted for secondary efficacy endpoints.*

OS (the key secondary efficacy endpoint) is defined as the time from randomization to death from any cause. Data for patients who have not died will be censored at the last date known to be alive or at the randomization date for patients with no post baseline information. Methods for comparison of OS between treatment arms will be the same as the methods for treatment comparison for the primary endpoint of *investigator*-assessed DFS.

Investigator-assessed DFS in patients with PD-L1 expression status of IC1/2/3 is defined as a secondary endpoint. The definition of DFS is the same as that of the primary endpoint of *investigator-assessed DFS.* Investigator-assessed DFS in this population will be analyzed similarly to the analysis of investigator-assessed DFS in the ITT population.

IRF-assessed DFS is defined as the time from randomization to death from any cause or the first documented recurrence assessed by IRF, whichever occurs first. IRF-assessed DFS will be analyzed similarly to the analysis of investigator-assessed DFS.

IRF-assessed DFS in patients with PD-L1 expression status of IC1/2/3 is defined as a secondary endpoint. The definition of DFS is the same as that of the secondary endpoint of IRF-assessed DFS. IRF-assessed DFS in this population will be analyzed similarly to the analysis of IRF-assessed DFS in ITT population.

IRF-assessed EFS is defined as the time from randomization to death from any cause, or the first documented recurrence in patients without baseline disease by IRF or the first documented disease progression in patients identified as having baseline disease by IRF, whichever occurs first. IRF-assessed EFS will be analyzed similarly to the analysis of IRF-assessed DFS.

DSS is defined as the time from randomization to death from RCC. Data for patients who have not died will be censored at the last date known to be alive. Data for patients who died from causes other than RCC will be censored at the date of death. Data for patients with no post baseline information will be censored at the randomization date. DSS will be analyzed similarly to the analysis of *investigator*-assessed DFS.

DMFS is defined as the time from randomization to *death from any cause or* the date of a DMFS event, defined as diagnosis of distant (i.e., non–locoregional) metastases

assessed by investigator, whichever occurs first. Data for patients without a DMFS event will be censored at the last date the patient was assessed to be alive and free of distant metastasis (or, for patients with no post-baseline disease assessment, at the randomization date). Patients who develop a local (e.g., renal bed or new tumor in ipsilateral kidney) recurrence will continue to be followed until the occurrence of a distant metastasis. Data for patients with no post–baseline disease assessment will be censored at the randomization date. DMFS will be analyzed similarly to the analysis of *investigator*-assessed DFS.

One–, two–, and three–year investigator-assessed DFS rate is defined as the probability of patients being alive and free of recurrence assessed by investigator at Year 1, 2, and 3 after randomization. The DFS rates will be estimated by Kaplan-Meier methodology, and the 95% CI will be estimated using Greenwood's formula. The 95% CI for the difference in one–, two–, and three–year DFS rates between the two arms will be estimated using the normal approximation to the binomial distribution.

One–, two–, and three–year IRF-assessed DFS rate is defined as the probability of patients being alive and free of recurrence assessed by IRF at Year 1, 2, and 3 after randomization. *One–,* two–, and three-year *IRF-assessed* DFS *rate* will be *analyzed similarly* to the *analysis of investigator-assessed DFS rate.*

6.4.3 Exploratory Efficacy Endpoints

Exploratory analyses of the following primary and secondary endpoints will be performed *at various timepoints (e.g., every 6 months after randomization)*: investigator-assessed DFS*, OS, IRF-assessed DFS, IRF-assessed EFS*, DSS, and DMFS. Event–free rates will be estimated by Kaplan-Meier methodology, and the 95% CI will be *estimated* using Greenwood's formula. The 95% CI for the difference in event–free rates between the two arms will be estimated using the normal approximation to the binomial distribution.

To assess the consistency of study results in subgroups defined by demographic and baseline characteristics, efficacy outcomes of *investigator*-assessed DFS, OS, *IRF*-assessed DFS*, IRF-assessed EFS*, DSS, and DMFS in patient subgroups will be examined. Summaries of these endpoints, including unstratified HRs estimated from the Cox proportional hazards model *and* Kaplan–Meier estimates of the median will be produced separately for each level of the subgroup.

Investigator–DFS will be summarized in patients with tumor Fuhrman Grade 4 or sarcomatoid histology (defined by investigator-assessed conventional histopathology).

6.5 SAFETY ANALYSES

The safety–evaluable population is defined as all randomized patients who received any amount of study treatment (i.e., atezolizumab or placebo), regardless of whether a full or partial dose was received. Specifically, for patients randomized to the placebo arm, if

atezolizumab was received by mistake, patients will be grouped under the atezolizumab arm in the safety analyses. Safety summaries will be provided for the safety-evaluable population.

Summaries of exposure to study treatment will include treatment duration, number of doses, and dose intensity.

Verbatim description of adverse events will be summarized by mapped thesaurus term using MedDRA, and graded according to NCI CTCAE v4.0. All adverse events occurring during or after the first study–drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, Grade $\geq$3 adverse events, adverse events of special interest, adverse events leading to treatment discontinuation, and adverse events leading to treatment interruption will be summarized. Multiple occurrences of the same event will be counted once at the maximum grade.

Selected laboratory data will be summarized by treatment arm. Changes in selected vital signs will be summarized by treatment arm.

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

6.6 PHARMACOKINETIC ANALYSES

Atezolizumab serum concentration data (minimum [C_{min}] and maximum [C_{max}]) will be reported and summarized (e.g., mean, standard deviation, coefficient of variation, median, range, geometric mean, geometric mean coefficient of variation) for each cycle where collected as appropriate.

Additional PK analyses will be conducted as appropriate based on the available data.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment for atezolizumab. The *post-baseline ADA evaluable population* will *include all patients who received at least one dose of atezolizumab and* with at least one post-dose ADA assessment, with patients grouped according to treatment received.

