Official Title: A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH BEVACIZUMAB VERSUS SUNITINIB IN PATIENTS WITH UNTREATED ADVANCED RENAL CELL CARCINOMA

NCT Number: NCT02420821

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SAP Version 2: 04-April-2018

PROTOCOL

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH BEVACIZUMAB VERSUS SUNITINIB IN PATIENTS WITH UNTREATED ADVANCED RENAL CELL CARCINOMA**
PROTOCOL NUMBER:	WO29637
VERSION NUMBER:	7
EUDRACT NUMBER:	2014-004684-20
IND NUMBER:	119039
TEST PRODUCT:	Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	24 December 2014
DATES AMENDED:	Version 2: 10 January 2015 Version 3: 8 May 2015 Version 4: 10 October 2015 Version 5: 10 December 2015 Version 6: 14 July 2016 Version 7: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	03-Apr-2018 15:31:43

PROTOCOL AMENDMENT, VERSION 7: RATIONALE

Protocol WO29637 has been amended [redacted]
Changes to the protocol, along with a rationale for each change, are summarized below:

- An additional overall survival (OS) interim analysis, including updated alpha adjustment of the sequential testing of the OS interim analyses in the statistical analysis plan, [redacted] for the IMmotion151 study. The overall type 1 error of OS analyses is controlled at 5% per pre-specified O'Brien-Fleming boundary where the 5% alpha is determined given the co-primary endpoint of PFS was met. A total of four analyses of OS will be performed according to the new analysis plan, including three interim analyses and one final analysis. The first OS interim was performed at the PFS primary analysis, the second OS interim analysis has now been added to the original interim analyses plan, and the third interim and final OS analyses remain unchanged in terms of the event rate that will trigger the interim analysis, as per the original interim analyses plan (described in Protocol WO29637, Version 6) (Section 6.9.2). The analysis plan in Sections 6.2–6.8 remain unchanged.
- The Medical Monitor name and contact information have been updated (Section 5.4.1).

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

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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 the signed original of this form as instructed by F. Hoffmann-La Roche Ltd.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH BEVACIZUMAB VERSUS SUNITINIB IN PATIENTS WITH UNTREATED ADVANCED RENAL CELL CARCINOMA**
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IND NUMBER:	119039
TEST PRODUCT:	Atezolizumab (RO5541267)
PHASE:	Phase III
INDICATION:	Renal cell carcinoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Analyses of the following objectives will be performed for the population of patients with inoperable, locally advanced, or metastatic renal cell carcinoma (RCC), unless otherwise indicated. Where specified, a comparison of the treatment arms will be performed in the patient population defined according to tumor programmed death–ligand 1 (PD-L1) expression as evaluated by immunohistochemistry (IHC).

Efficacy Objectives

The primary and secondary efficacy objectives will be evaluated in the PD-L1–selected population (tumor-infiltrating immune cell [IC]1/2/3) as well as in the intent-to-treat (ITT) population (includes all IC scores).

The primary efficacy objective of the study is as follows:

- To evaluate the efficacy of atezolizumab + bevacizumab compared with sunitinib as measured by the co-primary endpoints of investigator-assessed progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and overall survival (OS).

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by Independent Review Committee (IRC)–assessed PFS according to RECIST v1.1
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by investigator-assessed objective response rate (ORR) (complete + partial response rates) per RECIST v1.1
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by investigator-assessed duration of response (DOR) among patients with an objective response per RECIST v1.1
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by IRC-assessed ORR and DOR according to RECIST v1.1
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by investigator-assessed PFS, DOR, and ORR per modified RECIST

- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib among patients with sarcomatoid histology (defined by investigator-assessed conventional histopathology) as measured by investigator assessed PFS per RECIST v1.1 and OS
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib on symptom interference as measured by the M.D. Anderson Symptom Inventory [MDASI Part II])

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab + bevacizumab versus sunitinib
- To evaluate the incidence of anti-therapeutic antibodies (ATAs) against atezolizumab and to explore the potential relationship of immunogenicity response with pharmacokinetics, safety, and efficacy

Pharmacokinetic Objectives

The pharmacokinetic objectives for this study are as follows:

- To characterize the pharmacokinetics of atezolizumab when administered in combination with bevacizumab
- To characterize the pharmacokinetics of bevacizumab when administered in combination with atezolizumab

Patient-Reported Outcome Objectives

The additional patient-reported outcome (PRO) objectives of the study are as follows:

- To assess symptom severity associated with atezolizumab + bevacizumab versus sunitinib in patients with RCC as measured by the MDASI and Brief Fatigue Inventory (BFI)
- To document patients' perspective regarding the tolerability of the treatments (from the treatment side-effects subscale from the Functional Assessment of Cancer Therapy Kidney Symptom Index [FKSI-19])
- To obtain general measures of health as measured by the EuroQoL 5 Dimensions (EQ-5D) questionnaire for health economic modeling of atezolizumab + bevacizumab versus sunitinib in patients with RCC

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the relationship between the expression of other candidate predictive immune, angiogenic, or hypoxia biomarkers, as defined by IHC or quantitative polymerase chain reaction (qPCR), and efficacy as defined by PFS and ORR
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib among patients with tumor Fuhrman Grade 4 or sarcomatoid histology (defined by investigator-assessed conventional histopathology) as measured by PFS and ORR
- To assess immune-mediated predictive and prognostic exploratory biomarkers in tumor tissue and blood from archival specimens, fresh biopsy specimens, or specimens obtained during the study and their association with disease status and/or efficacy as defined by PFS and ORR

Study Design

Description of Study

This is a Phase III, multicenter, randomized, open-label study designed to evaluate the efficacy and safety of atezolizumab + bevacizumab versus sunitinib in patients with inoperable, locally advanced, or metastatic RCC who have not received prior systemic active or experimental therapy, either in the adjuvant or metastatic setting.

Number of Patients

The study will enroll approximately 900 patients, including a minimum of 351 patients with a PD-L1 IHC of IC score of 1/2/3 (PD-L1–selected population), at approximately 150–180 centers globally. A maximum of approximately 180 patients *(20%)* with a Memorial Sloan Kettering Cancer Center (MSKCC [Motzer]) score of 0 (good risk) will be enrolled.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Unresectable advanced or metastatic RCC with clear-cell histology and/or component of sarcomatoid carcinoma

  Renal cell carcinoma with any component of high-grade malignant spindle cells consistent with sarcomatoid histology is eligible. (See the protocol for further guidelines regarding defining sarcomatoid histology.)
- Evaluable MSKCC risk score (i.e., "Motzer" score)

  All MSKCC risk scores are included

  Patients with good risk MSKCC (risk score 0) will comprise no more than 20% of the study population
- Definitive diagnosis of RCC on the basis of a representative, formalin-fixed, paraffin-embedded tumor specimen accompanied by an associated pathology report collected within 24 months prior to Cycle 1, Day 1 available at the study site that allows determination of PD-L1 expression status (IC) (required prior to randomization)

  The archival specimen must contain adequate viable tumor tissue to establish PD-L1 expression status by a central laboratory prior to randomization.

  The specimen may consist of a tissue block (preferred) or at least 15 unstained, serial sections.

  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 embedded into a single paraffin block should be submitted for evaluation. Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

  If the archival tissue was acquired >24 months prior to Cycle 1, Day 1, the patient may still be eligible provided the patient is willing to consent to and undergo a pre-treatment core or excisional biopsy of the tumor. If the location of the tumor renders the tumor biopsy medically unsafe, eligibility may be provided with Medical Monitor approval. A local analysis to confirm the diagnosis of RCC is required.
- Measurable disease, as defined by RECIST v1.1
- Age ≥ 18 years
- Karnofsky performance status ≥ 70
- Ability and capacity to comply with study and follow-up procedures
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 28 calendar 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 cells/μL

  Lymphocyte count ≥ 300 cells/μL

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

  Hemoglobin ≥ 9.0 g/dL

  AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ ULN, with the following exceptions:

  Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN

Patients with documented liver or bone metastases: alkaline phosphatase $\leq 5 \times$ 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, unless on a stable dose of warfarin

Serum albumin > 2.5 g/dL

Creatinine clearance ≥ 30 mL/min (Cockcroft-Gault formula or based on 24-hour urine collection)

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 6 months after the last dose of atezolizumab and bevacizumab or 30 days after the last dose of sunitinib.

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

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

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

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 6 months after the last dose of bevacizumab or 30 days after the last dose of sunitinib. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for the duration of the pregnancy to avoid exposing the embryo.

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

- Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:

  Evaluable or measurable disease outside the CNS

  Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)

  No history of intracranial or spinal cord hemorrhage

  No evidence of significant vasogenic edema

  No ongoing requirement for corticosteroids as therapy for CNS disease

  No stereotactic radiation within 14 days

  No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment,

these patients may then be eligible without the need for an additional brain scan prior to enrollment [or randomization], if all other criteria are met.

Exclusion Criteria

Disease-Specific Exclusions

- Prior treatment with active or experimental systemic agents, including treatment in the neoadjuvant or adjuvant setting. Prior treatment with placebo in adjuvant setting is allowed.
- Radiotherapy for RCC within 14 calendar days prior to Cycle 1, Day 1
- Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated at least 14 days prior to Cycle 1, Day 1.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
- Uncontrolled hypercalcemia ($>$ 1.5 mmol/L ionized calcium or calcium $>$ 12 mg/dL) or symptomatic hypercalcemia refractory to bisphosphonate therapy or denosumab

  Patients who are currently receiving bisphosphonate therapy without current hypercalcemia (corrected serum calcium greater than the upper limit of normal) are eligible.
- Malignancies other than RCC within 5 years prior to Cycle 1, Day 1

  Patients with localized low risk prostate cancer (defined as stage $\leq$ T2b, Gleason score $\leq$ 7, and PSA at prostate cancer diagnosis $\leq$ 20 ng/mL) treated with curative intent and without prostate-specific antigen (PSA) recurrence are eligible

  Patients with low risk prostate cancer (defined as Stage T1/T2a, Gleason score $\leq$ 6, and PSA $\leq$ 10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible

  Patients with malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death $<$ 5% at 5 years) are eligible provided they meet all of the following criteria:

  Malignancy treated with expected curative intent (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent)

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

General Medical Exclusions

- Life expectancy of $<$ 12 weeks
- Current, recent (within 4 weeks of Cycle 1, Day 1), or planned participation in another experimental drug study
- Pregnant and lactating , or intending to become pregnant during the study
- Women who are not postmenopausal ($\geq$ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- 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 the protocol for a more comprehensive list of autoimmune diseases)

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

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

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan; however, history of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive test for HIV
- Patients with active or chronic hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening)

  Patients with past/resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. A negative HBV DNA test must be obtained in patients with positive hepatitis B core antibody prior to Cycle 1, Day 1.
- Patients with active hepatitis C

  Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) analysis is negative for HCV RNA.
- Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of infection (including active tuberculosis) within 2 weeks prior to Cycle 1, Day 1
- Received therapeutic oral or intravenous antibiotics within 2 weeks prior to Cycle 1, Day 1

  Patients receiving routine antibiotic prophylaxis (e.g., to prevent chronic obstructive pulmonary disease exacerbation or for dental extraction) are eligible.
- Significant cardiovascular or cerebrovascular disease, such as New York Heart Association cardiac disease (Class II or greater), unstable angina, myocardial infarction or cerebrovascular events within the previous 6 months or unstable arrhythmias within the previous 3 months.

  Patients with known coronary artery disease, arrhythmias, congestive heart failure not meeting the above criteria must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. Baseline evaluation of left ventricular ejection fraction (LVEF) should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease.

  Patients with known LVEF $< 50\%$
- Major surgical procedure other than for diagnosis within 21 days prior to Cycle 1, Day 1, or planned procedure or surgery during the study
- Prior allogeneic stem cell or solid organ transplant
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1

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

Exclusion Criteria Related to Medications

- 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 interferon α, interleukin-2) for the treatment of non-malignant conditions within 6 weeks or five half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1
- Any prior use of systemic immunostimulatory agents for the management of metastatic RCC is excluded.
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [anti–TNF] agents) within 2 weeks prior to Cycle 1, Day 1.

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) or physiologic replacement doses (i.e., prednisone 5–7.5 mg/day) for adrenal insufficiency may be enrolled in the study.

  The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for adrenal insufficiency), and mineralocorticoids (e.g., fludrocortisone) is allowed.

Bevacizumab- and Sunitinib-Specific Exclusions

- Inadequately controlled hypertension (defined as systolic blood pressure $>$ 150 mmHg and/or diastolic blood pressure $>$ 100 mmHg)

  Anti-hypertensive therapy to maintain a systolic blood pressure $<$ 150 mmHg and/or diastolic blood pressure $<$ 100mmHg is permitted.
- Prior history of hypertensive crisis or hypertensive encephalopathy
- New York Heart Association Class II or greater congestive heart failure
- History of stroke or transient ischemic attack within 6 months prior to Cycle 1, Day 1
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Cycle 1, Day 1
- Patients with a baseline ECG demonstrating a QTc $>$ 460 ms
- Evidence of bleeding diathesis or clinically significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (within 10 calendar days prior to Cycle 1, Day 1) use of dipyramidole, ticlopidine, clopidogrel, or cilostazol.
- Prophylactic or therapeutic use of low molecular weight heparin (e.g., enoxaparin), direct thrombin inhibitors, or warfarin are permitted, provided, where appropriate anticoagulation indices are stable. Patients should have been on a stable dose (for therapeutic use) for at least 2 weeks (or until reaching steady state level of the drug) prior to the first study treatment
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 calendar days prior to the first dose of bevacizumab
- History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to Cycle 1, Day 1
- Clinical signs or symptoms of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Proteinuria, as demonstrated by urine dipstick or $>$ 1.0 g of protein in a 24-hour urine collection

  All patients with $\geq$ 2+ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection for protein.

Length of Study

On the basis of accrual projections and projected median OS for each treatment arm, the final analysis of OS is projected to occur at Month 63 from the time the first patient is randomized.

End of Study

The end of study will occur when the number of deaths required for the final analysis of OS has been observed. On the basis of accrual projections and projected median OS for each treatment arm, the final analysis of OS is projected to occur at Month 63 from the time the first patient is randomized.

Outcome Measures

Efficacy Outcome Measures

The co-primary efficacy outcome measures are:

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator from tumor assessments based on RECIST v1.1, or death from any cause and
- OS, defined as the time from randomization to death due to any cause

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

- PFS based on IRC assessment of radiographic progression per RECIST v1.1
- ORR, defined as the proportion of patients with an objective response (either complete response or partial response, confirmation not required) as determined by investigator per RECIST v1.1
- Duration of response (DOR), defined as the time from the first documented response to documented disease progression as determined by the investigator per RECIST v1.1 or death due to any cause, whichever occurs first
- ORR and DOR based on IRC assessment per RECIST v1.1
- PFS, ORR, and DOR based on investigator assessment per modified RECIST criteria
- Change from baseline in symptom interference (from MDASI Part II)

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of all adverse events, including Grade ≥ 3 laboratory toxicities (grading per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0; laboratory toxicities based on local laboratory assessments), during first-line treatment
- Incidence of ATA response to atezolizumab and potential correlation with pharmacokinetics, safety, and efficacy parameters

Pharmacokinetic Outcome Measures

The pharmacokinetic outcome measures for this study are as follows:

- Maximum atezolizumab serum concentration (C_{max}) after infusion on Cycle 1, Day 1
- Minimum atezolizumab serum concentration (C_{min}) prior to the infusion on Day 1 of Cycles 1, 2, 4, 8 and every eight cycles thereafter; Day 22 of Cycles 1, 2, and 4; and at study termination
- Bevacizumab C_{max} after infusion on Day 1 of Cycles 1 and 2
- Bevacizumab C_{min} prior to the infusion on Day 1 of Cycles 1 and 2 and at study termination

Patient-Reported Outcome Measures

The other PRO outcome measures for this study are as follows:

- Change from baseline in symptom severity as measured by the MDASI and BFI
- Change from baseline in treatment side effects subscale (from FKSI-19)

In addition, health status will be collected the EuroQoL 5 Dimensions (EQ-5D) questionnaire to derive utilizes for health economic modeling.

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Status of PD-L1, immune-, angiogenic-, and RCC-related and other exploratory biomarkers in archival and/or freshly obtained tumor tissues and blood collected before, during, or after treatment with atezolizumab + bevacizumab or sunitinib or at progression
- PFS and ORR in patients with tumor Fuhrman Grade 4 or sarcomatoid histology (defined by investigator-assessed conventional histopathology)
- Status of tumor-infiltrating immune cells and biomarkers in biopsy specimens and blood collected at the first evidence of radiographic disease progression

Investigational Medicinal Products

Test Product (Investigational Drugs)

Atezolizumab + bevacizumab will be dosed in 6-week cycles. Atezolizumab will be administered intravenously at a fixed dose of 1200 mg on Days 1 and 22 of each 42-day cycle. Bevacizumab will be administered intravenously at 15 mg/kg on Days 1 and 22 of each 42-day cycle.

Comparator

Sunitinib will be administered in 6-week cycles at 50 mg/day given orally for 4 weeks, followed by 2 weeks of rest.

Statistical Methods

Primary Analysis

The co-primary efficacy endpoints are investigator-assessed PFS per RECIST v1.1 and OS. Because type I error will be controlled accounting for two co-primary endpoints, the study will be considered a positive study if statistical significance is achieved for either of the co-primary endpoints.

PFS will be analyzed in the PD-L1–selected population and OS will be analyzed first in the ITT population; additional analyses of OS will be performed in a hierarchical fashion.