The numbers and proportions of ADA–positive patients and ADA–negative patients *at baseline (baseline prevalence) and after drug administration (post-baseline incidence)* will be summarized by treatment group. *When considering post-baseline incidence,* patients are considered to be ADA positive if they are ADA negative or with missing data at baseline but develop an ADA response following study treatment administration (treatment–induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 4–fold greater (i.e., ≥0.60 titer units) than the titer of the baseline sample (treatment–enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or with missing data at baseline and all post–baseline samples are negative, or if they are ADA positive at baseline but do not have any post–baseline samples with a titer that is at least 0.60 titer units greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, *and* PK endpoints may be analyzed and reported descriptively via subgroup analyses.

6.8 BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug response and mechanism of action, including efficacy and/or adverse events. Biomarker analyses may be reported in a separate report.

6.9 PATIENT–REPORTED OUTCOMES ANALYSES

6.9.1 FKSI–19

The PRO–evaluable population is defined as patients with a non-missing baseline PRO assessment and at least one post-baseline assessment.

Instruments will be scored per their user manual; *sub*scales with less than 50% of the items completed will be considered missing. Missing data will not be imputed.

The patients' perspective on symptoms and other concepts captured in the questionnaire (e.g., bothersomeness of side effect, enjoyment of life) will be summarized using descriptive analyses including summary statistics and change from baseline at each assessment by treatment arm.

Time to clinically confirmed deterioration (TTCD) using FKSI-19 (total score and subscales) is defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration. Confirmed clinically meaningful deterioration is defined as a clinically meaningful decrease from baseline that must be held for at least two consecutive assessments, or an initial clinically meaningful decrease from baseline followed by death.

TTCD will be assessed in ITT population. Patients who have not experienced a confirmed clinically meaningful deterioration at the clinical cutoff date will be censored at the last time when they completed an assessment. If no baseline or post-baseline assessment is performed, patients will be censored at the randomization date. TTCD using the FSKI-19 scale will be analyzed similarly to the analysis of investigator-assessed DFS. Further details regarding this analysis is described in the SAP.

To assess the consistency of the FKSI-19 results, the TTCD analysis (as defined above) will be performed on the subgroups defined by demographic and baseline characteristics. The outputs will include unstratified HRs estimated from the Cox proportional hazards model with associated 95% confidence interval and, Kaplan-Meier estimates of the median will be produced separately for each level of the subgroup.

6.9.2 EQ–5D–5L

Health economic data, as assessed by the EQ–5D–5L, will be used to derive utilities for pharmacoeconomic models. The results from the health economic data analysis will be reported separately from the Clinical Study Report.

6.10 INTERIM ANALYSES

6.10.1 Planned Interim Analyses

There is no planned interim efficacy analysis of the primary endpoint of *investigator-assessed* DFS for this study. A total of three analyses of OS will be performed (two interim analyses and one final analysis). OS will be evaluated on the basis of the generalized Haybittle–Peto boundary (Haybittle 1971) for statistical significance, with p–value *boundaries* at each interim or final analysis specified as the following: 0.036, 0.036, and 0.011.

The first interim analysis of OS will be performed at the time of the *investigator*-assessed DFS analysis (projected to occur at Month 67 after the first patient is randomized), if DFS is statistically significant. On the basis of the projected median OS for each treatment arm, the projected number of deaths observed at the DFS

analysis is approximately 190 deaths (25% of 764 patients), which corresponds to approximately 75% of the number of deaths required for the final analysis of OS. The observed HR of OS that is projected to result in a statistically significant difference between treatment arms at the DFS analysis is less than or equal to 0.73.

The second interim analysis of OS will be performed when approximately 222 deaths have occurred (29% of 764 patients), corresponding to approximately 87.5% of the number of deaths required for the final analysis of OS. The required number of OS events for the second interim analysis of OS is projected to occur at Month 77. The observed HR that is projected to result in a statistically significant difference between treatment arms at this analysis is OS HR 0.75 or lower.

The boundary for statistical significance at the OS interim and final analyses will be adjusted based on the actual number of events observed. Specifically, if at the DFS analysis, the observed number of OS events is significantly less than the projected 190 events, a nominal alpha value (1E–05) will be spent at the first OS interim analysis and the team will conduct another interim analysis of OS when 190 events have occurred.

6.10.2 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct an additional interim efficacy analysis beyond what is specified in Section 6.10.1 (e.g., an additional interim analysis of OS). This is because the external data such as results for other atezolizumab or competitor studies may indicate the need for an unplanned interim analysis (e.g., due to a treatment effect that is substantially larger than currently assumed). Below are the specifications in place to ensure that the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details (including type I error control) for the analysis, will be documented in the Statistical Analysis Plan (SAP), and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC Charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy) if necessary, and the iDMC Charter will also be made available to relevant health authorities.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of

discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and any other externally–generated electronic study data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data (i.e., FKSI–19 and EQ 5D–5L) will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor–designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient–reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for study-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re–consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised

Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate

authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after the last patient has completed the study.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol are not allowed, including requests to waive protocol eligibility criteria. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of GCP and require reporting to the Competent Authority.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann La Roche Ltd. Approximately 215 sites globally will participate in the study and approximately 764 patients will be randomized with the aid of an IxRS.

Central facilities will be used for study assessments throughout the study (e.g., specified laboratory tests, and PK analyses). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be convened to evaluate safety data during the study according to policies and procedures detailed in an iDMC Charter.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer–reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following Web site:

http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical study results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know–how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

Study Procedures		Arm A (Atezolizumab) and Arm B (Placebo)			
	Screening for Randomization	All Cycles (1 Cycle = 21 Days)	Discontinuation [a] (End of treatment)	Post–Treatment Visit	
	Days –28 to –1	Day 1 (±3 Days for Cycles ≥ 2)	≤30 Days after Last Dose	3 Months (±2 Weeks) after Last Study Treatment Dose	Follow–Up [b]
Signed Informed Consent Form(s) [c]	x				
Review of eligibility criteria	x				
Medical, surgical, and cancer histories, including demographic information [d]	x				
Pregnancy test [e]	x	x	x		
ECOG performance status	x	x [f]	x	x	
Clinical history [g]	x	x	x	x	x [h]
Complete physical examination [i]	x		x		
Limited physical examination [j]		x [f]		x	
Weight	x	x	x	x	
Height	x				
Vital signs [k]	x	x	x	x	
12–lead electrocardiogram [l]	x	On Day 1 of every third cycle, and more frequently if clinically indicated			
HIV, HBV, HCV serology [m]	x				
Hematology [n]	x	x [f]	x	x	
Serum chemistry [o]	x	x [f]	x	x	

Appendix 1
Schedule of Assessments (cont.)

Study Procedures		Arm A (Atezolizumab) and Arm B (Placebo)			
	Screening for Randomization	All Cycles (1 Cycle = 21 Days)	Discontinuation [a] (End of treatment)	Post–Treatment Visit	
	Days –28 to –1	Day 1 (±3 Days for Cycles ≥ 2)	≤ 30 Days after Last Dose	3 Months (±2 Weeks) after Last Study Treatment Dose	Follow–Up [b]
Coagulation panel (aPTT, INR) [p]	x		x	x	
Urinalysis [q]	x	As clinically indicated			
TSH, free T3, free T4	x	x [f, r]	x	x	
Imaging assessment [s]	x				
CRP and auto–antibody testing [t]		x [t]			
Serum sample for ADA assessment		See Appendix 2			
Serum sample for PK sampling		See Appendix 2			
Blood samples for biomarkers		See Appendix 2			
Optional whole blood sample for RBR [u]		x (Cycle 1, Day 1) [u]			
Atezolizumab or placebo infusion [v]		x			
Archival/screening FFPE tumor tissue specimen or 15 unstained slides [w]	x				
Fresh biopsy (mandatory sample [x] and optional RBR sample [y])			At the time of radiographic confirmation of disease recurrence [x, y]		
Assessments for RCC recurrence [h]		Every 3 months following randomization (± 2 weeks) in first 3 years; every 6 months (±4 weeks) thereafter until death, disease recurrence, loss to follow-up, or withdrawal of consent.			

Appendix 1
Schedule of Assessments (cont.)

Study Procedures		Arm A (Atezolizumab) and Arm B (Placebo)			
	Screening for Randomization	All Cycles (1 Cycle = 21 Days)	Discontinuation [a] (End of treatment)	Post–Treatment Visit	
	Days –28 to –1	Day 1 (±3 Days for Cycles ≥ 2)	≤ 30 Days after Last Dose	3 Months (±2 Weeks) after Last Study Treatment Dose	Follow–Up [b]
Concomitant medications [z]	x	x	x		
Adverse events [aa]	x	x	x	x	x
Survival and anti–cancer therapy follow-up [bb]				x	x
PRO questionnaires (FKSI–19, EQ–5D–5L) [cc]		x [dd]	x [ee]	x	x [ee]

anti–HBc = antibody to hepatitis B core antigen; ADA = anti–drug antibody; CRP = C-reactive protein; eCRF = electronic case report form; ECOG = Eastern Cooperative Oncology Group; EQ–5D–5L = Euro QoL 5 Dimensions 5-Level; FDG-PET = fluorodeoxyglucose positron-emission tomography; FFPE = formalin-fixed paraffin-embedded; FKSI-19 = Functional Assessment of Cancer Therapy Kidney Symptom Index-19; HBV = hepatitis B virus; HCV = hepatitis C virus; PD = pharmacokinetic; PRO = patient-reported outcome; RBR = Roche Biosample Repository; RCC = renal cell carcinoma; TSH = thyroid stimulating hormone.

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

[a] Patients will be asked to return to the clinic not more than 30 days after the last dose of study treatment (Arm A or B) for a discontinuation visit. The visit at which tumor assessment shows disease recurrence may be used as the treatment discontinuation visit.

[b] Patients will be assessed for tumor recurrence every 3 months (±2 weeks) for Years 1–3 and every 6 months (±4 weeks) thereafter until occurrence of an IRF-assessed DFS event, loss to follow-up, withdrawal of consent, or study termination, whichever occurs first, regardless of length of treatment/observation.

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

[d] Medical history includes clinically significant diseases, surgeries, cancer history (includes stage, date of diagnosis, and prior anti-tumor treatment), reproductive status, smoking history, and all medications used by the patients within 7 days prior to written informed consent. Demographic information includes sex, age, and self-reported race/ethnicity.

[e] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 14 days prior to Cycle 1, Day 1. Either serum or urine pregnancy test (positive urine test results will be confirmed with a serum pregnancy test) must be performed every cycle during the study treatment, at the treatment discontinuation and first post-treatment visit, and as clinically indicated.

[f] ECOG performance status, limited physical examination and local laboratory assessments (when these assessments are required) may be obtained ≤ 96 hours before Day 1 of each cycle.

[g] Symptom-directed clinical history should be performed. Changes from baseline or subsequent visits should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[h] Surveillance for tumor recurrence will be performed every 3 months ±2 weeks for three years (Years 1–3). After three years, patients will undergo tumor assessment every 6 months ±4 weeks for Year 4 until IRF-assessed disease recurrence, death, study termination by the Sponsor, or consent withdrawal, whichever occurs first. Results of FDG-PET scans alone will not be sufficient for purposes of documenting disease recurrence. Disease recurrence will be based on radiographic evidence and whenever possible supported/confirmed by biopsy results. In the absence of IRF-assessed disease recurrence, tumor assessments should continue, regardless of whether patients start a new anti-cancer therapy, until death, loss of follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. At each visit for tumor recurrence surveillance, a follow-up visit including clinical history; physical exam, as clinically indicated; laboratory evaluation, as clinically indicated or per local surveillance guideline for RCC recurrence; imaging studies of the chest, abdomen, and pelvis; and monitoring for potential late adverse events should be performed. Any changes in medications and allergies should be recorded. All scans, as outlined above, should be submitted to the central review facility for independent review.

[i] 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 (see Section 4.5.3).

[j] Symptom-directed physical examination; see Section 4.5.3 for details.

[k] Vital signs include heart rate, respiratory rate, blood pressures, and temperature and will be performed as standard of care. Vital signs should be measured within 60 minutes prior to each infusion, and, if clinically indicated, during or after the infusion.