PFS is defined as the time from randomization to disease progression, as determined by the investigator per RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. Data for patients with no post-baseline tumor assessments will be censored at the randomization date + 1 day.

For United States registrational purposes, the co-primary efficacy endpoint of PFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits.

OS is defined as the time from randomization to death due to any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization + 1 day.

The following analyses will be performed for both PFS endpoints described above and OS. PFS and OS will be compared between treatment arms with use of the stratified log-rank test. The HR will be estimated using a stratified Cox proportional hazards model. The 95% CI for the HR will be provided. The stratification factors will be the same as the randomization stratification factors: presence of liver metastasis (yes/no); tumor PD-L1 status (IC0 vs. IC1/2/3); and the MSKCC (Motzer) score (0, 1–2, ≥ 3). The stratification factors will be obtained from the IxRS at the time of randomization. Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate the median PFS and OS for each treatment arm, and Kaplan-Meier curves will be produced. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and OS for each treatment arm.

The following analyses will be performed for both PFS endpoints described above and (as applicable) for OS:

- Analyses described in the protocol for landmark timepoints
- Analyses described in the protocol for subgroups
- Secondary endpoint of PFS by IRC assessment, PD-L1–selected population and ITT population, based on RECIST v1.1
- Secondary endpoint of PFS by investigator assessment in the ITT population, based on RECIST v1.1

Patient-Reported Outcome Analysis

MDASI, and BFI, and FKSI-19

Scoring for the MDASI and BFI questionnaires will be based on their corresponding user manuals. For MDASI and BFI scales with more than 50% of the constituent items completed, a prorated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered missing.

The impact of symptoms on patients' functioning will be compared between treatment arms as a change from baseline on the interference items in the MDASI Part II.

The severity of symptoms captured in the MDASI and the BFI will be summarized using descriptive analyses including summary statistics and change from baseline at each assessment by treatment arm.

Determination of Sample Size

This study will randomize approximately 900 patients, including a minimum of approximately 351 patients with a PD-L1 IHC IC score of 1/2/3.

Type I Error Control

The type I error (α) for this study is 0.05 (two-sided). There are two co-primary efficacy endpoints for this study: PFS by investigator assessment per RECIST v1.1 and OS. To control the overall type I error rate at $\alpha = 0.05$ (two-sided) while accounting for two co-primary endpoints, α will be split between PFS ($\alpha = 0.04$) and OS ($\alpha = 0.01$). Because type I error will be controlled accounting for two co-primary endpoints, the study will be considered a positive study if statistical significance is achieved for either of the co-primary endpoints.

Formal treatment comparisons will be performed in a hierarchical fashion in which α may be recycled as follows:

1. PFS in the PD-L1–selected population will be evaluated at $\alpha = 0.04$ (two-sided).
2. If PFS results in the PD-L1–selected population are statistically significant at $\alpha = 0.04$, then $\alpha = 0.04$ will be recycled to OS in the ITT population, and OS in the ITT population will be evaluated at $\alpha = 0.05$ (two-sided). If PFS results in the PD-L1–selected population are not statistically significant at $\alpha = 0.04$, then no recycling of α will occur, and OS in the ITT population will be evaluated at $\alpha = 0.01$ (two-sided).
3. OS will be compared between treatment arms in a hierarchical fashion as follows. If OS results in the ITT population are statistically significant at the appropriate α level, then OS in the PD-L1–selected population will be evaluated at same α-level as for OS in the ITT population. If OS results in the ITT population are not statistically significant, formal treatment comparison of OS in the PD-L1–selected population will not be performed.

Interim analyses of OS and the final analysis of OS will be based on the α allocated to the comparison of OS, as described above. Statistical significance at interim analyses of OS will be evaluated.

Co-Primary Endpoint: Progression-Free Survival in the PD-L1–Selected Population

The analysis of the co-primary endpoint of PFS will take place when approximately 228 PFS events in the PD-L1–selected population (65% of the estimated 351 PD-L1–population) as defined for the primary analysis of PFS have occurred based on the following assumptions:

- Two-sided, stratified log-rank test
- $\alpha = 0.04$ (two-sided)

- Approximately 88% power
- Median PFS for the sunitinib arm of 11 months and estimated median PFS in the atezolizumab + bevacizumab arm of 17 months (corresponding to HR of 0.65)
- 5% annual loss to follow-up for PFS
- No interim analysis

Accrual is projected to occur over 20months, assuming a ramp-up period of 9 months.

On the basis of these assumptions, the required number of PFS events in the PD-L1–selected population is projected to occur at Month 34 from the time the first patient is randomized. Also on the basis of these assumptions, it is projected that an observed HR of 0.76 or lower will result in a statistically significant difference between treatment arms (i.e., an HR of 0.76 will be the minimally detectable difference for the analysis; this corresponds to an improvement of 3.5 months in median PFS from 11 months in the sunitinib arm to 14.5 months in the atezolizumab + bevacizumab arm).

Co-Primary Endpoint: Overall Survival in the ITT Population

The final analysis of the co-primary endpoint of OS will take place at the later of the time points when the required number of events has occurred in the PD-L1–selected population and in the ITT population, where the required number of events is as follows:

- 639 OS events in the ITT population (71% of the estimated 900 patients)
- 246 OS events in the PD-L1–selected population (70% of the estimated 351 patients)

The number of events required for the final OS analysis in these populations is based on the following assumptions:

- Two-sided, stratified log-rank test
- $\alpha = 0.01$ (two-sided)
- 1% annual loss to follow-up for OS
- For the ITT population:
  - 85% power
  - Median OS in the control arm of 24 months
  - Estimated median OS in the atezolizumab + bevacizumab arm of 32 months (an increase of 8 months, corresponding to an HR of 0.75
- For the PD-L1–selected population:
  - 53% power
  - Median OS in the control arm of 24 months
  - Estimated median OS in the atezolizumab + bevacizumab arm of 33.8 months (an increase of 9.8 months, corresponding to an HR of 0.71)

On the basis of these assumptions, the required number of OS events for the final analysis of OS in both the PD-L1–selected population and the ITT population is projected to occur at Month 63 from the time the first patient is randomized.

At the final OS analysis, on the basis of these assumptions, it is projected that an observed OS HR of 0.83 or lower in the ITT population will result in a statistically significant difference between treatment arms (i.e., the minimally detectable difference at the analysis; this corresponds to an improvement of 4.9 months in median OS, from 24 months in the control arm to 28.9 months in the atezolizumab + bevacizumab arm).

Also at the final OS analysis, on the basis of these assumptions, it is projected that an observed OS HR of 0.72 or lower in the PD-L1–selected population will result in a statistically significant difference between treatment arms (i.e., an HR of 0.72 will be the minimally detectable difference at the analysis; this corresponds to an improvement of 9.5 months in median OS, from 24 months in the control arm to 33.5 months in the atezolizumab + bevacizumab arm).

Interim Analyses

Progression-Free Survival

There are no planned interim analyses of the co-primary endpoint of PFS.

Overall Survival

A total of four analyses of OS will be performed, including three interim analyses and one final analysis. The α level for OS testing is 0.05 given that the co-primary endpoint of PFS was met in the study. The boundary for statistical significance at each interim analysis and the final analysis will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming function to maintain the overall type 1 error rate at 0.05 level. The O'Brien-Fleming (OBF) boundary for statistical significance is provided. The OS endpoint will be considered positive in the ITT population if statistical significance is achieved for any of the three OS interim analyses or the final analysis.

The first interim analysis of OS was performed at the time of the PFS primary analysis. A total of 264 deaths (29% of 915 patients in the ITT population) was observed at the first interim analysis of OS, which corresponds to 41% of the events information required for the final analysis of OS in the ITT population. The first OS interim analysis did not pass the OBF boundary at 0.0009.

The second interim analysis of OS will be time driven and will occur approximately 11 months from the clinical cutoff of the first OS interim. [redacted]*. It is projected that at the second interim OS analysis, 377 deaths (41% of 915 patients in the ITT population) will occur, corresponding to approximately 59% of the events required for the final analysis of OS in the ITT population. Statistical significance will be declared if $p \leq 0.0067$ when 377 deaths have occurred at the time of the second OS interim analysis.*

The third interim analysis of OS is event driven and remains the same as the original plan (Protocol WO29637, Version 6). The third interim analysis of OS will be performed when approximately 518 deaths (57% of 915 patients in the ITT population) have occurred, which corresponds to approximately 81% of the events information required for the final analysis of OS in the ITT population. Statistical significance will be declared if $p \leq 0.0233$ when 518 deaths have occurred at the time of the third OS interim analysis.

The final analysis of OS is event driven and remains the same as the original plan (Protocol WO29637, Version 6). The final analysis of OS will be performed when 639 deaths (70% of 915 patients in the ITT population) have occurred. Statistical significance will be declared if $p \leq 0.0420$ when 639 deaths have occurred at the time of the final OS analysis.

The interim and final analyses of OS, including analyses in both the ITT and PD-L1–selected populations, will follow the testing hierarchy described in the protocol. Specifically, for each OS interim and final analysis, OS in the PD-L1–selected population will be evaluated for statistical significance only when the OS results in the ITT population are statistically significant at the OBF boundary. The actual OBF boundary will be calculated at time of analysis based on actual number of events observed. If OS results in the ITT population are not statistically significant, formal testing of OS in the PD-L1–selected population will not be performed.

All efficacy analyses, including the interim analyses of OS, will be performed by the Sponsor.

Optional Interim Analysis

In addition to the planned interim analyses of OS, one additional interim analysis of OS may be performed at the discretion of the Sponsor. The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the Statistical Analysis Plan (SAP), and the SAP will be submitted to relevant health authorities prior to the conduct of the interim analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
anti-HBc	antibody to hepatitis B core antigen
anti–TNF	anti-tumor necrosis factor
ATA	anti-therapeutic antibody
BFI	Brief Fatigue Inventory
C_{min}	minimum serum concentration
CR	complete response
CRP	c-reactive protein
CT	computed tomography
C_{trough}	trough concentration
DOR	duration of response
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D	EuroQoL 5 Dimensions
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FKSI-19	Functional Assessment of Cancer Therapy Kidney Symptom Index
FDA	U.S. Food and Drug Administration
HBsAg	hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
IC	tumor-infiltrating immune cells
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	intent-to-treat
IV	intravenous
IxRS	interactive voice/Web response system
KPS	Karnofsky performance status
LFT	liver function test

Abbreviation	Definition
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
MDASI	M.D. Anderson Symptom Inventory
MDSC	myeloid-derived suppressor cells
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
OBF	*O'Brien-Fleming*
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
q2w	every 2 weeks
q3w	every 3 weeks
qPCR	quantitative polymerase chain reaction
RCC	renal cell carcinoma
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SPD	sum of the product of the longest perpendicular dimensions
SQLQ	Supplementary Quality of Life Questionnaire
TBNK	T, B, and natural killer cells
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VHL	von Hippel-Lindau

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 industrialized countries. Worldwide, in 2012, there were an estimated 337,860 new diagnoses and approximately 143,369 deaths secondary to RCC (GLOBOCAN 2012). The average age-adjusted incidence of RCC is approximately 12 in 100,000 men and 5 in 100,000 women (Patel et al. 2006): RCC age-adjusted incidence has been rising for the past 30 years within the United States and most European countries at an annual rate of approximately 3% (Chow et al. 2010).

RCC has several histologic types, each arising from distinct regions of the renal epithelia caused by a separate 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 I (5%) and Type II (10%) papillary, chromophobe (5%), and oncocytoma (5%; Motzer et al. 1996). 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 arising from epithelial elements within proximal tubules of nephrons. An early event during the evolution of clear-cell RCC leads to 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 that stimulates growth and angiogenesis.

Radical nephrectomy is the treatment of choice for early-stage RCC; however, 30% of these patients will relapse and develop future metastasis. Cytotoxic chemotherapy and radiotherapy have been largely ineffective for treating for RCC (Motzer et al. 1996). Several agents that target the VEGF pathway (sunitinib, pazopanib, axitinib, bevacizumab) and mTor pathway inhibitors (temsirolimus, everolimus) are approved in the treatment of RCC. Additionally, RCC is responsive to immunomodulation (interleukin [IL]-2, interferon alfa, anti–programmed death–1 [anti–PD-1], and anti–programmed death–ligand 1 [anti–PD-L1]) (McDermott 2009; Brahmer et al. 2012; Topalian et al. 2012). Immunotherapy with IL-2 is associated with a low response rate, yet durable long-term benefit in patients who respond (approximately 10% durable response rate); however, as a result of toxicity, high-dose IL-2 is generally only feasible in young patients with good performance status. To date, RCC is typically managed with VEGF-directed therapy, as well as immune therapy.

1.1.1 First-Line Treatment for Renal Cell Carcinoma

1.1.1.1 Anti-VEGF Therapies in Renal Cell Carcinoma

Clear-cell RCC is associated with an overproduction of VEGF as a result of the mutation/inactivation of the *VHL* tumor-suppressor gene (George and Kaelin 2003; Kaelin 2003). Thus, there has been substantial effort for more than 10 years to test agents that target VEGF in RCC. These studies have demonstrated significant

anti-tumor activity (e.g., by objective responses and prolonged progression-free survival [PFS]), placing VEGF blockade strategies at the forefront of RCC therapy. Approved therapies in the first-line metastatic setting now include, among others, sunitinib, pazopanib, and the combination of bevacizumab + interferon alfa-2a. Treatment with each of these agents results in a median PFS of approximately 9.2–10.8 months and an objective response rate (ORR) of approximately 35% (see Table 1). However, these therapies are associated with significant adverse events and do not result in a sustained, durable clinical benefit (Patel et al. 2006).

Table 1 Approved First-Line Targeted Therapies for Advanced Renal Cell Carcinoma

Agent and Population	Comparison	PFS (months)	HR	p-Value	OS (months)	HR (95% CI)
Sunitinib (first-line, all [a])	IFN α	10.8 vs. 5.1	0.44 [b]	< 0.01	24.5 vs. 20.4	0.82 0.67–1.00
Bev + IFN α (first-line, all [a])	IFN α	10.2 vs. 5.4	0.60 [c]	< 0.01	23 vs. 21	0.96 0.73–1.04
Pazopanib (first-line or prior cytokine, all [a])	Placebo	9.2 vs. 4.2	0.46 [d]	< 0.001	22.9 vs. 20.5	0.91 0.71–1.16
Temsirolimus (first-line, poor risk)	IFN α	5.5 vs. 3.1	0.66 [e]	0.008	10.9 vs. 7.3	0.73 0.58–0.92

HR = hazard ratio; mo = months; IFN = interferon; OS = overall survival; PFS = progression-free survival.

[a] "All" refers good + intermediate + poor risk.

[b] Motzer et al. 2007, 2009.

[c] Escudier et al. 2007.

[d] Sternberg et al. 2010.

[e] Hudes et al. 2007.

Avastin® (bevacizumab) is a recombinant, humanized therapeutic antibody directed against VEGF that has demonstrated single agent activity in a series of studies. In the first seminal study at the National Institutes of Health published in 2003 (Yang et al. 2003), 116 patients with RCC who were refractory to IL-2 were randomized to receive bevacizumab at a high dose (10 mg/kg every 2 weeks [q2w]), a low dose (3 mg/kg q2w), or placebo. In this IL-2 refractory population, the median PFS was 4.8, 3.0, and 2.5 months in the three treatment groups, respectively. In a more recent study (see Table 2), bevacizumab monotherapy as first-line therapy was examined in comparison studies of bevacizumab combined with erlotinib versus bevacizumab alone (Bukowski et al. 2007). Bevacizumab monotherapy in patients with untreated RCC demonstrated an ORR of 13% and a PFS of 8.5 months. In the most recent study (BEST Study) comparing single-agent bevacizumab (ORR of 12% and PFS of 8.7 months) with the combination of bevacizumab and either sorafenib or temsirolimus,

single-agent bevacizumab was found to be as efficacious as the combinations and less toxic (McDermott et al. 2013).

Table 2 Efficacy of Bevacizumab Monotherapy in Renal Cell Carcinoma

	No. of Patients	PFS (months)	ORR (%)	Patient Population
Placebo [a]	40	2.5	0	IL-2 Refractory
Bev 3 mg/kg q2w [a]	37	3.0	0	
Bev 10 mg/kg q2w [a]	39	4.8	10	
Bev 10 mg/kg q2w [b]	53	8.5	13	1st line
Bev 10 mg/kg q2w + erlotinib [b]	51	9.9	14	
Bev 10 mg/kg q2w [c]	87	8.7	12	1st line

Bev = bevacizumab; IL = interleukin; ORR = overall response rate; PFS = progression-free survival q2w = every 2 weeks.

[a] Yang et al. 2002.

[b] Bukowski et al. 2007.

[c] Mc Dermott et al. 2013.

The role of combining bevacizumab with immunomodulation with interferon (IFN) α in RCC is well established. In combination studies of bevacizumab with interferon alfa-2a compared with interferon alfa-2a alone, the PFS (approximately 10 months vs. approximately 5 months; hazard ratio [HR] 0.60), as well as tumor shrinkage (ORR 31% vs. 13%), were improved (Escudier et al. 2007; Rini et al. 2010), suggesting an incremental benefit when anti-VEGF and immune therapies are combined.

The efficacy of VEGF antagonism highlights the central role of VEGF in RCC pathogenesis. In addition, VEGF may also modulate the immune response through diverse mechanisms described in Section 1.3.