[l] ECG recordings will be obtained during screening/enrollment period, on Day 1 of every third cycle (starting from Cycle 3), and more frequently if clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

[m] Documentation of HIV, HBsAg, HBsAb, HBcAb, and HCV antibody testing is required. The most recent testing must have occurred within 3 months prior to randomization. If such testing has not been done, it must be performed during screening. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[n] Blood samples collected to monitor safety will be collected in patients randomized to both arms. Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated (see Section 4.5.6).

[o] Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin. Serum bicarbonate is not required as a laboratory assessment in the screening or on-study serum measurements in countries where it is not considered a standard chemistry measurement (e.g., Japan).

[p] PTT is acceptable if aPTT cannot be performed.

[q] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood); dipstick is permitted.

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

[s] CT of the, chest, abdomen, and pelvis with contrast at screening for all patients. MRI of the abdomen and pelvis with a non-contrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance).For patients who are eligible on the basis of completely resected metachronous or synchronous lung, adrenal, or soft tissue metastasis, brain imaging is required no more than 4 weeks prior to randomization.

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

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

[v] Patients will receive their first dose of study drug the day of randomization, if possible. If this is not possible, the first dose should occur no later than 5 days after randomization. The initial dose of treatment will be delivered over 60 (±15) minutes. If the first infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. Study treatment may be continued for a maximum of 16 cycles (or 12 months, whichever occurs first) in the absence of disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor.

[w] Tumor tissue from surgical resection should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status). Prior to signing the main consent form for the study, patients may specifically allow for the collection and testing of archival or fresh tumor tissue by signing the prescreening consent form. After signing the Informed Consent Form, retrieval and submission of archival tumor sample can occur outside the 28-day screening period. Representative FFPE tumor specimens in paraffin blocks (blocks preferred) or at least 15 unstained slides of the highest tumor grade portion of the RCC tumor, with an associated pathology report, must be submitted for central testing for determination of sufficient viable tumor content prior to study enrollment. The pathology report should include tumor size, stage (e.g., T3a), nodal status (e.g., N2), Fuhrman Grade 1-4, and presence or absence of tumor necrosis. Fuhrman grade will be assessed by a central laboratory with expert pathologists for monitoring purposes. Eligibility will be determined locally by the investigator.

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

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

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

[aa] After informed consent has been obtained but prior to randomization, only serious adverse events caused by a protocol-mandated intervention should be reported. Upon randomization into study, patients who experience a serious adverse event or protocol-defined adverse events of special interest will be followed for safety for 90 days following their last dose of study drug or until they receive another systemic anti-cancer therapy, whichever comes first. Patients who experience all other adverse events will be reported for patients until 30 days after the last dose of study, or until initiation of another systemic anti-cancer therapy, whichever occurs first. After this period, investigators should ensure any deaths, serious adverse events, or other adverse events of concern are reported if they are later assessed to be related to study treatment. Post-study treatment follow-up visits for tumor recurrence surveillance should include monitoring for potential late serious adverse events and adverse events of special interest. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or study-related procedures until a final outcome can be reported. Any medications given as treatment for an adverse event should be reported, even if given after the Treatment Discontinuation Visit.

[bb] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (±7 days) until death, loss to follow-up, consent withdrawal, or study termination by the Sponsor. All patients (irrespective of which arm they are randomized to) will be followed for survival and new anti-cancer therapy information (including targeted therapies and immunotherapies) and subsequent progressions, unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If *a* patient withdraws from *the* study, study staff may use a public information source (e.g., county records) to obtain information about survival status.

[cc] The PRO questionnaires (FKSI–19 and EQ–5D–5L) will be completed by the patients at the investigational site while patients are receiving study treatments. All PRO questionnaires completed at the clinic are required to be completed prior to the exchange of meaningful information (e.g., lab results), prior to administration of study treatment and/or prior to any other study assessment(s) that could bias patients' responses to ensure that the validity of the instruments is not compromised and to ensure that data quality meets regulatory requirements. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site, and the hard copy originals of the questionnaires must be maintained as part of the patient's medical record when relevant at the site for source data verification. Study personnel will record patient responses on a paper copy as a record of source documentation.

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

[ee] After discontinuation of the study treatment, the PRO questionnaires will be administered by trained site staff over the phone or at the site at end of treatment visit, the post–treatment visit, any visit for assessment of RCC recurrence, and at two timepoints after disease recurrence during survival follow–up.

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Sample Type
Cycle 1, Day 1	Pre–dose	Serum atezolizumab ADA Serum atezolizumab pharmacokinetics Plasma PD biomarker Serum PD Biomarker Whole blood PBMC
	30 min (± 10 min) (after the end of infusion)	Serum atezolizumab pharmacokinetics
Cycles 2 and 4, Day 1	Pre–dose	Plasma PD biomarker Serum PD biomarker
Cycles 2, 3, and 4, Day 1	Pre–dose	Serum atezolizumab ADA Serum atezolizumab pharmacokinetics
Cycle 8, Day 1	Pre–dose	Serum atezolizumab ADA Serum atezolizumab pharmacokinetics
Treatment discontinuation visit [a]	At visit	Serum atezolizumab ADA Serum atezolizumab pharmacokinetics
	At visit	Plasma PD biomarker Serum PD biomarker
At disease recurrence [b, c]	At visit [d]	Plasma PD biomarker Serum PD biomarker

ADA = anti–drug antibody; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic.

[a] Treatment discontinuation visit occurs within 30 days after last dose of study treatment and applies to all patients who discontinue study treatment (regardless of the reason).

[b] If a patient discontinues the study due to disease recurrence, it is acceptable to collect PD blood at the visit at which tumor assessment shows disease recurrence only, and waive collection at the treatment discontinuation visit.

[c] Disease recurrence blood sample collection should occur at the same time as disease recurrence tissue biopsy sample collection. Disease recurrence blood sample should still be collected even if the Medical Monitor waives the requirement for tissue biopsy sample.

[d] It is acceptable to collect the disease recurrence samples at either investigator-assessed recurrence or IRF-assessed disease recurrence. The disease recurrence samples must be collected within 2 weeks after disease recurrence has been confirmed.

Appendix 3
Tumor, Lymph Node, Metastasis Staging System

Primary tumors (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney
T1b	Tumor >4 cm but ≤7 cm in greatest dimension, limited to the kidney
T2	Tumor >7 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney
T2b	Tumor >10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond the Gerota fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond the Gerota fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional lymph node (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 1 High Risk as Defined by a Modified UISS TNM/Grading System

Tumor Stage	Fuhrman Grade	Nodal Stage
T2	4	Any
T3a	3–4	Any
T3b/c T4	Any	Any
Any	Any	Positive

UISS = University of California Los Angeles integrated staging system;
T = primary tumors; TLM = tumor, lymph node, metastasis.

Reference: Zisman et al. 2002.

Appendix 4
Fuhrman Grading System for Renal Cell Carcinoma

The recommended histologic grading schema for renal cell carcinoma (RCC) is the Fuhrman system (Furman et al. 1982), which is an assessment based on the microscopic morphology of a neoplasm with hematoxylin and eosin (H&E staining). This system categorizes RCC with Grades I, II, III, IV on the basis of nuclear characteristics. The details of the Fuhrman grading system for RCC are shown below.

Grade Level	Nuclear Characteristics
Grade I	Nuclei appear round and uniform, 10 μm; nucleoli are inconspicuous or absent at ×400 magnification.
Grade II	Nuclei have a round to slightly irregular appearance, 15 μm; nucleoli are mildly enlarged at ×400 magnification.
Grade III	Nuclei appear irregular, 20 μm; nucleoli are prominent at ×100 magnification.
Grade IV	Nuclei show extreme nuclear pleomorphism and/or containing tumor giant cells, 20 μm or more; nucleoli are prominent.

Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol 1982;6:655–63.

Appendix 5
National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Kidney Symptom Index–19: FKSI–19

NCCN-FACT FKSI-19 (Version 2)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	H7	I feel fatigued	0	1	2	3	4
	B1	I have been short of breath	0	1	2	3	4
	BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	L2	I have been coughing	0	1	2	3	4
	H12	I feel weak all over	0	1	2	3	4
	RCC 2	I have had blood in my urine	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
	GP5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
TSE	GP2	I have nausea	0	1	2	3	4
	C5	I have diarrhea (diarrhoea)	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
FWB	GF1	I am able to work (include work at home)	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

English (Universal)

03 March 2010

Appendix 6
EuroQol 5–Dimension Questionnaire: EQ–5D–5L

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Health Questionnaire

English version for the USA

Appendix 6
EuroQol 5-Dimension Questionnaire: EQ-5D-5L (cont.)

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

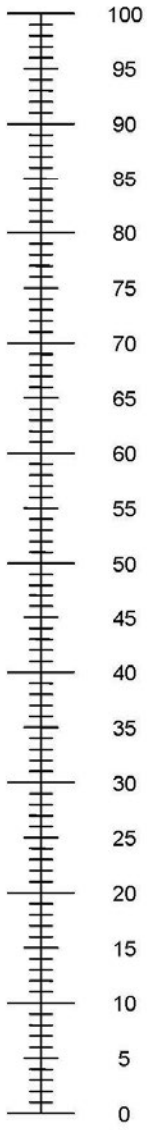
- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

Appendix 6
EuroQol 5-Dimension Questionnaire: EQ-5D-5L (cont.)

The best health you can imagine

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



The worst health you can imagine

Appendix 6
EuroQol 5-Dimension Questionnaire: EQ-5D-5L (cont.)

Health Questionnaire

English version for the USA

SCRIPT FOR TELEPHONE INTERVIEW

GENERAL INTRODUCTION

It is suggested that the telephone interviewer follows the script of the EQ-5D. Although allowance should be made for the interviewer's particular style of speaking, the wording of the questionnaire instructions should be followed as closely as possible. In the case of the EQ-5D descriptive system on pages 2 and 3, the exact wording must be followed.

It is recommended that the interviewer has a copy of the EQ-5D in front of him or her as it is administered over the telephone. This enables the respondent's answers to be entered directly on the EQ-5D by the interviewer on behalf of the respondent (i.e. the appropriate boxes on pages 2 and 3 are marked and the scale on page 4 is marked at the point indicating the respondent's 'health today'). If the respondent asks for clarification, the interviewer can help by re-reading the question verbatim. The interviewer should not try to offer his or her own explanation but suggest that the respondent uses his or her own interpretation.

If the respondent has difficulty regarding which box to mark, the interviewer should repeat the question verbatim and ask the respondent to answer in a way that most closely resembles his or her thoughts about his or her health today.

Appendix 6
EuroQol 5-Dimension Questionnaire: EQ-5D-5L (cont.)

INTRODUCTION TO EQ-5D

(Note to interviewer: please read the following)

We are trying to find out what you think about your health. I will first ask you some simple questions about your health TODAY. I will then ask you to rate your health on a measuring scale. I will explain what to do as I go along but please interrupt me if you do not understand something or if things are not clear to you. Please also remember that there are no right or wrong answers. We are interested here only in your personal view.

EQ-5D DESCRIPTIVE SYSTEM: INTRODUCTION

First I am going to read out some questions. Each question has a choice of five answers. Please tell me which answer best describes your health TODAY. Do not choose more than one answer in each group of questions.

(Note to interviewer: it may be necessary to remind the respondent regularly that the timeframe is TODAY. It may also be necessary to repeat the questions verbatim)

EQ-5D DESCRIPTIVE SYSTEM

MOBILITY

First I'd like to ask you about mobility. Would you say that:

1. **You have no problems walking?**
2. **You have slight problems walking?**
3. **You have moderate problems walking?**
4. **You have severe problems walking?**
5. **You are unable to walk?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

SELF-CARE

Next I'd like to ask you about self-care. Would you say that:

1. **You have no problems washing or dressing yourself?**
2. **You have slight problems washing or dressing yourself?**
3. **You have moderate problems washing or dressing yourself?**
4. **You have severe problems washing or dressing yourself?**
5. **You are unable to wash or dress yourself?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

Appendix 6
EuroQol 5-Dimension Questionnaire: EQ-5D-5L (cont.)