1.1.1.2 Immune-Based Therapy in Renal Cell Carcinoma

Immunotherapy historically has had a significant role in the management of metastatic RCC. Treatment with interferon alfa and/or IL-2 results in objective responses in approximately 5% of patients with RCC and 10% of patients treated with IL-2 exhibit durable disease stabilization or remission (Yang and Childs 2006). Data from the Phase I anti–PD-L1 antibody (atezolizumab, MPDL3280A) Study PCD4989g in RCC is outlined in Section 1.4.1. This agent, atezolizumab, blocks the inhibitory receptors expressed on tumor cells called programmed death–ligand 1 (PD-L1), resulting in enhanced anti-tumor immune activity. The observed level of activity with this agent suggests that the enhancement of immune function by targeting the PD-L1 axis may be of critical importance in RCC.

1.2 BACKGROUND ON PD-L1 BIOLOGY AND ATEZOLIZUMAB

PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors, programmed death–1 (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 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 the downregulation of immune responses, including inhibition of T-cell activation and cytokine production (Butte et al. 2007; Yang et al. 2011; Chen et al. 2012).

Aberrant expression 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. PD-L1 expression is prevalent in many human tumors and may be associated with poor prognosis in certain cancers (Mu et al. 2011).

Atezolizumab is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc‑effector function and depletion of cells expressing PD-L1. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptors, PD-1 and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells.

See the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.3 RATIONALE FOR TESTING ATEZOLIZUMAB AND THE COMBINATION ATEZOLIZUMAB+BEVACIZUMAB

In multiple murine tumor models, the interruption of the interaction between PD-L1 and PD-1 resulted in anti-tumor effects (Iwai et al. 2002; Strome et al. 2003). [redacted]

In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. VEGF is believed to be involved in immune response via the induction of myeloid-derived

suppressor cells (MDSCs). These VEGF-induced MDSCs can suppress both T-cell and dendritic-cell function (Gabrilovich 2012). Anti-VEGF therapies may elicit immune responses through diverse mechanisms, including increased trafficking of T cells into tumors (Manning et al. 2007; Shrimali et al. 2010), reduced frequency of MDSC (Kusmartsev et al. 2008), reduction of suppressive cytokines and tumor-infiltrating T regulatory cells and MDSCs (Roland et al. 2009), and increased $CD8^+$ and $CD4^+$ central memory T cells (Hodi et al. 2011).

PD-L1 expression is prevalent in many human tumors (e.g., lung, ovarian, melanoma, colon carcinoma, and RCC). This elevated PD-L1 expression is often associated with a worse prognosis in RCC (Choueiri et al. 2014). Atezolizumab has demonstrated activity in advanced refractory cancer patients in the Phase I monotherapy Study PCD4989g (Cho et al. 2013; Herbst et al. 2013), as well as in combination with bevacizumab, (McDermott et al. 2014; see Section 1.4).

Collectively, the role of VEGF in the immune response and its critical role in RCC pathogenesis provide a compelling rationale to test whether inhibition of the PD-L1/PD-1 pathway with a human anti–PD-L1 IgG1 effectorless antibody with anti-VEGF therapies will result in improved clinical benefit for patients with RCC.

1.4 CLINICAL EXPERIENCE WITH ATEZOLIZUMAB IN RENAL CELL CARCINOMA

The experience to date with atezolizumab in RCC consists of three ongoing studies: an atezolizumab monotherapy Phase Ia study (Study PCD4989g) and two atezolizumab + bevacizumab combination studies (a Phase Ib Study GP28328 and a randomized Phase II Study WO29074).

1.4.1 Phase Ia Study PCD4989g

Study PCD4989g is an ongoing Phase Ia, open-label, dose-escalation trial assessing the safety and pharmacokinetics of atezolizumab administered as a single agent to patients with solid tumors and hematologic malignancies.

1.4.1.1 Safety Analysis of Study PCD4989g

As of 10 May 2014, atezolizumab has been administered to approximately 775 patients with solid tumors and hematologic malignancies. The safety profile of atezolizumab is primarily based on data from this ongoing Phase Ia study. Refer to the Atezolizumab Investigator's Brochure for the safety profile of all patients enrolled in this study. The safety profile for the subset of patients enrolled in this study (patients with renal cell cancer) is summarized below.

1.4.1.1.1 Clinical Safety in Renal Cell Carcinoma Cohort (Study PCD4989g)

Study PCD4989g included 69 patients with RCC. As of the 10 May 2014 data cutoff date, the median duration of treatment for this cohort was 239.0 days

(range: 21–855 days) and the median number of atezolizumab cycles administered was 12 cycles (range: 2–36 cycles).

As of May 10 2014, 66 of 69 treated RCC patients (95.7%) reported one or more adverse events. The most frequently observed adverse events (occurring in ≥10% of treated patients) are presented in Table 3. The most frequently observed adverse events (occurring in ≥10% of treated patients) included fatigue, cough, arthralgia, pyrexia, constipation, nausea, decreased appetite, dyspnea, rash, diarrhea, chills, pruritus, anemia, back pain, headache, insomnia, upper respiratory tract infection, pain in extremity, vomiting, asthenia, edema peripheral, dizziness, oropharyngeal pain, dry skin, hypothyroidism, and influenza-like illness.

No new safety concerns were observed in this cohort and RCC findings are consistent with the overall larger population in Study PCD4989g.

Table 3 Adverse Events in ≥10% of Atezolizumab-Treated Patients in the Renal Cell Carcinoma Cohort of Study PCD4989g

Preferred Term	No. (%) of Adverse Events	
	Total	Treatment-Related
Fatigue	24 (34.8)	14 (20.3)
Cough	21 (30.4)	1 (1.4)
Arthralgia	20 (29.0)	10 (14.5)
Pyrexia	18 (26.1)	8 (11.6)
Constipation	18 (26.1)	2 (2.9)
Nausea	16 (23.2)	7 (10.1)
Decreased appetite	16 (23.2)	11 (15.9)
Dyspnoea	14 (20.3)	4 (5.8)
Rash	13 (18.8)	10 (14.5)
Diarrhoea	12 (17.4)	8 (11.6)
Chills	12 (17.4)	7 (10.1)
Pruritus	12 (17.4)	8 (11.6)
Anaemia	12 (17.4)	5 (7.2)
Back pain	12 (17.4)	2 (2.9)
Headache	11 (15.9)	5 (7.2)
Insomnia	11 (15.9)	2 (2.9)
Upper respiratory tract infection	10 (14.5)	1 (1.4)
Pain in extremity	9 (13.0)	0 (0.0)
Vomiting	8 (11.6)	4 (5.8)
Asthenia	8 (11.6)	5 (7.2)
Oedema peripheral	8 (11.6)	3 (4.3)
Dizziness	8 (11.6)	1 (1.4)
Oropharyngeal pain	8 (11.6)	1 (1.4)
Dry skin	8 (11.6)	6 (8.7)
Hypothyroidism	8 (11.6)	6 (8.7)
Influenza-like illness	7 (10.1)	6 (8.7)

RCC = renal cell carcinoma.

Grade ≥ 3 adverse events occurred in 32 patients (46.4%; see Table 4). The most frequently reported related Grade ≥ 3 adverse events included fatigue, anemia, dehydration, and hypophosphatemia.

Table 4 Grade 3–5 Adverse Events Reported in 2 or More Patients: Atezolizumab-Treated Renal Cell Carcinoma Cohort in Study PCD4989g

	No. (%) of Grade ≥3 Adverse Events	
Preferred Term	Total	Treatment-Related
Anaemia	4 (5.8)	2 (2.9)
Asthenia	2 (2.9)	0 (0.0)
Fatigue	2 (2.9)	2 (2.9)
Dehydration	2 (2.9)	2 (2.9)
Hyperglycaemia	2 (2.9)	1 (1.4)
Hyponatraemia	2 (2.9)	0 (0.0)
Hypophosphataemia	2 (2.9)	2 (2.9)
Malignant neoplasm progression	2 (2.9)	0 (0.0)
Proteinuria	2 (2.9)	0 (0.0)
Dyspnoea	4 (5.8)	1 (1.4)
Hypoxia	2 (2.9)	0 (0.0)
Pleural effusion	2 (2.9)	0 (0.0)

RCC = renal cell carcinoma.

1.4.1.1.2 Clinical Activity in Renal Cell Carcinoma in Study PCD4989g

As of 21 April 2014, a total of 69 patients with RCC have been treated with atezolizumab monotherapy at the following dose levels: 3 mg/kg (n = 2), 10 mg/kg (n = 12), 15 mg/kg (n = 19), and 20 mg/kg (n = 36). Best responses in the 62 patients with clear-cell RCC evaluable for efficacy who were dosed prior to 21 October 2013 included the following: 9 patients (15%) with confirmed partial responses (PRs)/complete responses (CRs), 35 patients (57%) with stable disease, and 17 patients (27%) with disease progression. The 24-week PFS rate was 51%, and stable disease was maintained for ≥24 weeks in 31% of patients with RCC. As of 21 April 2014, 5 of 9 responding patients with clear-cell RCC have continued to respond. The median duration of response (DOR) is 75.7 weeks. In addition, 4 of 18 patients (22%) with Fuhrman Grade 4 clear-cell or sarcomatoid histology achieved a response by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria.

Preliminary results suggest that PD-L1 expression in tumor tissue is likely to be associated with response to atezolizumab. A prototype immunohistochemistry (IHC) assay that measures specific PD-L1 signals in tumor-infiltrating immune cells (ICs) was used in Study PCD4989g. PD-L1 staining categories in ICs are defined as IC0, IC1, IC2, and IC3 (see Table 5). In the efficacy-evaluable patients with clear-cell RCC (n = 62), an ORR of 20.0% (7 of 35 patients, 95% CI: 8.7%–36.6%) was observed in the PD-L1–positive patients (IC1/2/3 group) compared with an ORR of 9.5%

(2 of 21 patients, 95% CI: 1.7%–29.8%) in patients with low PD-L1 staining or who were PD-L1 negative (IC0 group) (Table 6). Note that protocol enrollment criteria for PD-L1 expression status varied over time; as a result, the IC1/2/3 group (n = 35 patients) is enriched for IC2/3 patients (n = 20 patients) and interpretation of results for the overall RCC population and PD-L1–selected groups must take this into consideration. A total of 3 of 15 (20%) IC1 patients and 4 of 20 (20%) had an overall response of CR or PR.

Table 5 Criteria for PD-L1 Expression

Description of IC Scoring Algorithm	PD-L1 Expression Level
Presence of discernible PD-L1 staining of any intensity in tumor infiltrating immune cells covering ≥ 10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC3
Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering between ≥ 5–< 10**%** of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC2
Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering between ≥ 1–< 5**%** of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC1
Absence of any discernible PD-L1 staining OR Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering < 1% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC0

IC = tumor-infiltrating immune cells; PD-L1 = programmed death–ligand 1.

Table 6 Efficacy in Patients with Clear-Cell Renal Cell Carcinoma in Study PCD4989g: Best Overall Response Rate and 24-Week PFS Rate by PD-L1 Expression (n=62)

PD-L1 IHC Expression Level	No. of Patients	ORR by RECIST, Version 1.1 (95% CI)	CR	PR	SD	24-Week PFS Rate (95%CI) [a]
All patients	62	9 (14.5%) 7.5%, 25.2%	1 (1.6%)	8 (12.9%)	35 (56.5%)	50.9% 38.4, 63.4
IC0	21	2 (9.5%) 1.7%, 29.8%	0	2 (9.5%)	11 (52.4%)	45.2% 23.4, 67.1
IC1/2/3 [b]	35	7 (20.0%) 8.7%, 36.6%	1 (2.9%)	6 (17.1%)	20 (57.1%)	54.3% 37.8, 70.8
Fuhrman Grade 4/ sarcomatoid	18	4 (22.2%) 8.0%, 46.5%	1 (5.6%)	3 (16.7%)	8 (44.4%)	NA

IC = tumor-infiltrating immune cell; IHC = immunohistochemistry; ORR = objective response rate; CR = complete response; NA = not available; PFS = progression–free survival; PR = partial response; SD = stable disease; PD-L1 = programmed death–ligand 1; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: This table is based on a data cutoff date of 21 April 2014. Patients with RCC were dosed by 21 October 2013.

[a] Kaplan-Meier estimates.

[b] Partially enriched for patients with IC2/3; IC1: 3 of 15 (ORR 20%), IC 2/3: 4 of 20 (ORR 20%).

1.4.1.2 Phase Ib Study GP28328

Study GP28328 is an ongoing Phase Ib study evaluating the safety and pharmacokinetics of atezolizumab administered in combination with bevacizumab (Arm A) or in combination with bevacizumab plus chemotherapy (Arms B–E) in patients with advanced solid tumors.

1.4.1.2.1 Safety Analysis of Arm A of Study GP28328

Restricting the safety discussion to components of Study GP28328 without cytotoxic chemotherapy (i.e., Arm A), atezolizumab + bevacizumab has been generally well tolerated. No dose-limiting toxicities have been reported during the dose-escalation stage (only one dose level of atezolizumab was tested). As of 7 July 2014, clinical data were available for 35 patients who received at least one dose of the combination of atezolizumab + bevacizumab (Arm A). Table 7 and Table 8 summarize all reported events among the 35 patients enrolled in Arm A.

Table 7 All Reported Adverse Events in Arm A of Study GP28328

Parameter	No. (%) of Adverse Events (n=35)	
	Total	Treatment-Related
Any adverse event	35 (100.0)	27 (77.1)
Grade 3–5 adverse event	18 (51.4)	1 (2.9)
Serious adverse event	14 (40.0)	0 (0.0)
Adverse event leading to death (Grade 5)	1 (2.9)	0 (0.0)

Table 8 All Reported Adverse Events in ≥10% Patients in Arm A of Study GP28328

Preferred Term	No. (%) of Adverse Events	
	Total	Treatment-Related
Any adverse event	35 (100.0)	27 (77.1)
Fatigue	16 (45.7)	7 (20.0)
Nausea	13 (37.1)	7 (20.0)
Pyrexia	13 (37.1)	6 (17.1)
Diarrhea	11 (31.4)	8 (22.9)
Decreased appetite	9 (25.7)	5 (14.3)
Abdominal pain	7 (20.0)	(0.0)
Chills	7 (20.0)	4 (11.4)
Hypertension	7 (20.0)	0 (0.0)
Vomiting	7 (20.0)	2 (5.7)
Cough	6 (17.1)	3 (8.6)
Dyspnoea	6 (17.1)	2 (5.7)
Oedema peripheral	6 (17.1)	0 (0.0)
Upper respiratory tract infection	6 (17.1)	0 (0.0)
Anaemia	5 (14.3)	2 5.7)
Anxiety	5 (14.3)	0 (0.0)
Epistaxis	5 (14.3)	1 (2.9)
Headache	5 (14.3)	0 (0.0)
Pain in extremity	5 (14.3)	1 (2.9)
Pneumonia	5 (14.3)	0 (0.0)
Pruritus	5 (14.3)	3 (8.6)
Rash	5 (14.3)	3 (8.6)
Arthralgia	4 (11.4)	1 (2.9)
Constipation	4 (11.4)	0 (0.0)
Insomnia	4 (11.4)	0 (0.0)
Productive cough	4 (11.4)	0 (0.0)
Bone pain	3 (8.6)	2 (5.7)
Musculoskeletal pain	3 (8.6)	1 (2.9)

AE = adverse event.

Of the 35 patients enrolled in Arm A, 100% reported one or more adverse events. Adverse events reported in > 10% of patients included anemia, nausea, diarrhea, constipation, vomiting, abdominal pain, fatigue, pyrexia, chills, edema peripheral, upper respiratory tract infection, pneumonia, arthralgia, pain in extremity, bone pain,

musculoskeletal pain, headache, anxiety, insomnia, cough, epistaxis, dyspnea, productive cough, rash, pruritus, hypertension, and decreased appetite.

Adverse events attributed to the atezolizumab + bevacizumab combination occurred in 27 patients (77%). The majority of these related events were Grade 1 and 2 in severity, with Grade ≥ 3 related adverse events occurring in only 1 patient with neutropenia. The five most commonly reported related adverse events included fatigue, nausea, diarrhea, decreased appetite, and pyrexia. Two patients developed adverse events leading to treatment discontinuation (liver function test [LFT] abnormalities, hypercalcemia). Other adverse events included upper respiratory tract infection, flu-like symptoms, vomiting, constipation, and sinus infection. The majority of these events were Grade 1 or 2 in severity.

Grade ≥ 3 AEs (regardless of attribution) were reported for 18 patients (51.4%) in Arm A. The most frequently reported related Grade ≥ 3 AE included abdominal pain, pneumonia, and hypertension (each occurring in 3 patients [8.6%]). Only 1 patient had a Grade 3 event of neutropenia that was assessed as related to the study treatment by the investigator. Other Grade 3 events included reduced lymphocyte count, increased alkaline phosphatase, chest pain, colonic perforation, and abdominal pain. The event of colonic perforation occurred in a patient with a history of abscess and prior radiation to the affected area; the investigator attributed the event to bevacizumab and not to atezolizumab.

There were no deaths attributed to atezolizumab.