USUAL ACTIVITIES

Next I'd like to ask you about your usual activities, for example work, study, housework, family or leisure activities. Would you say that:

1. **You have no problems doing your usual activities?**
2. **You have slight problems doing your usual activities?**
3. **You have moderate problems doing your usual activities?**
4. **You have severe problems doing your usual activities?**
5. **You are unable to do your usual activities?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

PAIN / DISCOMFORT

Next I'd like to ask you about pain or discomfort. Would you say that:

1. **You have no pain or discomfort?**
2. **You have slight pain or discomfort?**
3. **You have moderate pain or discomfort?**
4. **You have severe pain or discomfort?**
5. **You have extreme pain or discomfort?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

ANXIETY / DEPRESSION

Finally I'd like to ask you about anxiety or depression. Would you say that :

1. **You are not anxious or depressed?**
2. **You are slightly anxious or depressed?**
3. **You are moderately anxious or depressed?**
4. **You are severely anxious or depressed?**
5. **You are extremely anxious or depressed?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

Appendix 6
EuroQol 5-Dimension Questionnaire: EQ-5D-5L (cont.)

EQ VAS: INTRODUCTION

(Note for interviewer: If possible, it might be useful to send a visual aid (i.e. the EQ VAS) before the telephone call so that the respondent can have this in front of him or her when completing the task)

Now, I would like to ask you to say how good or bad your health is TODAY.

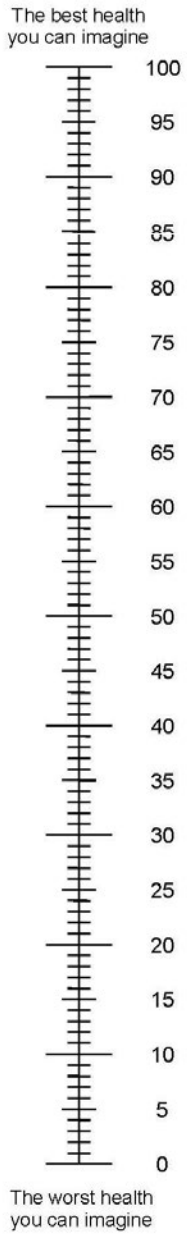
I'd like you to try to picture in your mind a scale that looks a bit like a thermometer. Can you do that? The best health you can imagine is marked 100 (one hundred) at the top of the scale and the worst health you can imagine is marked 0 (zero) at the bottom.

EQ VAS: TASK

I would now like you to tell me the point on this scale where you would put your health today.

(Note to interviewer: mark the point on the scale at the point indicating the respondent's 'health today')

Thank you for taking the time to answer these questions.



Appendix 7
Preexisting Autoimmune Diseases

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of auto-immune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. 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). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction while receiving another immuno-stimulator anti-cancer agent. The Medical Monitor *is available to advise on* any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune nephritis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behcet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Chung–Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa *acquisita* • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain–Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert–Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis *nodosa* • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary *cholangitis* • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren's syndrome • Stiff–Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt–Kovanagi–Harada disease • Wegener granulomatosis

Appendix 8
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Maintain an adequate airway.
3. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations.

Appendix 9
Guidelines for the Assessment of Renal Cell Carcinoma at Screening and Disease Recurrence

Assessment of renal cell carcinoma (RCC) at screening and disease recurrence will be made on the basis of radiographic evidence and whenever possible supported/confirmed by biopsy results. The following are intended as general radiographic guidelines.

RCC Assessment at Screening

Determination of absence of residual disease and absence of metastasis will be made on the basis of radiographic evidence, supported/confirmed by biopsy results (from biopsies performed before or during the screening period) and/ or historical scans (if available). Disease-free status by imaging is defined as meeting all of the following criteria:

- Lymph nodes must be normal. A non–pathological lymph node is less than 10 mm in short axis.
- Absence of non–nodal lesions (e.g., no skin or subcutaneous lesions and no presence of CNS metastases or leptomeningeal disease), with the exception of non-nodal lesions that are diagnosed as histologically benign.
- Presence of stable pulmonary nodules is acceptable, provided either of the following conditions are met:
  - Pulmonary nodules 6 mm or less in diameter are diagnosed as histologically benign.
  - Pulmonary nodules greater than 6 mm in diameter require either evidence that the lesion is histologically benign or demonstration of radiographic stability across imaging tests at least 4 weeks apart.

Pleural effusion should not be considered as disease presence unless there is a suspicion for underlying pulmonary/pleural malignancy based on CT or additional imaging.

Confirmation of disease–free status will be assessed by an independent central radiologic review of imaging data. All imaging data and supportive data (e.g., historical images and pathology report forms) must be submitted to the imaging vendor.

RCC Assessment at Disease Recurrence

As a general guideline for recurrence, if a suspected lesion is equivocal, for example because of its small size, continued study treatment (if applicable) and follow–up evaluation will clarify whether it represents true recurrence. If repeat scans confirm the presence of new lesions or intervening growth, then recurrence should be declared using the date of the scan that the new equivocal lesion or equivocal progression was first prospectively identified as equivocal.

Appendix 9
Guidelines for the Assessment of Renal Cell Carcinoma at Screening and Disease Recurrence (cont.)

Renal bed: There is potential for some radiographic changes in the postoperative setting to be related to inflammation. Thus, in the absence of biopsy confirmation, assessment of recurrence in the ipsilateral renal bed should be determined by lesions that are radiographically consistent with RCC, or demonstrating growth over at least two sequential imaging tests (either computed tomography [CT] or magnetic resonance imaging [MRI]) at least 4 weeks apart. New contralateral lesions that are radiographically consistent with RCC (either recurrence or new RCC primary) are considered a disease–free survival (DFS) event.