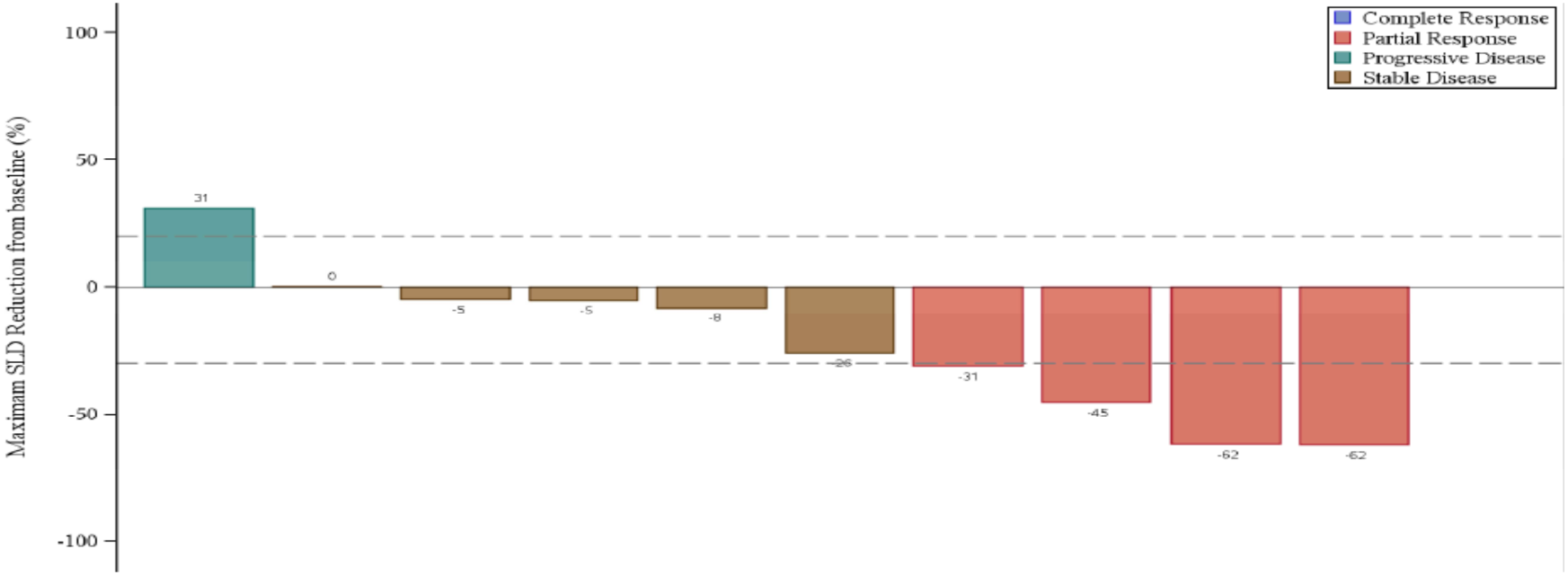
Fourteen serious adverse events were reported including abdominal pain, catheter site infection, dyspnea, pneumonia, colonic perforation, and pyrexia. None of these serious adverse events were attributed to atezolizumab.

1.4.1.3 Clinical Activity in Renal Cell Carcinoma in Arm A of Study GP28328

Study GP28328 is a Phase Ib trial of atezolizumab administered with bevacizumab (in Arm A) in patients with advanced solid tumors. Ten first-line RCC patients enrolled and dosed by 7 April 2014 were evaluable for efficacy by the cutoff date of 7 July 2014.

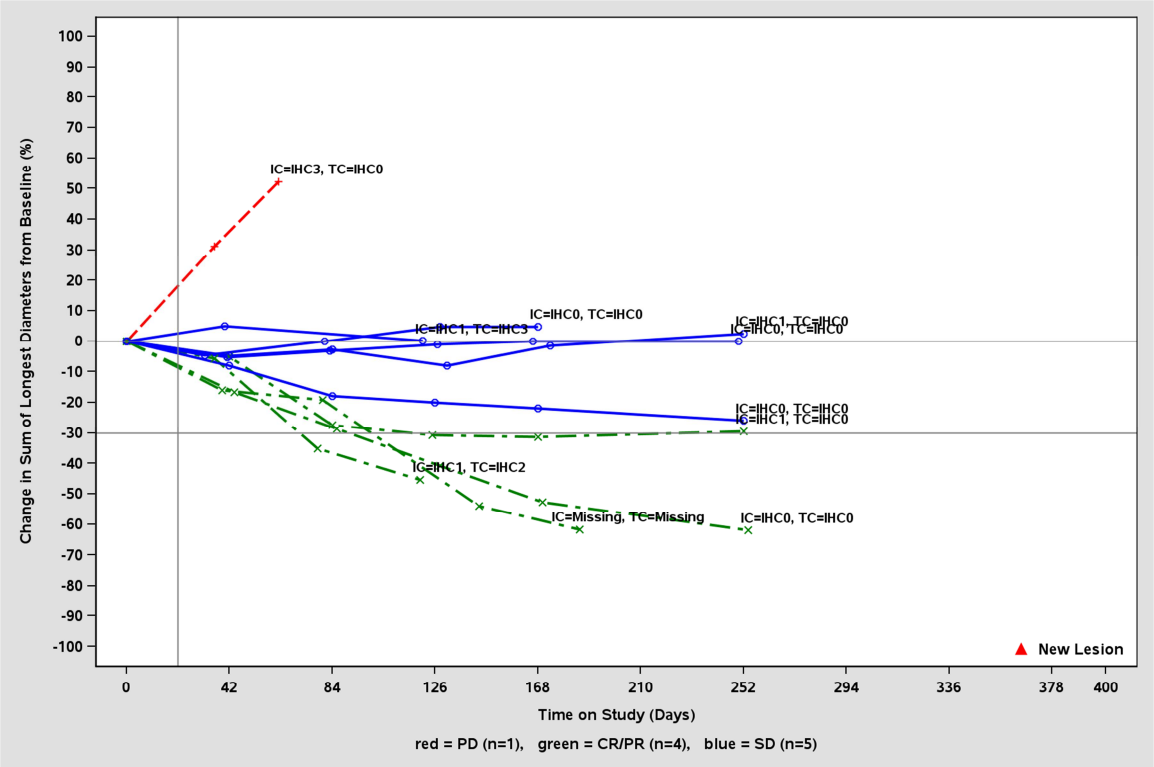
An ORR of 40% (4 of 10 patients, 95% CI: 15.0%, 73.3%) was observed in patients with the combination therapy of atezolizumab and bevacizumab (see Figure 1). Given a median duration of follow-up of 7.8 months, 9 of 10 patients have remained in the combination treatment with 4 patients achieving at least stable disease in ≥ 24 weeks (24–42 weeks) and 4 patients achieving at least a PR (17–36 weeks; see Figure 2). Among the 9 patients evaluable for PD-L1 IHC staining at baseline, 2 of 5 (40%) responded in the IC1/2/3 group, while 1 of 4 (25%) responded in the IC0 group. One responder was unevaluable for PD-L1 IHC staining.

Figure 1 Best Change from Baseline in SLD per RECIST v1.1: Unconfirmed Best Response in Efficacy-Evaluable Arm A Patients in Study GP28328 with First-Line Clear-Cell Renal Cell Carcinoma



RECIST = Response Evaluation Criteria in Solid Tumors; SLD = sum of longest diameter.
Note: The efficacy-evaluable patients were dosed by 7 April 2014.

Figure 2 Tumor Burden over Time by Investigator-Assessed Unconfirmed Response and Corresponding PD-L1 IC Status



CR = complete response; IC = tumor-infiltrating immune cell; PD = progressive disease; PD-L1 = programmed death–ligand 1; PR = partial response; SD = stable disease; TC = tumor cell.

1.4.2 Phase II Study WO29074

The ongoing Phase II RCC Study WO29074 randomized 305 patients in a 1:1:1 fashion to either the combination of atezolizumab + bevacizumab, atezolizumab monotherapy, or sunitinib. The study is still ongoing. A preliminary review by the Internal Monitoring Committee demonstrated no safety or efficacy concerns with the combination of atezolizumab and bevacizumab study arm and no impact upon the conduct of Study WO29637.

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Despite recent advancements, metastatic RCC cancer remains an incurable disease because a substantial majority of patients develop resistance to standard therapies, including VEGF-directed and/or immunotherapy. Furthermore, patients exhibit poor tolerance with current oral VEGF-directed receptor tyrosine kinase inhibitors, as well as current immune-based therapy. Approved therapies with current VEGF-directed receptor tyrosine kinase inhibitors (including sunitinib) are associated with significant toxicities (e.g., fatigue, diarrhea, mucositis, hand-foot syndrome, and mucositis) that negatively impact quality of life and often limit treatment continuation (see Table 9). In a

recent comparative study of sunitinib and pazopanib, an equal percentage of both groups of patients (74%) developed Grade ≥3 toxicities, and 20% and 24% of these patients, respectively, discontinued the study drug because of adverse events (Motzer et al. 2013). Therefore, there is an ongoing need for more efficacious and better-tolerated treatments.

Table 9 Grade ≥3 Toxicities and Discontinuations of First-Line Renal Cell Carcinoma Agents

Agent	Grade 3 Hypertension	Grade 3 Asthenia	Any Grade ≥3 Adverse Event	Discontinuation Due to Study Drug
Sunitinib (n=548) [a]	15%	17%	74%	20%
Pazopanib (n=554) [a]	15%	10%	74%	24%
Bev+IFN (n=337) [b]	3%	10%	60%	28%
Temsirolimus (n=209) [c]	N/A	11%	67%	7%
Atezolizumab + Bev (n=59) [d]	14%	2%	34%	3%

Bev=bevacizumab; IFN=interferon; N/A=not available; RCC=renal cell carcinoma.

[a] Motzer et al.2013.

[b] Escudier et al. 2007.

[c] Hudes et al. 2007.

[d] Preliminary, unpublished, internal data from Arm A of the Phase II Study WO29074.

Encouraging clinical data 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).

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. PD-L1 expression is prevalent in many human tumors and elevated PD-L1 expression on tumor or immune cells are associated with a poor prognosis in patients with RCC (Choueiri et al. 2014).

Importantly, preliminary evidence suggests that patients with RCC and PD-L1–expressing tumors are more likely to benefit from PD-L1 pathway–targeted therapies than are patients with low PD-L1–expressing (IC0) tumors. Data from the Phase Ia Study PCD4989g showed that patients with RCC and PD-L1–positive (IC1/2/3)

tumors have a numerically higher ORR than patients with PD-L1–negative (IC0) tumors (see Table 6 and McDermott et al. 2014).

The safety profile and associated benefit and risk of atezolizumab as a single agent (Phase Ia Study PCD4989g) and in combination with bevacizumab (Phase Ib Study GP28328 and Phase II Study WO29074) support its continued development in metastatic RCC. In a cohort of predominantly heavily pre-treated patients with RCC, single-agent atezolizumab demonstrated evidence for single-agent activity with tumor shrinkage (ORR of approximately 15%) and/or disease stabilization ≥6 months (approximately 50% of patients). Responses have been durable, and the median duration of response for atezolizumab monotherapy was 75.7 weeks. In the Phase Ib study of atezolizumab + bevacizumab (Study GP28328), the combination has been well tolerated, with 4 of 10 patients achieving a PR and another 4 of 10 maintaining stable disease for >24 weeks.

In contrast to the current approved targeted agents or combinations, atezolizumab + bevacizumab has been generally well tolerated (see Table 9), and the preliminary response rates for atezolizumab + bevacizumab compare favorably to the 30%–35% historical ORR for sunitinib, pazopanib, and the bevacizumab/interferon combination.

In summary, treatment with atezolizumab + bevacizumab offers the potential for clinical benefit in patients with RCC.

Given that both the VEGF and PD-L1 pathways are important in RCC pathogenesis, this study is designed to test the hypothesis that inhibition of VEGF signaling will enhance the efficacy of immunotherapy in the front-line treatment of patients with metastatic RCC. On the basis of the information summarized above, the Sponsor believes that the assessment of atezolizumab in combination with bevacizumab for the treatment of metastatic RCC presents a positive benefit-risk.

2. OBJECTIVES

Analyses of the following objectives will be performed for the population of patients with inoperable, locally advanced, or metastatic RCC, unless otherwise indicated. Where specified, a comparison of the treatment arms will be performed in the patient population defined according to tumor PD-L1 expression as evaluated by IHC.

2.1 EFFICACY OBJECTIVES

The primary and secondary efficacy objectives will be evaluated in the PD-L1–selected population (IC1/2/3) as well as in the ITT population (includes all IC scores; see Table 5 for a description of IC score).

2.1.1 Primary Efficacy Objective

The primary efficacy objective of the study is as follows:

- To evaluate the efficacy of atezolizumab + bevacizumab compared with sunitinib as measured by the co-primary endpoints of investigator-assessed PFS per RECIST v1.1 and overall survival (OS).

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objectives of the study are as follows:

- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by Independent Review Committee (IRC)–assessed PFS according to RECIST v1.1
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by investigator-assessed ORR (complete + partial response rates) per RECIST v1.1
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by investigator-assessed DOR among patients with an objective response per RECIST v1.1
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by IRC-assessed ORR and DOR according to RECIST v1.1
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by investigator-assessed PFS, DOR, and ORR per modified RECIST (see Appendix 4)
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib among patients with sarcomatoid histology (defined by investigator-assessed conventional histopathology) as measured by investigator assessed PFS per RECIST v1.1 and OS
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib on symptom interference as measured by the M.D. Anderson Symptom Inventory [MDASI Part II])

2.2 SAFETY OBJECTIVES

The safety objectives of the study are as follows:

- To evaluate the safety and tolerability of atezolizumab + bevacizumab versus sunitinib
- To evaluate the incidence of anti-therapeutic antibodies (ATAs) against atezolizumab and to explore the potential relationship of immunogenicity response with pharmacokinetics, safety, and efficacy

2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objectives of the study are as follows:

- To characterize the pharmacokinetics of atezolizumab when administered in combination with bevacizumab
- To characterize the pharmacokinetics of bevacizumab when administered in combination with atezolizumab

2.4 PATIENT-REPORTED OUTCOME OBJECTIVES

The additional patient-reported outcome (PRO) objectives of the study are as follows:

- To assess symptom severity associated with atezolizumab + bevacizumab versus sunitinib in patients with RCC as measured by the MDASI and Brief Fatigue Inventory (BFI)
- To document patients' perspective regarding the tolerability of the treatments (from the treatment side-effects subscale from the Functional Assessment of Cancer Therapy Kidney Symptom Index [FKSI-19])
- To obtain general measures of health as measured by the EuroQoL 5 Dimensions (EQ-5D) questionnaire for health economic modeling of atezolizumab + bevacizumab versus sunitinib in patients with RCC

2.5 EXPLORATORY OBJECTIVES

The exploratory objectives of the study are as follows:

- To evaluate the relationship between the expression of other candidate predictive immune, angiogenic, or hypoxia biomarkers, as defined by IHC or quantitative polymerase chain reaction (qPCR), and efficacy as defined by PFS and ORR
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib among patients with tumor Fuhrman Grade 4 or sarcomatoid histology (defined by investigator-assessed conventional histopathology) as measured by PFS and ORR
- To assess immune-mediated predictive and prognostic exploratory biomarkers in tumor tissue and blood from archival specimens, fresh biopsy specimens, or specimens obtained during the study and their association with disease status and/or efficacy as defined by PFS and ORR

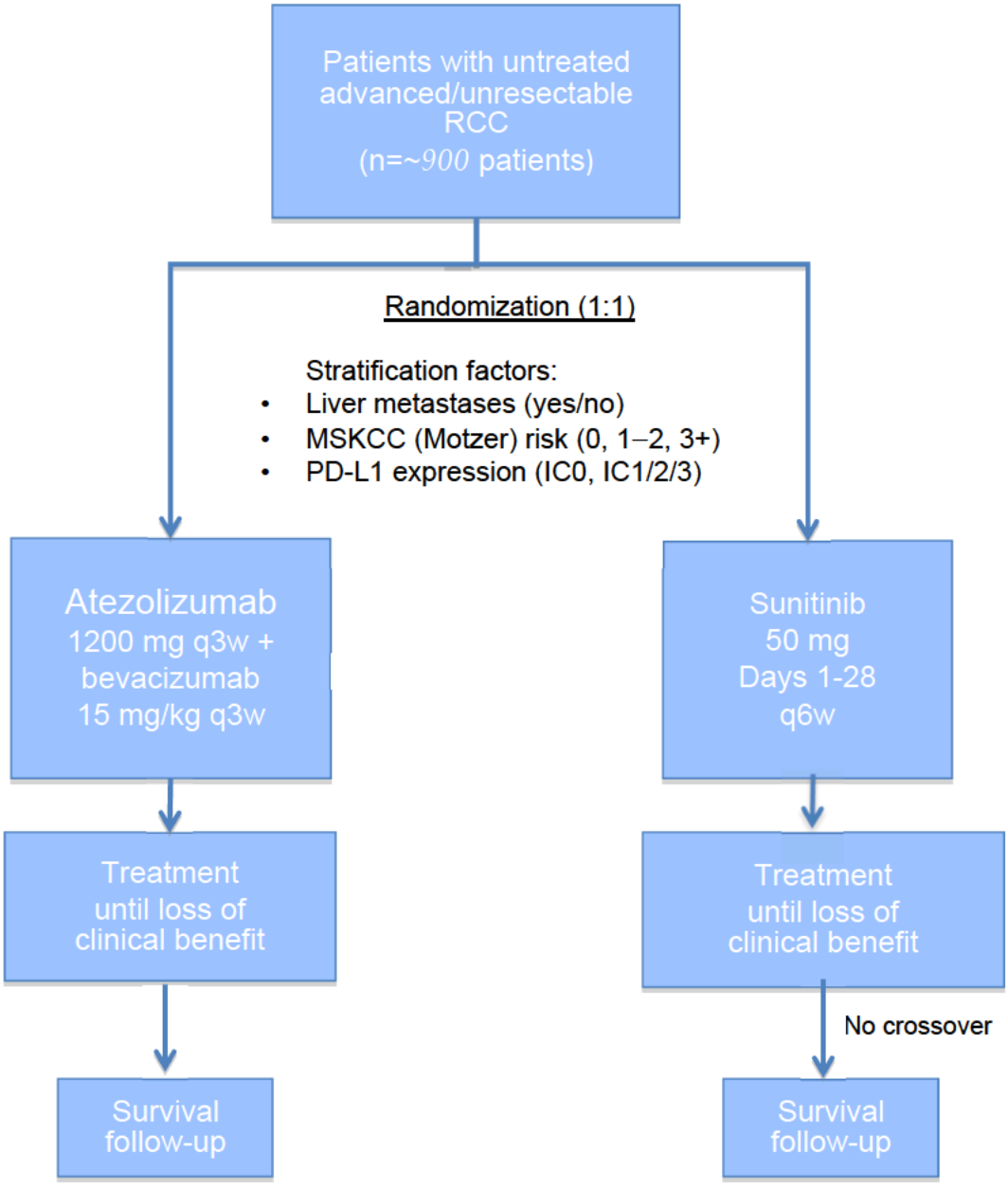
3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a Phase III, multicenter, randomized, open-label study designed to evaluate the efficacy and safety of atezolizumab + bevacizumab versus sunitinib in patients with inoperable, locally advanced, or metastatic RCC who have not received prior systemic active or experimental therapy, either in the adjuvant or metastatic setting. The study will enroll approximately 900 patients, including a minimum of 351 patients with a PD-L1 IHC of IC score of 1/2/3 (PD-L1–selected population), at approximately 150–180 centers globally. A maximum of approximately 180 patients (20%) with a Memorial Sloan

Kettering Cancer Center (MSKCC [Motzer]) score of 0 (good risk) will be enrolled (see Appendix 9). The study schema is shown in Figure 3.

Figure 3 Study Schema



IC = tumor-infiltrating immune cell; PD-L1 = programmed death–ligand 1; MSKCC = Memorial Sloan Kettering Cancer Center; q3w = every 3 weeks; q6w = every 6 weeks; RCC = renal cell carcinoma.

[a] Patients may continue atezolizumab + bevacizumab or sunitinib if there is evidence of clinical benefit as outlined in Sections 3.1 and 4.6.2.

The key inclusion criteria include:

- Male and female patients aged ≥18 years with Karnofsky performance status (KPS) ≥70% who have histologically proven, unresectable locally advanced or metastatic RCC with clear cell histology and/or a component of sarcomatoid histology and who have not received prior treatment in the metastatic setting
- Tumor specimens from patients meeting eligibility criteria will be prospectively tested for PD-L1 expression by a central laboratory. PD-L1 expression must be determined prior to randomization.

Patients will be randomized in a 1:1 ratio to one of two treatment arms:

- Arm A (experimental arm): Atezolizumab 1200 mg intravenous (IV) infusions every 3 weeks (q3w; dosed in 6-week cycles)+bevacizumab 15 mg/kg q3w (dosed in 6-week cycles)
- Arm B (control arm): Sunitinib 50 mg/day orally for 4 weeks, followed by 2 weeks of rest (dosed in 6-week cycles)

Randomization will be stratified by:

- Presence of liver metastasis (yes vs. no)
- MSKCC (Motzer) score (low, intermediate, or high risk; 0, 1–2, or ≥3), which comprises the following five risk factors: KPS <80%, LDH >1.5×upper limit of normal (ULN), hemoglobin less than the lower limit of normal (LLN), corrected serum calcium >10 mg/dL, and time from nephrectomy to systemic therapy (≤12 months vs. >12 months) (see Appendix 9).
- PD-L1 status: IC1/2/3 versus IC0

Atezolizumab will be administered intravenously at a fixed dose of 1200 mg on Days 1 and 22 of each 42-day cycle. Bevacizumab will be administered intravenously at 15 mg/kg on Days 1 and 22 of each 42-day cycle. Patients randomized to the atezolizumab+bevacizumab arm who transiently withhold or permanently discontinue either atezolizumab or bevacizumab may continue on single-agent therapy until disease progression (i.e., patients holding bevacizumab transiently for adverse effects may continue atezolizumab monotherapy and vice versa). Guidelines for dosage modification, treatment interruption or discontinuation, and the management of specific adverse events are provided in Sections 5.1.3, 5.1.4, and 5.1.5.

Sunitinib will be administered at the starting dose of 50 mg/day orally on Day 1 through Day 28 of each 42-day cycle.

Patients will receive atezolizumab and/or bevacizumab or sunitinib as long as they continue to experience clinical benefit in the opinion of the investigator until unacceptable toxicity or symptomatic deterioration attributed to disease progression (e.g., pain secondary to disease or unmanageable ascites) as determined by the

investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

Patients in both study arms will be permitted to continue their treatments after RECIST v1.1 criteria for progressive disease are met if they meet all of the following criteria:

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

Patients in whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the investigator if they continue to meet the criteria above (see Figure 4). Collection of a tumor biopsy tissue sample at the time of first radiographic progression for all consenting patients in both treatment arms is required, if clinically feasible per the investigator and not prohibited by country or institution, in order to evaluate the utility of the biopsy tissue sample in distinguishing pseudoprogression/tumor immune infiltration from true disease progression. These data will be analyzed for the association between changes in tumor tissue and clinical outcome.

No crossover will be allowed from the control arm to the experimental arm.

Patients will undergo scheduled tumor assessment at baseline, Week 12, and then every 6 weeks through Week 78 followed by every 12 weeks thereafter. Tumor assessments will continue until disease progression per both RECIST v1.1 and modified RECIST (see Appendix 4), regardless of whether treatment has been discontinued (e.g. for toxicity). Patients who meet RECIST v1.1 criteria for progression will undergo tumor assessments until disease progression per modified RECIST. In the absence of disease progression, tumor assessments should continue regardless of whether patients start new anti-cancer therapy, until consent is withdrawn, death, or the study is terminated by the Sponsor, whichever occurs first. Following disease progression, patients will be followed for survival and subsequent anti-cancer therapies until death, loss to follow-up, withdrawal of consent, or study termination by Sponsor, whichever occurs first. The following information regarding all subsequent anti-neoplastic agents upon treatment discontinuation will be collected: line of therapy, date of first dose of agent, date of last dose of agent (or if ongoing), patient's best response, and date of disease progression.

Schedules of assessments are provided in Appendix 1 and Appendix 2.

Sites will provide imaging used for tumor assessment to the IRC to enable centralized, independent review of response and progression endpoints. IRC membership and procedures will be detailed in an IRC Charter.

Safety assessments will include the incidence, nature, and severity of adverse events 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 and blood chemistry. Serum samples will be collected to monitor atezolizumab and bevacizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab and bevacizumab. Patient samples, including archival tumor tissues, as well as serum, plasma, and blood will be collected for future exploratory biomarker assessments.

PRO data will be obtained from patients with use of the MDASI (see Appendix 11), the BFI (see Appendix 12), the treatment side-effect subscale (FKSI-19; see Appendix 13), and the EQ-5D (see Appendix 14) (see Section 4.5.6).

The co-primary efficacy endpoints are investigator-assessed PFS using RECIST v1.1 and OS. PFS will be analyzed in the PD-L1–selected population, and OS will be analyzed first in the ITT population; additional analyses of OS will be performed in a hierarchical fashion (see Section 6.1.1). See Sections 6.1.2 and 6.1.3 for a description of the timing of analyses of PFS and OS. No interim analyses of PFS are planned. See Section 3.4 for other outcome measures.

3.1.1 Independent Data Monitoring Committee

An external independent Data Monitoring Committee (iDMC) will evaluate safety data during the study on a periodic basis, approximately every 6 months, until the time of the analysis of the co-primary efficacy endpoint of PFS according to policies and procedures detailed in an iDMC Charter. No interim efficacy analyses are planned for PFS.

Staff at an independent Data Coordinating Center (iDCC) will prepare all summaries and analyses for iDMC review. The safety summaries will include demographic data, adverse events, serious adverse events, and relevant laboratory data.

Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Following the data review, the iDMC will provide a recommendation to the Sponsor whether to continue the study, amend the protocol, or stop the study. 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 the investigators for notification of the Institutional Review Boards/Ethics Committees (IRBs/ECs).

3.2 END OF STUDY

The end of study will occur when the number of deaths required for the final analysis of OS has been observed (see Section 6.1.3). On the basis of accrual projections and projected median OS for each treatment arm, the final analysis of OS is projected to occur at Month 63 from the time the first patient is randomized.

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

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Primary and Secondary Endpoints

The co-primary efficacy endpoints are investigator-assessed PFS using RECIST v1.1 and OS. PFS will be analyzed in the PD-L1–selected population (defined as IC1/2/3), and OS will be analyzed first in the ITT population; additional analyses of OS will be performed in a hierarchical fashion in the PD-L1–selected population (see Section 6.1.1). On the basis of other immunotherapy studies, including Studies PCD4989g and GP28328, as well as other studies involving renal, lung, and bladder tumors, the treatment benefit of atezolizumab may be greater among patients with higher PD-L1 expression (IC1/2/3). OS benefit may also be observed in the ITT population.

PFS of sufficient magnitude constitutes clinical benefit to the patient. PFS also allows evaluation of treatment benefit without possible confounding effects of subsequent therapies. This has historically been the standard measure of effectiveness in RCC trials given the availability of secondary and tertiary lines of therapy for metastatic RCC. The hypothesis that treatment with atezolizumab and bevacizumab will prolong PFS compared with treatment with sunitinib is based on the durable response rates observed in both the Phase I Study PCD4989g with atezolizumab monotherapy and the Phase Ib Study GP28328 of atezolizumab and bevacizumab. Patients will be evaluated for disease progression at predefined, standard intervals to minimize evaluation-time biases.

OS is an accepted measure of clinical benefit for patients.

Centralized independent PFS assessment will be performed by the IRC and will be used to support results of the investigator-assessed PFS. ORR and DOR measurements will permit the evaluation of differences in response and progression patterns between the two treatment arms. Given the potential limitations of conventional response criteria to assess activity of immunotherapeutic agents (see Section 3.3.7) modified RECIST assessments will also be performed.

Patients' rating of their symptom interference on daily functioning will provide further evidence of the clinical benefit between the two treatment groups.

3.3.2 Rationale for Inclusion of All Patients (All Levels of PD-L1 Expression by Immunohistochemistry) in the Study

In Study PCD4989g, the Phase Ia monotherapy study of atezolizumab, the response rate in patients with PD-L1 IC1/2/3 RCC has been higher (20%) than that observed for the PD-L1 IC0 patients (10%; see Section 1.4.1.1.2).

Responses to the combination of atezolizumab with bevacizumab have been observed in both PD-L1 IC1/2/3 and PD-L1 IC0 patients. In the Phase Ib Study GP28328, among patients who received atezolizumab in combination with bevacizumab and assessed for PD-L1 expression level, responses were seen in 2 of 5 PD-L1 IC1/2/3 (40%) and 1 of 4 PD-L1 IC0 (25%) patients. Therefore, given available evidence, it is too early to exclude PD-L1 IC0 patients from potential benefit from the combination.

3.3.3 Rationale for Stratification Factors

In order to balance the distribution of risk factors between the treatment arms, the randomization will be stratified for the following factors:

- The presence of liver metastases (yes/no) is included as a stratification factor because it is a well-described clinical factor portending a poor prognosis (Motzer et al. 1999) and specifically noted to be predictive for poorer survival in the CALBG 90206 bevacizumab and interferon study (Rini et al. 2010).
- MKSCC (Motzer) risk score is a well-established prognostic index stratifying patients into three categories: good, intermediate, and poor risk depending upon five criteria (see Appendix 9) (Motzer et al. 1999).
- The PD-L1 status (i.e., IC0 vs. IC1/2/3) is included as a stratification factor to account for potential differences in efficacy between patients with varying PD-L1 expression levels at study entry. Both investigators and the Sponsor will remain blinded to the results of an individual patient's PDL1 status.

3.3.4 Rationale for Evaluating Atezolizumab in Renal Cell Carcinoma

Immune checkpoint inhibitors, including atezolizumab, have demonstrated the potential to deliver significant clinical benefit to patients with advanced cancer (see Section 1.1.1.2). In this respect, atezolizumab is an example of an agent that is well tolerated and has the potential to deliver an excellent therapeutic index. In addition, because these therapies have the potential to induce potent anti-tumor immunity, there exists the potential for long-term durable responses.

Early unpublished data from the Phase Ia Study PCD4989g suggest that tumor PD-L1 status (as determined by IC0 vs. IC1/2/3) in patients with RCC correlates with response to single-agent atezolizumab, with 15% of patients (9 of 62 efficacy-evaluable patients with clear-cell RCC) achieving a PR (confirmed PR or unconfirmed PR) or CR and 57% of patients achieving stable disease. Thirty-one percent of patients had stable disease at $\geq$24 weeks. The 24-week PFS was 51%. Notably, 7 of 35 patients (20%) with PD-L1 IC1/2/3 RCC achieved an objective response compared with 2 of 21 patients (10%) who

were PD-L1 IC0. A potential benefit in terms of PFS or OS remains to be tested in controlled studies.

These data provide a rationale for evaluating the efficacy of atezolizumab in patients with RCC.

3.3.5 Rationale for Testing Atezolizumab + Bevacizumab in Renal Cell Carcinoma

Bevacizumab is a recombinant, humanized therapeutic antibody directed against VEGF. In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggest that in the tumor microenvironment, VEGF may reduce lymphocyte adhesion to vessel walls, thus contributing to decreased immune-cell recruitment to the tumor site (Bouzin et al. 2007). Some immunosuppressive activities of VEGF can be reversed by inhibition of VEGF signaling. Thus, mice exposed to pathophysiologic levels of VEGF exhibited impaired dendritic cell function, which could be restored by blockade of VEGFR2 (Huang et al. 2007). In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). Synergistic effects have also been observed in a clinical study of melanoma patients combining an immunomodulatory antibody (anti–CTLA-4; ipilimumab) and bevacizumab (Hodi et al. 2011). In this study of an immunomodulatory agent and bevacizumab, best overall responses were PR in 8 of 22 patients (35%) and stable disease in 6 of 22 patients (27%). All responses were durable for $>$6 months. Therefore, the combined treatment with atezolizumab and bevacizumab may augment the anti-tumor immune response, resulting in improved and more durable clinical benefit.

3.3.6 Rationale for Atezolizumab Dose and Schedule

The fixed dose of 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) 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, pharmacokinetic, and immunogenicity data. Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg. The maximum tolerated dose of atezolizumab

was not reached, and no dose-limiting toxicities have been observed at any dose in Study PCD4989g. Available preliminary pharmacokinetic (PK) data (0.03–20 mg/kg) from Study PCD4989g suggest that for doses ≥1 mg/kg, overall atezolizumab exhibits pharmacokinetics that are both linear and consistent with typical IgG1 antibodies. Detectable ATAs 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 ATAs and reduced exposure would necessarily restore exposure to expected levels. No clear relationship between the development of measurable ATAs and safety or efficacy has been observed. Available data suggest that development of detectable ATAs does not appear to have a significant impact on pharmacokinetics for doses from 10 to 20 mg/kg in most patients. Correspondingly, patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained target trough levels of drug despite the detection of ATAs. Currently available PK and ATA 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 potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent). 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 is selected (equivalent to a body weight–based dose of 15 mg/kg).

Selection of an every 21-day dosing interval both is supported by this preliminary pharmacokinetics evaluation and allows for a convenient integration with common chemotherapeutic regimens.

3.3.7 Rationale to Allow Dosing Post–RECIST v1.1 Progression and Use of Modified RECIST

Immunotherapy approaches to the treatment of solid tumors has resulted in distinct patterns of response different from those of traditional cytotoxic therapies and other targeted therapies. Traditional response criteria may be insufficient to characterize clinical benefit with use of this class of compounds. In a review of clinical data from the ipilimumab Phase II melanoma study, four distinct response patterns were observed: a) shrinkage of baseline lesions without new lesions, b) durable stable disease, sometimes followed by prolonged gradual decline in total tumor burden, c) response after an increase in tumor burden, and d) response in the presence of new lesions (Wolchok et al. 2009; O'Regan et al. 2011). In the ipilimumab study, patients with

disease progression before Week 12 (first tumor assessment) who did not have evidence of clinical deterioration were allowed to continue on study at the discretion of the investigator. Some of these patients were noted to have objective responses or stable disease at later tumor assessments without the addition of other anti-cancer therapies. This led to the proposal for immune-related (i.e., modified) response criteria, taking into account index and measurable new lesions. The sum of the product of the longest perpendicular dimensions (SPD) of index lesions and any new, measurable lesions (tumor burden) are taken into account for each tumor assessment. Disease progression must be confirmed by a repeat, consecutive assessment no fewer than 4 weeks after the initial, unconfirmed disease progression, provided the patient is experiencing no evidence of clinical deterioration. With use of these criteria, 9.7% of subjects initially characterized as disease progression by the World Health Organization criteria had evidence of clinical benefit (PR or stable disease).