Pulmonary: Disease recurrence should be unequivocal, and competing diagnoses (e.g., infectious, inflammatory) should be excluded. If there are multiple lesions ≥ 10mm that are radiographically consistent with RCC, or innumerable lesions that are unequivocally consistent with RCC, radiographic criteria would be met. If a suspected lesion is equivocal (e.g., because of its small size), continued study treatment (if applicable) and follow–up evaluation will clarify whether it represents true recurrence. If repeat scans confirm the presence of additional new lesions or intervening growth, then recurrence should be declared using the date of the initial scan. As a general guideline during the study, if there is a new, solitary radiographic nodule > 8mm, the lesion should be followed serially by imaging and/or should be biopsied to exclude secondary malignancy or benign process. Comprehensive guidelines for the evaluation of pulmonary nodules are described in Gould et al. 2013 (see Figure 1).

Bone: Bone recurrence can be determined by unequivocal findings that are consistent with RCC on a single image (e.g., CT, MRI) in the context of appropriate clinical symptoms. Prostate–specific antigen (PSA) testing in men, or other testing as clinically indicated, is recommended to exclude secondary malignancies. If imaging is indeterminate or non–diagnostic, serial imaging should be performed for confirmation.

Lymph node: To be considered pathologically enlarged, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Liver: Arterial phase contrast enhancement is recommended for imaging. A single lesion ≥ 10mm in a single dimension and radiographically consistent with RCC is considered pathologically enlarged and meets radiographic criteria for disease recurrence.

Adrenal: Arterial phase contrast enhancement is recommended for imaging. A single lesion ≥ 10mm in a single dimension and radiographically consistent with RCC is

considered pathologically enlarged and meets radiographic criteria for disease recurrence.

Brain: A single lesion ≥5mm or multiple lesions radiographically consistent with RCC is sufficient to meet criteria. Given the challenges in this location, biopsy is not required for disease assessment.

Other sites: As a general guideline, new lesions ≥10mm and radiographically consistent with RCC should be considered recurrence. Multiple lesions of any size consistent with metastatic RCC involvement may also be considered recurrence. Non-measurable lesions (such as leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread) suggestive of unequivocal involvement with metastatic RCC may also be considered recurrence. Competing diagnoses such as alternative malignancies, infectious, or inflammatory etiologies should always be excluded.

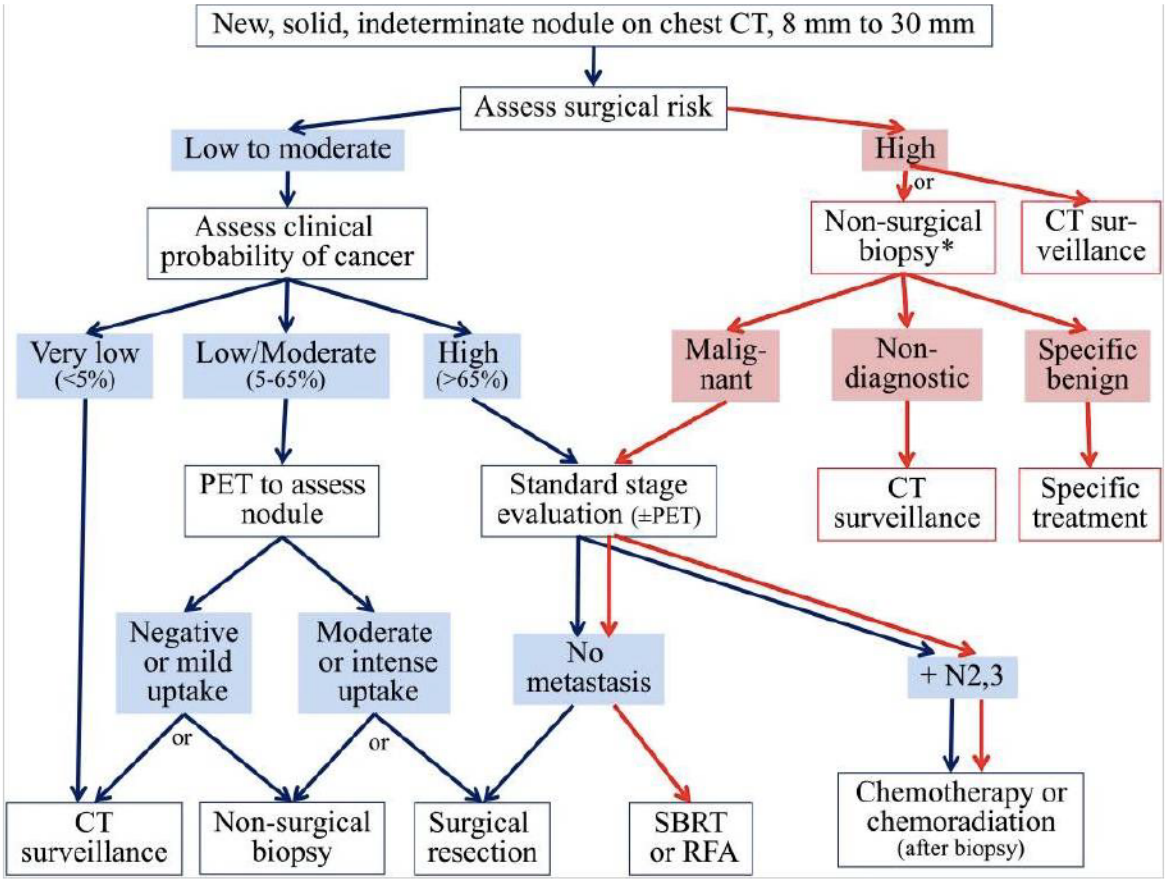
References

Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence–based clinical practice guidelines. Chest. 2013;143(5 Suppl):e93S–120S.

Naidich DP, Bankier AA, MacMahon H, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: A statement from the Fleischner Society. Radiology 2013:266;304–317.

Appendix 9
Guidelines for the Assessment of Renal Cell Carcinoma at Screening and Disease Recurrence (cont.)

Figure 1 Guidelines for the Evaluation of New, Solid Indeterminate Nodules



CT = computed tomography; PET = positron–emission tomography; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy.

Source: Gould et al 2013.