In the preliminary experience of atezolizumab in Study PCD4989g, similar patterns of response have been observed. Evidence of tumor growth followed by response has been observed in several tumor types including RCC. Because of the complexity of response patterns observed with immunotherapeutic approaches, efficacy parameters will be evaluated by investigator assessment with use of both standard RECIST v1.1, as well as modified RECIST (see Appendix 4).

There may also be benefit to continuing sunitinib beyond RECIST v1.1 radiographic progression provided the patient remains clinically stable. This has been described by several studies as a protracted stabilization of the tumor growth rate (Teo and McDermott 2012; Burotto et al. 2014). The PFS benefit with continuing sunitinib in this retrospective evaluation appears to be comparable, if not superior, to current second-line options (Burotto et al. 2014).

Patients will be permitted to continue study treatment on either study arm after progression by RECIST v 1.1, provided there is believed to be clinical benefit and a careful assessment of the risks by investigators and patients.

3.3.8 Rationale for Pharmacokinetic Evaluation Schedule

The proposed sampling scheme for atezolizumab and bevacizumab concentration assessments will contribute to the characterization of atezolizumab and bevacizumab pharmacokinetics, respectively. The atezolizumab and bevacizumab concentration results may be compared with available data from other clinical studies and correlated with safety events in this study as appropriate.

3.3.9 Rationale for Blood Sampling for Biomarkers

Changes in biomarkers in blood 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 baseline levels and potential changes upon treatment in

surrogate pharmacodynamic markers (including but not limited to cytokines, such as IFN-γ) in blood samples.

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

3.3.10 Rationale for the Collection of Archival and/or Fresh Tumor Specimens

Pathway activation in tumors, as demonstrated by PD-L1 levels, may be an important predictive diagnostic for atezolizumab. A fraction of patients with RCC appear to derive a long-term benefit from PD-L1–based therapy. The pathway biomarkers responsible for this long-term benefit are unknown. Published results suggest that expression of PD-L1 in tumors correlates with response to anti–PD-1 therapy (Topalian et al. 2012). This correlation is also observed with atezolizumab in preliminary data from Study PCD4989g such that patients with PD-L1 expression appear to derive the most benefit from atezolizumab, as judged by RECIST response and/or prolonged stable disease (see Section 3.3.4). In this study, PD-L1 status will be used initially for stratification; tumor specimens from patients meeting eligibility criteria will be prospectively tested for PD-L1 expression by a central laboratory. In addition, PD-L1 status (as defined by expression of PD-L1 on tumor cells and/or tumor-infiltrating cells), will be correlated to treatment efficacy as defined by PFS and ORR.

In order to determine PD-L1 status, prior to study initiation, patients will be required to submit tumor tissue that was collected within 24 months of Cycle 1, Day 1. If a recent archival sample is not available, patients must undergo fresh tumor biopsy to meet eligibility. An archival specimen that was collected >24 months prior, if available, should also be submitted to evaluate change in PD-L1 status over time. Biopsy tissue samples must be obtained in a manner that minimizes risk (see Appendix 8).

These archival and/or fresh biopsy samples will be used to determine level of PD-L1 expression in tumor and tumor-infiltrating (i.e., immune) cells. Other exploratory markers, such as potential predictive and prognostic markers that are related to response or clinical benefit of atezolizumab, tumor immunobiology, angiogenesis, hypoxia, or tumor type, may also be analyzed.

3.3.11 Rationale for the Collection of Tumor Specimens at the Time of Initial Radiological Progression

Following documented RECIST v1.1 disease progression, patients are required to undergo tumor biopsy tissue sample collection of a progressing lesion (unless the location of the tumor renders tumor biopsy tissue sample collection unsafe or not clinically feasible per the investigator or is prohibited by the institution or country) in patients providing consent. Biopsy tissue sample collection must be obtained in a manner that minimizes risk (see Appendix 8). Anti-tumor immune responses such as those associated with atezolizumab may result in objective responses that are delayed

and can be preceded by initial apparent radiological progression. This initial apparent progression, called pseudoprogression, may occur as a result of either delayed anti-tumor activity and/or robust tumor immune infiltration of the tumor with a concomitant increase in tumor size. In addition, lesions that would otherwise be undetectable with conventional imaging (i.e., micrometastatic disease) may increase in size as a result of these processes and be recorded as new lesions (Hales et al. 2010). In order to characterize the kinetics and biological basis of the potential anti-tumor activity of atezolizumab, all consenting patients will be required to undergo a tumor biopsy tissue sample collection (with exceptions as described above). Data will be analyzed for the association between changes in tumor tissue and clinical outcome to further understand the potential mechanisms of resistance and progression to atezolizumab + bevacizumab when compared to such mechanisms after treatment with sunitinib. Biopsy tissue samples collected at progression will be analyzed to determine changes in PD- expression, CD8 T-cell infiltration, next generation DNA targeted sequencing related to tumor biology (Foundation Medicine), as well as vascular density (e.g., CD31). DNA and/or RNA extraction may be performed to enable identification of somatic mutations, with use of next-generation sequencing (NGS), that are associated with disease progression or acquired resistance to atezolizumab and to increase understanding of disease pathobiology. In addition, markers related to tumor biology may also be analyzed.

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 progression in the form of an NGS report, which is available directly from Foundation Medicine upon request. 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 the U.S. Food and Drug Administration (FDA); results from these investigational tests should not be used to guide future treatment decisions.

3.3.12 Rationale for Comparator Arm

Targeted therapy with tyrosine kinase inhibitors is widely used in the management of RCC in the first-line setting. Sunitinib is a multi-targeted receptor kinase inhibitor targeting several receptor tyrosine kinases, including VEGF receptors (VEGFR-1, -2, and -3), platelet-derived growth factor receptors, stem cell factor receptor (c-KIT), and FMS-like tyrosine kinase (FLT-3). Sunitinib is the most widely used agent globally for the management of RCC in the first-line setting.

Sunitinib was granted accelerated approval by the FDA in January 2006 for the treatment of patients with advanced RCC following the demonstration of favorable ORR in two separate Phase II trials. Sunitinib was approved by the European Commission in July 2006 under conditional approval, and was later granted full approval in January 2007 on the basis of a large multi-institutional, randomized Phase III trial in

which 750 patients with clear-cell RCC were randomized 1:1 to receive either sunitinib or IFN α. The results of the pivotal Phase III trial demonstrated better outcomes in the sunitinib arm compared to the IFN α arm (PFS of 11 months vs. 5 months; HR: 0.42; Motzer et al. 2007). The study enrolled patients with all MSKCC (Motzer) risk categories and the results demonstrated PFS benefit regardless of the prognostic category (HR: 0.37, 0.39, and 0.53 in good, intermediate, and poor-risk strata, respectively). In comparison, the pivotal temsirolimus study in exclusively patients with poor risk demonstrated a HR of 0.66 compared to IFN α and remains the only RCC study to demonstrate an overall survival benefit (Hudes et al. 2007). With longer follow-up, sunitinib further demonstrated a trend toward an OS benefit (HR: 0.82; $p=0.05$), extending OS from 21.8 months to 26.4 months (Motzer et al. 2009). A recent trial comparing pazopanib and sunitinib in front-line metastatic RCC demonstrated a median PFS of approximately 8.4 months for pazopanib and 9.5 months for sunitinib (HR 1.05; Motzer et al. 2013). The study enrolled patients with all MSKCC (Motzer) risk categories and the results suggested similar efficacy between the two agents.

Furthermore, sunitinib is considered by the National Comprehensive Cancer Network (NCCN) a Category 1 option for the management of metastatic RCC in previously untreated patients. Similarly, European Society for Medical Oncology (ESMO) Guidelines recommend sunitinib for good or intermediate risk (Category I) and poor risk (Category II) patients (Escudier et al. 2012). Sunitinib is widely administered for all MSKCC (Motzer) risk categories.

3.3.13 Rationale for Patient-Reported Outcomes

Treatment tolerability is a key issue in the treatment of first-line advanced RCC. The progression of RCC is often asymptomatic, and the symptoms, functional interference, and impact of quality of life that patients experience may be attributable in large part to treatment-related side effects. The treatment-related symptoms associated with the current standard of care for first-line RCC, VEGF-directed tyrosine kinase inhibitors (including sunitinib), are extensive and well documented (Motzer et al. 2013, Escudier et al. 2014) and include fatigue, gastrointestinal symptoms, such as diarrhea, hand-foot syndrome, dysgeusia, and stomatitis, among others. Despite the superior safety and quality-of-life profile of pazopanib compared with sunitinib demonstrated in the COMPARZ trial, approximately 20% of patients in both treatment arms discontinued study drug as a result of adverse events and patients in both study arms reported increased fatigue, functional interference from treatment-related side effects and physical symptoms, and worsened mouth, hand and foot soreness, as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), the treatment side-effects subscale of the FKSI-19 and the Supplementary Quality of Life Questionnaire (SQLQ), respectively (Motzer et al. 2013). Therefore, characterizing the tolerability of the atezolizumab + bevacizumab combination compared with sunitinib from the patient's perspective is important in demonstrating overall comparative treatment benefit.

3.3.14 Rationale for Open-Label Design

An open-label design was considered appropriate for this patient population because of the unique characteristics associated with the sunitinib control arm, including toxicities (i.e., hand-foot syndrome, mucositis, and dysgeusia) and delivery method (i.e., oral agent vs. IV administration) that would make it difficult to maintain the treatment blind. In the COMPARZ study, hand-foot syndrome, stomatitis, dysgeusia, and yellow skin of any grade occurred in 50%, 36%, 27%, and 15% respectively, in the sunitinib arm (Motzer et al. 2013) and have not been observed with the combination of atezolizumab and bevacizumab. Validation of tumor assessments by investigators will also be conducted with a centralized IRC as a secondary endpoint to evaluate any potential bias.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The co-primary efficacy outcome measures are:

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator from tumor assessments based on RECIST v1.1, or death from any cause and
- OS, defined as the time from randomization to death due to any cause

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

- PFS based on IRC assessment of radiographic progression per RECIST v1.1
- ORR, defined as the proportion of patients with an objective response (either CR or PR, confirmation not required) as determined by investigator per RECIST v1.1
- DOR, defined as the time from the first documented response to documented disease progression as determined by the investigator per RECIST v1.1 or death due to any cause, whichever occurs first
- ORR and DOR based on IRC assessment per RECIST v1.1
- PFS, ORR, and DOR based on investigator assessment per modified RECIST criteria (see Appendix 4)
- Change from baseline in symptom interference (from MDASI Part II)

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of all adverse events, including Grade ≥ 3 laboratory toxicities (grading per NCI CTCAE v4.0; laboratory toxicities based on local laboratory assessments), during first-line treatment
- Incidence of ATA response to atezolizumab and potential correlation with pharmacokinetics, safety, and efficacy parameters

3.4.3 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Maximum atezolizumab serum concentration (C_{max}) after infusion on Cycle 1, Day 1
- Minimum atezolizumab serum concentration (C_{min}) prior to the infusion on Day 1 of Cycles 1, 2, 4, 8 and every eight cycles thereafter; Day 22 of Cycles 1, 2, and 4; and at study termination
- Bevacizumab C_{max} after infusion on Day 1 of Cycles 1 and 2
- Bevacizumab C_{min} prior to the infusion on Day 1 of Cycles 1 and 2 and at study termination

3.4.4 Patient-Reported Outcome Measures

The other PRO outcome measures for this study are as follows:

- Change from baseline in symptom severity as measured by the MDASI and BFI
- Change from baseline in treatment side effects subscale (from FKSI-19)

In addition, health status will be collected the EuroQoL 5 Dimensions (EQ-5D) questionnaire to derive utilizes for health economic modeling.

3.4.5 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Status of PD-L1, immune-, angiogenic-, and RCC-related and other exploratory biomarkers in archival and/or freshly obtained tumor tissues and blood collected before, during, or after treatment with atezolizumab + bevacizumab or sunitinib or at progression
- PFS and ORR in patients with tumor Fuhrman Grade 4 or sarcomatoid histology (defined by investigator-assessed conventional histopathology)
- Status of tumor-infiltrating immune cells and biomarkers in biopsy specimens and blood collected at the first evidence of radiographic disease progression

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Unresectable advanced or metastatic RCC with clear-cell histology and/or component of sarcomatoid carcinoma

  Renal cell carcinoma with any component of high-grade malignant spindle cells consistent with sarcomatoid histology is eligible. (See Appendix 15 for further guidelines regarding defining sarcomatoid histology.)

- Evaluable MSKCC risk score (i.e., “Motzer” score, see Appendix 9)

  All MSKCC risk scores are included

  Patients with good risk MSKCC (risk score 0) will comprise no more than 20% of the study population

- Definitive diagnosis of RCC on the basis of a representative, formalin-fixed, paraffin-embedded tumor specimen accompanied by an associated pathology report collected within 24 months prior to Cycle 1, Day 1 available at the study site that allows determination of PD-L1 expression status (IC) (required prior to randomization)

  The archival specimen must contain adequate viable tumor tissue to establish PD-L1 expression status by a central laboratory prior to randomization.

  The specimen may consist of a tissue block (preferred) or at least 15 unstained, serial sections.

  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 embedded into a single paraffin block should be submitted for evaluation. Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

  If the archival tissue was acquired $>$24 months prior to Cycle 1, Day 1, the patient may still be eligible provided the patient is willing to consent to and undergo a pre-treatment core or excisional biopsy of the tumor. If the location of the tumor renders the tumor biopsy tissue sample collection medically unsafe, eligibility may be provided with Medical Monitor approval. A local analysis to confirm the diagnosis of RCC is required.

- Measurable disease, as defined by RECIST v1.1 (see Appendix 3)
- Age $\geq$18 years
- KPS $\geq$70 (see Appendix 5)
- Ability and capacity to comply with study and follow-up procedures
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 28 calendar 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 $\geq$2500 cells/μL

  Lymphocyte count $\geq$300 cells/μL

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

  Hemoglobin $\geq$9.0 g/dL

  AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ ULN, with the following exceptions:

    Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN

Patients with documented liver or bone metastases: alkaline phosphatase $\leq 5 \times$ 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, unless on a stable dose of warfarin

Serum albumin > 2.5 g/dL

Creatinine clearance ≥ 30 mL/min (Cockcroft-Gault formula or based on 24-hour urine collection)

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 6 months after the last dose of atezolizumab and bevacizumab or 30 days after the last dose of sunitinib.

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

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

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

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<$1% per year during the treatment period and for at least 6 months after the last dose of bevacizumab or 30 days after the last dose of sunitinib. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for the duration of the pregnancy to avoid exposing the embryo.

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

- Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:

  Evaluable or measurable disease outside the CNS

  Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)

  No history of intracranial or spinal cord hemorrhage

  No evidence of significant vasogenic edema

  No ongoing requirement for corticosteroids as therapy for CNS disease

  No stereotactic radiation within 14 days

  No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to enrollment [or randomization], if all other criteria are met.

4.1.2 Exclusion Criteria

4.1.2.1 Disease-Specific Exclusions

- Prior treatment with active or experimental systemic agents, including treatment in the neoadjuvant or adjuvant setting. Prior treatment with placebo in adjuvant setting is allowed.
- Radiotherapy for RCC within 14 calendar days prior to Cycle 1, Day 1
- Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated at least 14 days prior to Cycle 1, Day 1.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
- Uncontrolled hypercalcemia (>1.5 mmol/L ionized calcium or calcium >12 mg/dL) or symptomatic hypercalcemia refractory to bisphosphonate therapy or denosumab

  Patients who are currently receiving bisphosphonate therapy without current hypercalcemia (corrected serum calcium greater than the upper limit of normal) are eligible.

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

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

Patients with low risk prostate cancer (defined as Stage T1/T2a, Gleason score ≤6, and PSA ≤10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible

Patients with malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death <5% at 5 years) are eligible provided they meet all of the following criteria:

Malignancy treated with expected curative intent (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent)

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

4.1.2.2 General Medical Exclusions

- Life expectancy of <12 weeks
- Current, recent (within 4 weeks of Cycle 1, Day 1), or planned participation in another experimental drug study
- Pregnant and lactating, or intending to become pregnant during the study
- Women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- 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 6 for a more comprehensive list of autoimmune diseases)

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

  Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen may be eligible for this study.
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan; however, history of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive test for HIV

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

  Patients with past/resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. A negative HBV DNA test must be obtained in patients with positive hepatitis B core antibody prior to Cycle 1, Day 1.

- Patients with active hepatitis C

  Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) analysis is negative for HCV RNA.

- Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of infection (including active tuberculosis) within 2 weeks prior to Cycle 1, Day 1
- Received therapeutic oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1

  Patients receiving routine antibiotic prophylaxis (e.g., to prevent chronic obstructive pulmonary disease exacerbation or for dental extraction) are eligible.

- Significant cardiovascular or cerebrovascular disease, such as New York Heart Association cardiac disease (Class II or greater), unstable angina, myocardial infarction or cerebrovascular events within the previous 6 months or unstable arrhythmias within the previous 3 months.

  Patients with known coronary artery disease, arrhythmias, congestive heart failure not meeting the above criteria must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. Baseline evaluation of left ventricular ejection fraction (LVEF) should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease.

  Patients with known LVEF $< 50\%$

- Major surgical procedure other than for diagnosis within 21 days prior to Cycle 1, Day 1, or planned procedure or surgery during the study
- Prior allogeneic stem cell or solid organ transplant
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1

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

- Any other 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

4.1.2.3 Exclusion Criteria Related to Medications

- Prior treatment with CD137 agonists, anti–CTLA-4, anti–PD-1, or anti–PD-L1 therapeutic antibody or pathway-targeting agents
- Treatment with systemic immunostimulatory agents (including but not limited to IFN α, IL-2) for the treatment of non-malignant conditions within 6 weeks or five half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1
- Any prior use of systemic immunostimulatory agents for the management of metastatic RCC is excluded.
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti–TNF] agents) within 2 weeks prior to Cycle 1, Day 1.

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) or physiologic replacement doses (i.e., prednisone 5–7.5 mg/day) for adrenal insufficiency may be enrolled in the study.

  The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for adrenal insufficiency), and mineralocorticoids (e.g., fludrocortisone) is allowed.

4.1.2.4 Bevacizumab- and Sunitinib-Specific Exclusions

- Inadequately controlled hypertension (defined as systolic blood pressure $>$150 mmHg and/or diastolic blood pressure $>$100 mmHg).

  Anti-hypertensive therapy to maintain a systolic blood pressure $<$150 mmHg and/or diastolic blood pressure $<$100 mmHg is permitted.
- Prior history of hypertensive crisis or hypertensive encephalopathy
- New York Heart Association Class II or greater congestive heart failure (see Appendix 7)
- History of stroke or transient ischemic attack within 6 months prior to Cycle 1, Day 1
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Cycle 1, Day 1
- Patients with a baseline ECG demonstrating a QTc $>$460 ms
- Evidence of bleeding diathesis or clinically significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (within 10 calendar days prior to Cycle 1, Day 1) use of dipyramidole, ticlopidine, clopidogrel, or cilostazol.
- Prophylactic or therapeutic use of low molecular weight heparin (e.g., enoxaparin), direct thrombin inhibitors, or warfarin are permitted, provided, where appropriate anticoagulation indices are stable. Patients should have been on a stable dose (for

therapeutic use) for at least 2 weeks (or until reaching steady state level of the drug) prior to the first study treatment

- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 calendar days prior to the first dose of bevacizumab
- History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to Cycle 1, Day 1
- Clinical signs or symptoms of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Proteinuria, as demonstrated by urine dipstick or >1.0 g of protein in a 24-hour urine collection

    All patients with $\geq 2+$ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection for protein.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study. The investigator and patient will not be blinded to treatment assignment. The Sponsor study team will be blinded to the treatment assigned by randomization until the analysis of the primary endpoint is performed.

After written informed consent has been obtained and eligibility has been established, the study site will obtain the patient's identification number and treatment assignment from the Interactive Voice/Web Response System (IxRS). For patients who are eligible for enrollment, the study site will obtain the patient's randomization number and treatment assignment from the IxRS.

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

- Arm A: Atezolizumab + bevacizumab
- Arm B: Sunitinib

Randomization will be stratified by the following factors:

1. Presence of liver metastasis (yes vs. no)
2. MSKCC (Motzer) score (0, 1–2, or ≥ 3; corresponding to low, intermediate, or high risk), which comprises the following five risk factors: KPS $<80\%$, LDH $>1.5\times$ ULN, hemoglobin less than LLN, corrected serum calcium >10 mg/dL, and time from nephrectomy to systemic therapy (≤ 12 months vs. >12 months) (see Appendix 9)
3. PD-L1 status: IC1/2/3 versus IC0

A stratified, permuted-block randomization will be implemented in order to obtain a balanced assignment to each treatment within levels of the stratification factors.

4.3 STUDY TREATMENT

Atezolizumab and bevacizumab are considered the investigational medicinal products (IMP) in this study.

Sunitinib is considered a non-IMP in this study. Depending on local legislation, sunitinib may be considered an IMP. If considered an IMP, then appropriate information on formulation, packaging, handling, and administration will be provided.

Patients should receive their first dose of assigned study treatment no later than 5 business days after randomization.

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 Investigator's Brochure and Pharmacy Manual.

4.3.1.2 Bevacizumab

Bevacizumab is supplied by Roche/Genentech as a clear-to-slightly-opalescent, sterile liquid ready for parenteral administration. Each 400-mg (25-mg/mL) glass vial contains 16 mL of bevacizumab (25 mg/mL) with a vehicle consisting of sodium phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. Vials contain no preservative and are for single use only. For further details, see the Bevacizumab Investigator's Brochure.

Bevacizumab is intended for use solely in clinical trials. The drug provided for clinical trial use is expected to be very similar in safety and activity to the commercially marketed drug (Avastin®).

For additional details, see the Avastin® local label.

4.3.1.3 Sunitinib

Sutent is the malate salt of sunitinib. Sunitinib malate is described chemically as butanedioic acid, hydroxy- (2S)-, compounded with N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidine)methyl]-2,4-dimethyl-1Hpyrrole-3-carboxamide (1:1). The molecular formula is $C_{22}H_{27}FN_4O_2 \bullet C_4H_6O_5$. It will be provided by the Sponsor if it is considered an IMP by local regulations (see Section 4.3.3). Sunitinib capsules will be supplied as printed, hard-shell capsules containing sunitinib malate equivalent to 12.5 mg, 25 mg, or 50 mg of Sutent with mannitol, croscarmellose sodium, povidone (K-25), and magnesium stearate as inactive ingredients.

For additional details, see the Sutent® local label for Dosage, Administration, and Storage.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Atezolizumab

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

Patients randomized to atezolizumab will receive 1200 mg of atezolizumab administered by IV infusion every 21 days in a monitored setting where there is immediate access to trained personnel and adequate equipment/medicine to manage potentially serious reactions. For more detailed information regarding administration, refer to the Atezolizumab Investigator's Brochure and Pharmacy Manual.

For patients randomized to Arm A, atezolizumab will be administered first, followed by bevacizumab, with a minimum of 5 minutes between dosing.

Atezolizumab infusions will be administered per the instructions outlined in Table 10.

For additional details regarding management of infusion-related reactions, please refer to the Atezolizumab Investigator's Brochure: Guidelines for the Management of Infusion-Related Reactions during Cycle 1.

Table 10 Administration of First and Subsequent Infusions of Atezolizumab

First Infusion	Subsequent Infusions
• No premedication is administered • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • Infuse atezolizumab (one vial in 250 mL NaCl) over 60 (±15) minutes. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion at 15, 30, 45, and 60 minutes (±5-minute windows are allowed for all timepoints). • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) at 30 (±10) minutes and 2 hours (±15 minutes) after the infusion. • Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If patient experienced infusion-related reaction during any previous infusion, premedication with antihistamines may be administered for Cycles ≥2 at the discretion of the treating physician. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • If the patient tolerated the first infusion well without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) minutes. • If the patient had an infusion-related reaction during the previous infusion, the subsequent infusion must be delivered over 60 (±15) minutes. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during the infusion if clinically indicated or patient experienced symptoms during the previous infusion. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) 60 (±10) minutes after the infusion. • If no reaction occurs, continue subsequent infusions over 30 (±10) minutes with same schedule for recording vital signs.

For anaphylaxis precautions, see Appendix 10. Patients in Arm A may discontinue either atezolizumab or bevacizumab (e.g., for adverse events) and may continue on single-agent therapy until disease progression. Guidelines for dosage modification, treatment interruption or discontinuation, and the management of specific adverse events are provided in Sections 5.1.3 and 5.1.4.

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

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

4.3.2.2 Bevacizumab

The dose of bevacizumab in this study is 15 mg/kg administered by IV infusion every 3 weeks on Days 1 and 22 of each 42-day (6-week) cycle. The interval between infusions must not be <10 days. The bevacizumab dose will be based on the patient's weight at randomization and will remain the same throughout the study unless there is a weight change of $>10\%$ from baseline. It is not necessary to correct dosing based on ideal weight, unless warranted per institutional guidelines/standard.

The initial dose of bevacizumab will be delivered over 90 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60 (± 10) minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. For patients randomized to Arm A, the patient should be observed for at least 2 hours after the first administration of the combination and for at least 1 hour for subsequent infusions.

If a patient experiences an infusion-associated adverse event, he or she may be premedicated for the next bevacizumab infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 minutes as long as the patient continues to be premedicated. If a patient experiences a second episode of an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 (± 15) minutes. Similarly, if a patient experiences a second episode of an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60 (± 10) minutes.

Upon receipt of the bevacizumab, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until use. Vials should be protected from light. DO NOT FREEZE. DO NOT SHAKE. VIALS ARE FOR SINGLE USE ONLY. Vials used for one patient may not be used for any other patient.

4.3.2.3 Sunitinib

The comparator, sunitinib, will be used in the commercially available formulation, packaging, and handling. It will be provided by the Sponsor if it is considered an IMP by local regulations (see Section 4.3.3). Bottles of the appropriate dose will be dispensed on Day 1 of each cycle, and patients will be required to return empty bottles to the clinic on Day 1 of each cycle, starting at Cycle 2, for drug accountability by site study personnel.

Sunitinib will be taken at the approved dose level of 50 mg/day for 4 weeks followed by a 2-week rest period. For the purposes of this trial, a cycle is defined as 4 weeks of sunitinib and 2 weeks of rest (6 weeks). Under no circumstances may a patient receive sunitinib for >28 days (4 weeks) without a subsequent 2-week rest period. Capsules should be taken once daily with a glass of water and may be taken without regard to

meals. The study investigator may implement dose interruption or dose reduction (i.e., 50 mg to 37.5 mg or 37.5 mg to 25 mg) in order to ensure patient safety (see Section 5.1.7, Section 5.1.8, and Table 11).

For further details, see the Sutent® label.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for the completion of this study (atezolizumab, bevacizumab, and sunitinib if considered an IMP by local regulations) will be provided (or reimbursed) by the Sponsor. The investigational site will acknowledge receipt of atezolizumab and bevacizumab with use of the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. Where sunitinib is supplied by the Sponsor, shipment receipt will be documented using IxRS; otherwise, it will be documented per local practice.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or 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

A patient will be eligible to receive the study drug (atezolizumab) and bevacizumab after the end of the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and require continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

The patient will not be eligible to receive the study drug after the end of the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- Roche has discontinued development of the study drug or data suggest that the study drug is not effective for kidney cancer
- Roche has reasonable safety concerns regarding the study drug as treatment for kidney cancer

- Continued access to study drug is not permitted under the laws and regulations of the patient's country

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening until the treatment discontinuation visit. All such medications should be reported to the investigator.

Premedication with antihistamines may be administered for any atezolizumab infusions after Cycle 1.

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

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin, direct thrombin inhibitors, or warfarin at a stable dose level)
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)
- Low-dose corticosteroids ($\leq$10 mg prednisone equivalent) for patients with orthostatic hypotension or adrenocortical insufficiency

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, as per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 10).

The use of systemic corticosteroids is discouraged. A limited course of systemic steroids is permitted to treat immune-mediated adverse events when associated with atezolizumab therapy, at the discretion of the treating physician. For full details of the management of immune related events, refer to the Investigator's Brochure, Section 6.6.

All medications must be recorded on the Concomitant Medications eCRF.

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

Systemic corticosteroids and tumor necrosis factor-α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations where systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered first by the treating physician. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the treating physician.

4.4.3 Excluded Therapy

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

- Chemotherapy, immunotherapy, radiotherapy, investigational agents

  After Cycle 1, Day 14, radiotherapy may be considered for pain palliation if patients are deriving benefit (e.g., treatment of known bony metastases) and provided they do not compromise assessments of tumor target lesions. Study drug administration may be continued during radiotherapy for patients being treated with atezolizumab. Study drug should be suspended for patients being treated with sunitinib per institutional guidelines.

4.4.3.1 Excluded and Cautionary Therapy for Atezolizumab-Treated Patients

The following guidance applies only to patients randomized to receive atezolizumab. The following medications are excluded while the patient is receiving study treatment:

- Traditional herbal medicines; these therapies are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound the assessment of toxicity
- Immunomodulatory agents, including but not limited to interferons or interleukin-2 during the entire study; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab

Influenza vaccinations (inactivated forms only) should be given only during influenza season (approximately October to March in the Northern hemisphere; April to September in the Southern Hemisphere). Patients randomized to receive atezolizumab must agree not to receive live, attenuated influenza vaccines (such as FluMist®) 28 days prior to randomization, at any time during the study, or within 5 months following the last dose of atezolizumab (for patients randomized to atezolizumab) but may receive inactivated influenza vaccines.

In addition, patients treated with atezolizumab should not receive other immunomodulatory agents for 10 weeks after study treatment discontinuation.

4.5 STUDY ASSESSMENTS

Flowcharts of scheduled study assessments are provided in Appendix 1 and Appendix 2. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

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 and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date.

4.5.1 Informed Consent Forms and Screening Log

Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

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.

Re-screening is required if a patient has not met all of the eligibility criteria within 28 days from the original date of the screening visit. Re-screening refers to repeating the entire screening process with the exception of performing a repeat biopsy to collect a tumor tissue sample to be used to determine PD-L1 status and repeating CT and/or MRI imaging scans used for tumor assessment, provided the biopsy tissue sample and imaging scans were obtained during the original screening visit. Patients are only allowed to be re-screened twice. Blood samples may be redrawn due to sample handling problems, breakage, or sample integrity, without being considered a re-screen.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), 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 the screening. A history of pleural or pericardial effusion or of ascites requiring intervention should be entered in the medical history.

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

Cancer history will include an assessment of tumor histology.

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Height and weight should be measured and recorded in the 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 measurements of respiratory rate, pulse rate, systolic and diastolic blood pressures while the patient is in a seated position, and body temperature.

For patients randomized to Arm A, atezolizumab will be administered first, followed by bevacizumab, with a minimum of 5 minutes between dosing. For the first infusion of atezolizumab for patients in Arm A, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before, during (every 15 [±5] minutes), and 30 (±10) minutes and 2 hours (±15 minutes) after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated, and 1 hour (±10 minutes) after the infusion. For patients randomized to Arm A, observation should be for at least 2 hours after the first administration of the combination and for at least 1 hour for subsequent infusions. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

4.5.5 Tumor and Response Evaluations

Measurable and non-measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor assessments are to be performed regardless of drug delays or interruptions (i.e., independent of treatment cycles) as specified in Appendix 1 ±5 business days.

Screening assessments must include CT scans (with oral and IV contrast unless contraindicated) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis, and a brain scan (CT or MRI). For patients undergoing MRI, a non-contrast spiral CT scan of the chest should be obtained to evaluate lung parenchyma. CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

A CT (with contrast if not contraindicated) or MRI scan of the brain must be done at screening to exclude CNS metastasis. An MRI scan of the brain is required to confirm or

refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. Patients with definitively treated stable CNS metastases may be eligible for the study (see Sections 4.1.1 and 4.1.2.1).

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.

Bone scans (technetium-99m [TC-99m]) or sodium fluoride PET (NaF-PET) should be performed at screening if bone metastases are clinically suspected. If bone metastases are present at screening and cannot be seen on CT or MRI scans, bone scans should be performed at any time when progression in bone is suspected. Bone scans should be repeated when CR is identified in target disease or when progression in bone is suspected and not visualized by CT/MRI.

For subsequent tumor assessments, the same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). If IV contrast cannot be given, then the patient should undergo MRI of the abdomen and pelvis and non-contrast CT of the chest. If CT with contrast is used for baseline imaging, but subsequently IV contrast cannot be given, then non-contrast CT scans may be used.

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator with use of RECIST v1.1, as well as modified RECIST criteria (see Appendix 3 and Appendix 4). Assessments should be performed by the same evaluator if possible to ensure internal consistency across visits. At the investigator's discretion, CT scans should be repeated at any time if progressive disease is suspected.

Patients permitted to continue study therapy beyond radiographic disease progression per RECIST v1.1 (see Section 4.6.2) will be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 6 weeks. If the scan frequency is every 12 weeks (see Appendix 1), the follow-up scan must be performed every 12 weeks (± 5 business days), or earlier if clinically indicated.

If study treatment discontinues prior to disease progression per RECIST v1.1, tumor assessment should be followed according to Section 4.5.12.1.

All scans, as outlined above, should be submitted to the IRC for independent review. For patients who discontinue study therapy after investigator assessed, radiographic progression per RECIST v1.1, at least one scan, after RECIST v1.1 progression should continue to be submitted to the IRC.

4.5.6 Patient-Reported Outcomes

PRO data will be collected using an electronic PRO method, both during the trial and at post-progression assessments. Site staff will review PRO questionnaires for completeness ONLY.

PRO data will be obtained from patients with use of the MDASI (see Appendix 11), the BFI (see Appendix 12), the treatment side-effect subscale (FKSI-19; see Appendix 13), and the EQ-5D (see Appendix 14) to more fully characterize the clinical profile of atezolizumab.

The MDASI (Cleeland et al. 2000) is a cancer-related, multisymptom, valid, and reliable self-report questionnaire for clinical and research use. It consists of 23 items over two scales that assess symptom severity and symptom interference with different aspects of a patient's life. Seventeen items (pertaining to pain, fatigue, nausea, disturbed sleep, distressed, shortness of breath, remembering things, lack of appetite, drowsy, dry mouth, sad, vomiting, diarrhea, and numbness or tingling) ask patients to rate how severe the symptoms were when "at their worst" in the last 24 hours. An additional six items ask patients to rate how much the symptoms have interfered with six areas of function (general activity, walking, work, mood, relations with other people, and enjoyment of life) in the last 24 hours. Additionally, the MDASI contains tumor-specific modules to assess symptoms of disease and treatment. For this study, to specifically assess RCC symptoms and treatment side effects, patients will rate four additional symptoms (skin rash or change, sores in throat and mouth, diarrhea, and headache). The MDASI items are rated from 0 to 10, with 0 indicating that the symptom is either not present or does not interfere with the patient's activities and 10 indicating that the symptom is "as bad as you can imagine" or "interfered completely" with the patient's life. The MDASI takes approximately 5 minutes to complete.