Appendix 10
Definition of Sarcomatoid Renal Cell Carcinoma: Modified Stanford Surgical Pathology Criteria

Sarcomatoid renal cell carcinoma is defined as any histologic type of renal cell carcinoma containing a focus/foci of high–grade malignant spindle cells of any component relative to the entire tumor area.

Requires evidence of epithelial differentiation with concurrent areas of renal cell carcinoma

Or

Evidence of epithelial differentiation in the spindle cells with immuno-histochemical positivity for keratin or epithelial membrane antigen (EMA)

Spindle cells must show moderate to marked atypia and resemble any form of sarcoma.

Frequent patterns include: fibrosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma

Focal spindling because of non-cohesion of tumor cells is not considered to represent sarcomatoid differentiation.

Any spindle component relative to the entire tumor area

Degree of sarcomatoid differentiation should be recorded in the electronic case report form (eCRF) as 1) any component, 2) >20% component, or 3) predominant sarcomatoid component.

References:

Cheville JC, Lohse CM, Zincke H, et al. Sarcomatoid renal cell carcinoma: an examination of underlying histologic subtype and an analysis of associations with patient outcome. Am J Surg Pathol 2004;28:435–41.

Delahunt B, Cheville JC, Martingoni G, et al. The International Society of Urology Pathology (ISUP) Grading System for Renal Cell Carcinoma and Other Prognostic Parameters. Am J Surg Pathol 2013;37:1490–504.

de Peralta–Venturina M, Moch H, Amin M,et al. Sarcomatoid differentiation in renal cell carcinoma: a study of 101 cases. Am J Surg Pathol 2001;25:275–84.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune–mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator. *The* Medical Monitor *is available to advise as needed.*

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 1.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re–evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • *For Grade 1 pneumonitis, consider withholding atezolizumab.*
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events *or events with no improvement after 48–72 hours of corticosteroids*, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day *IV methylprednisolone*. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL=bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

HEPATIC EVENTS

Immune–mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

Patients with right upper–quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	All events: • Monitor LFTs more frequently until return to baseline values. Events of > 5 days' duration: • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *The* Medical Monitor *is available to advise as needed.*

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

LFT=liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *The* Medical Monitor *is available to advise as needed.*

GASTROINTESTINAL EVENTS

Immune–mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 3.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of

systemic inflammation or acute–phase reactants (e.g., increased C–reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist ≥5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI=gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle–stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • *Consider patient referral to endocrinologist.* **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism. • *Consider patient referral to endocrinologist.*
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti–thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune–mediated hyperthyroidism. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • *Evaluate for diabetic ketoacidosis and manage as per institutional guidelines.* • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI=magnetic resonance imaging; TSH=thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI =magnetic resonance imaging; TSH =thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *The* Medical Monitor *is available to advise as needed.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 5.

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE–MEDIATED MYOCARDITIS

Immune–mediated myocarditis has been associated with the administration of atezolizumab. Immune–mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. *Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly.* Immune–mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X–ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 6 Management Guidelines for Immune–Mediated Myocarditis

Event	Management
Immune–mediated myocarditis, Grade 2–4	• Permanently discontinue atezolizumab and contact Medical Monitor.[a] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed*.

INFUSION–RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, anti-pyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell

therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 7.

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-α (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 7 Management Guidelines for Infusion–Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 7 Management Guidelines for Infusion–Related Reactions and Cytokine-Release Syndrome (cont.)

Event	Management
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. [e] • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 7 Management Guidelines for Infusion–Related Reactions and Cytokine-Release Syndrome (cont.)

Event	Management
Grade 3 Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, nonrebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. [e] • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact Medical Monitor. [f] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. [e] For patients who are refractory to anti-cytokine therapy, experimental treatments [g] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=bi-level positive airway pressure; CAR=chimeric antigen receptor; CPAP=continuous positive airway pressure; CRS=cytokine-release syndrome; CTCAE=Common Terminology Criteria for Adverse Events; eCRF=electronic Case Report Form; HLH=hemophagocytic lymphohistiocytosis; ICU=intensive care unit; IRR=infusion-related reaction; MAS=macrophage activation syndrome; NCCN=National Comprehensive Cancer Network; NCI=National Cancer Institute.

Note: These management guidelines have been adapted from NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥38 C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤6 L/min, and high flow is defined as oxygen delivered at >6 L/min.

[e] There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

[f] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed*. . For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after *assessing* the benefit–risk ratio.

[g] Refer to Riegler et al. (2019) for information on experimental treatments for CRS.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work–up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune–mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune–mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

G = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

DERMATOLOGIC EVENTS

Treatment–emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher–potency topical corticosteroids if event does not improve. • *If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.*
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 9 Management Guidelines for Dermatologic Events (cont.)

Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain–Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work–up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune–mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune–mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology *and refer patient to neurologist.* • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune–mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • *Refer patient to neurologist.* • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain–Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. T*he Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

IMMUNE–MEDIATED MENINGOENCEPHALITIS

Immune–mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune–mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or

encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Immune–Mediated Meningoencephalitis

Event	Management
Immune–mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *T*he Medical Monitor *is available to advise as needed.*

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

RENAL EVENTS

Immune–mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti–inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine *and urine protein*, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune–mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. *Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.*

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 12 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The* Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). *The* Medical Monitor *is available to advise as needed.*

Table 13 Management Guidelines for Immune-Mediated Myositis (cont.)

Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, *permanently discontinue atezolizumab and contact Medical Monitor.* [c] *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever $\geq$38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin $<$90 g/L (9 g/dL) ($<$100 g/L [10 g/dL] for infants $<$4 weeks old)
  - Platelet count $<100\times10^9$/L (100,000/μL)
  - ANC $<1.0\times10^9$/L (1000/μL)
- Fasting triglycerides $>$2.992 mmol/L (265 mg/dL) and/or fibrinogen $<$1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin $>$500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated $\geq$2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin $>$684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq181\times10^9$/L (181,000/μL)
  - AST $\geq$48 U/L
  - Triglycerides $>$1.761 mmol/L (156 mg/dL)
  - Fibrinogen $\leq$3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019) • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH=hemophagocytic lymphohistiocytosis; MAS=macrophage activation syndrome.

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Appendix 11
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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