The BFI is a valid and reliable self-report questionnaire used to rapidly assess the severity and impact of cancer-related fatigue. It consists of three items to assess the severity of fatigue over 24 hours and an additional six items to assess the impact of fatigue on global domains (i.e., general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life) in the last 24 hours. Similar to the MDASI, items are rated from 0 to 10, with 0 indicating that the symptom is either not present or does not interfere with the patient's activities and 10 indicating that the symptom is "as bad as you can imagine" or "interfered completely" with the patient's life. For most patients, the BFI takes fewer than 5 minutes to complete.

The EQ-5D questionnaire is a generic, preference-based health utility measure with 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 (EQ-5D-3L User Guide Version 5.0). The EQ-5D will be utilized in this study for economic modeling. The EQ-5D questionnaire takes 5 minutes or less to complete.

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 the following items: lack of energy, pain, losing weight, fatigue, shortness of breath, fever, bone pain, coughing, weakness, hematuria, appetite, sleeping, worry, nausea, diarrhea, bother from side effects of treatment, ability to work, ability to enjoy life, and contentment. The nausea, diarrhea and bother from side effects of treatment items together comprise the side effects from treatment subscale. 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." It takes approximately 5 minutes to complete.

The PRO questionnaires will be translated as required in the local language, distributed by the investigator staff, and completed in their entirety by the patient.

PRO questionnaires should be self-administered using an electronic device prior to the completion of other study assessments and the administration of study treatment. The PRO questionnaires should be completed at Day 1 and Day 22 of each cycle, at the end-of-treatment visit, in case of early treatment discontinuation, as well as at 6, 12, 24, and 36 weeks after the end-of-treatment visit. In addition, the BFI ePRO questionnaire will be collected weekly during the first 12 weeks. Assessments on days when the patient does not come to the clinic (e.g., Days 8, 15, 29, 36) will be completed by the patient at home.

Adverse event reports will not be derived from PRO data by the Sponsor. However, any PRO responses suggestive of a possible adverse event that are identified during site review of the PRO data should be reported.

4.5.7 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, as listed below.
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, ATA assays, and auto-antibody 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, serum ferritin, and albumin)
- Coagulation (aPTT and INR)

- Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation)
- Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood)
- Thyroid function testing (thyroid stimulating hormone [TSH], free T3, free T4)
- HBV serology (HBsAg, antibody to HBsAg [anti-HBs], anti-HBc)
- HBV DNA required prior to Cycle 1, Day 1 in patients who are anti–hepatitis B core antibody–positive
- HCV serology (anti-HCV)
- All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical trial.

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

- T, B, and natural killer (TBNK) blood sample

  Samples will be assayed for T cells, B cells, and NK cells.
- C-reactive protein (CRP)
- ATA assays

  Serum samples will be assayed for the presence of ATAs to atezolizumab with use of validated immunoassays.
- PK assays

  Serum samples will be assayed for atezolizumab concentration (and bevacizumab concentration, if applicable) with the use of a validated immunoassay.
- Auto-antibody testing

  Anti-nuclear antibody

  Anti–double-stranded DNA

  Circulating anti–neutrophil cytoplasmic antibody

  Perinuclear anti–neutrophil cytoplasmic antibody
- Biomarker assays in blood samples

  Blood samples will be obtained for biomarker evaluation from all eligible patients at screening, before treatment, on treatment, and at the end of treatment visits. Samples will used for the determination of changes in surrogate pharmacodynamic biomarkers, including but not limited to cytokines such as IFN-γ, T-cell markers such as CD8, and other exploratory biomarkers. Whole blood samples may be processed to obtain peripheral blood mononuclear cells (PBMCs) and their derivatives (e.g., RNA and DNA). DNA samples will only tested for targeted analysis of genes involved in renal cancer such as Von-Hippel Lindau or the related immune response. If health

authorities or ethics committees do not approve the use of the blood for PBMCs and/or their derivatives (e.g., DNA, RNA), the related analysis will not be applicable. For example, in countries where DNA analysis is not permitted, then investigators may opt out of the DNA portion of the testing.

Any remaining samples collected for PK, biomarker assays, and ATAs may be used for exploratory biomarker profiling, identification, and pharmacodynamic assay development purposes and additional safety assessments (e.g., ATA assay) as appropriate.

- Archival and fresh tumor tissue samples

  Representative tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides (or 10−14 slides with monitor approval), with an associated pathology report, must be submitted for determination of PD-L1 status prior to study enrollment.

  All patients must have a tumor biopsy specimen acquired ≤24 months prior to Cycle 1 for the PD-L1 pathway assessment, unless, following discussion with the Medical Monitor, the location of the tumor renders the tumor biopsy medically unsafe or infeasible.

  If an archival sample acquired ≤24 months prior to Cycle 1, Day 1 is not available, patients must undergo fresh tumor biopsy to meet eligibility requirements. If a patient's PD-L1 status is determined on the basis of a fresh tumor specimen, the archival tissue sample, if available, should also be submitted.

  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, bone metastases, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores embedded in a single paraffin block should be submitted for evaluation. Tumor tissue from bone metastases that is subject to de-calcification is not acceptable.

  For fresh metastatic biopsy specimens, acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

  In addition, exploratory biomarkers (including, but not limited to markers related to immune or RCC biology or non-inherited biomarkers identified through NGS on extracted DNA and/or RNA) may be evaluated.

  At the time of progression by RECIST v1.1, patients randomized to the atezolizumab + bevacizumab arm or sunitinib arm, if clinically feasible and permitted by institution and country, are required to undergo a biopsy of a site of progression.

  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 progression in the form of an NGS report, which is available directly from Foundation Medicine upon request. 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 the FDA; results from these investigational tests should not be used to guide future treatment decisions.

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 patients who consent to the optional collection of samples for the Roche Clinical Repository (RCR):

  Core needle biopsies for deep tumor tissue or organs or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions will be obtained from consenting patients. Biopsy at the time of radiographic progression is highly recommended if there is any concern that it could represent pseudo-progression as opposed to true progression. Additional biopsy samples may be collected at any time during the study per investigator discretion.

- Use and storage of remaining samples from study-related procedures:

  The remainder of samples obtained for study-related procedures will be destroyed no later than 5 years after the end of the study or earlier depending on local regulations. If the patient provides optional consent for storing samples into the RCR for future research, the samples will be destroyed no later than 15 years after the date of final closure of the clinical database.

Refer to the laboratory manual for additional details on laboratory assessments and sample handling. Samples collected during the study may be evaluated for immune-related, tumor type-related, and other exploratory biomarkers (e.g., alterations in gene expression or targeted DNA sequencing of renal cancer-related genes in countries where this is permitted).

4.5.8 Cardiac Tests

4.5.8.1 Electrocardiograms and Evaluations of Left Ventricular Ejection Fraction (Echocardiograms or MUGA)

A twelve-lead ECG is required at screening, at the end of treatment visit, and when clinically indicated. ECGs for each patient should be obtained from the same machine whenever possible.

Patients receiving sunitinib or bevacizumab should be carefully monitored for clinical signs and symptoms of congestive heart failure, especially in patients with cardiac risk factors and/or history of coronary artery disease. Baseline and periodic evaluations of LVEF should also be considered (echocardiogram or MUGA). In patients receiving sunitinib who do not have any cardiac risk factors, a baseline evaluation of ejection fraction should also be considered. In countries where additional cardiac monitoring is

considered standard (e.g., France), additional cardiac monitoring as described below will be required:

- A baseline evaluation of LVEF in those patients with cardiac risk factors and/or an abnormal baseline ECG
- Electrocardiogram (ECG) on Cycle 1, Day 22 for patients randomized to the sunitinib arm

4.5.9 Anti-Therapeutic Antibody Testing

Atezolizumab may elicit an immune response. Patients with signs of any potential immune response to atezolizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ATAs at multiple timepoints before, during, and after treatment with atezolizumab (see Appendix 1 and Appendix 2 for the schedule). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Rosenberg and Worobec 2004; Koren et al. 2008) to characterize ATA responses to atezolizumab in support of the clinical development program. This tiered strategy will include an assessment of whether ATA responses correlate with relevant clinical endpoints. Implementation of ATA characterization assays will depend on the safety profile and clinical immunogenicity data.

4.5.10 Assessments during Treatment

Assessments across the two treatment arms will be conducted using the same visit schedule. If treatment is delayed for an adverse event, assessments should continue to be performed while treatment is on hold. All visits must occur within ± 3 days from the scheduled date unless otherwise noted (see Appendix 1 and Section 4.5). All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion unless otherwise noted. Local laboratory assessments from each cycle must be reviewed prior to study treatment administration for each cycle.

See the schedule of assessments provided in Appendix 1 and Appendix 2 for the schedule of treatment period assessments.

Karnofsky performance status and limited physical examination may be obtained ≤ 96 hours prior to Days 1 and 22 of each cycle.

For any study arm, if scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a regular dosing schedule. If treatment was postponed for fewer than 2 days, the patient can resume the original schedule.

After two complete cycles, treatment can be delayed by 1 week to allow for vacations.

Blood samples for pharmacodynamic biomarker analysis and pharmacokinetics will be obtained according to the schedules in Appendix 1 and Appendix 2.

4.5.11 End of Treatment Visit

Patients who discontinue from treatment will be asked to return to the clinic not more than 30 days after the last treatment for an end of treatment visit. The visit at which a response assessment shows progressive disease resulting in patient discontinuation may be used as the end of treatment visit.

See the schedule of assessments provided in Appendix 1 and Appendix 2 for assessments to be performed at the end of treatment visit.

4.5.12 Follow-Up Assessments

Patients who discontinue from treatment will be followed as outlined below.

4.5.12.1 Ongoing Tumor Assessments

Patients who discontinue study treatment (atezolizumab + bevacizumab, or sunitinib) for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments as if the patients were still on study treatment until the patient dies, experiences disease progression per RECIST v1.1 and modified RECIST, withdraws consent, or until the study closes, whichever occurs first. Patients who start a new anti-cancer therapy in the absence of disease progression per RECIST v1.1 should continue to undergo tumor assessments according to the protocol schedule unless they withdraw consent, die, experience disease progression per RECIST v1.1 and modified RECIST, or study closes, whichever occurs first.

4.5.12.2 Survival Follow-Up

Survival follow-up information will be collected by the Sponsor via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination, whichever occurs first. All patients will be followed for survival and new anti-cancer therapy information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws consent to be followed on the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. During survival follow-up, the following information regarding all subsequent anti-neoplastic agents upon treatment discontinuation will be collected: line of therapy, agent, date of first dose of agent, date of last dose of agent (or if ongoing), patient's best response, and date of disease progression.

4.5.12.3 Adverse Events

Serious adverse events (see Section 5.2.2) and adverse events of special interest (see Section 5.2.3), regardless of attribution, will be recorded until the end of the special reporting period (defined as 90 days after the last dose of atezolizumab or bevacizumab

or 30 days after the last dose of sunitinib or until the initiation of another anti-cancer therapy, whichever occurs first). All other adverse events will be recorded until 30 days after the last dose of atezolizumab, bevacizumab or sunitinib or until the initiation of another anti-cancer therapy, whichever occurs first. Ongoing adverse events thought to be related to study treatment will be followed until resolution of the adverse event, until an alternate cause has been identified, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event. The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the special reporting period, if the event is believed to be related to prior study drug treatment (see Section 5.6).

See the schedule of assessments provided in Appendix 1 for specified follow-up assessments.

4.5.13 Samples for Roche Clinical Repository

Roche participates in the collection and/or submission of biological samples to the RCR.

4.5.13.1 Overview of the Roche Clinical Repository

The RCR 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 and analysis of RCR 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 RCR will be collected from patients who give specific consent to participate in this optional research. RCR 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

4.5.13.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's IRB or EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.13) will not be applicable at that site.

4.5.13.3 Sample Collection

The following samples may be collected for patients who have signed the RCR optional consent:

- Optional fresh biopsy samples as clinically indicated. Optional tumor biopsies may be obtained at other timepoints at the investigator's discretion.
- Whole blood constitutive (inherited) DNA: single-nucleotide polymorphism array testing on DNA
- Remaining serum and plasma after study-related tests have been performed
- Remaining formalin-fixed, paraffin-embedded tissue (with the exception of archival FFPE blocks, which will be returned to sites) after study-related tests have been performed

For all samples, dates of consent should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

RCR specimens will be stored for 15 years or until they are exhausted. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.13.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

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

Patient medical information associated with RCR 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.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

4.5.13.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. 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 RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

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

4.5.13.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. 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 with use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study WO29637 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study WO29637.

4.5.13.7 Monitoring and Oversight

RCR 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. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. 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 RCR samples.

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. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

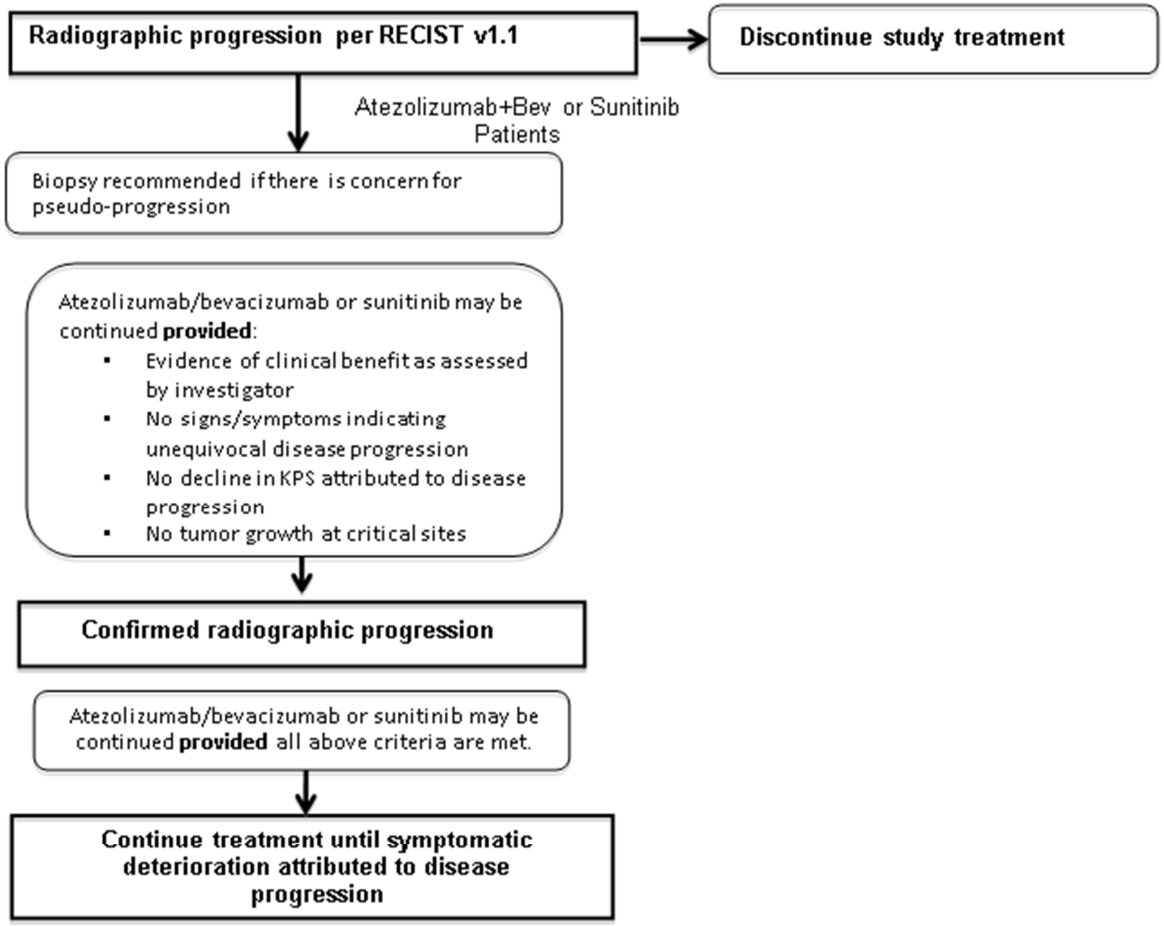
- Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status.
- Intolerable toxicity related to atezolizumab + bevacizumab or sunitinib, determined by the investigator and Medical Monitor 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 on study treatment
- Use of another anti-cancer therapy with the exception of anti-cancer therapies specified in the protocol (see Section 4.4.3)
- Pregnancy

Patients randomized to either study arm will be permitted to continue study treatment after RECIST v1.1 criteria for investigator-assessed progressive disease are met, at the discretion of the investigator, if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in KPS that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilized by protocol-allowed medical interventions prior to repeat dosing.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Figure 4 Conditions for Continuing Atezolizumab/Bevacizumab or Sunitinib in the Presence of Progression by RECIST v1.1 Criteria



Bev = bevacizumab; KPS = Karnofsky performance status; RECIST = Response Evaluation Criteria in Solid Tumors.

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 and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Atezolizumab is not approved and is currently in clinical development. Human experience is currently limited and the entire safety profile is not known at this time. The following information is based on results from nonclinical and clinical studies and published data on similar molecules.

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (see Sections 4.1.1, 4.1.2, and 5.1.2.1) and close monitoring (as indicated below and in Section 4.5).
See Section 5.3 (Methods and Timing for Capturing and Assessing Safety Parameters) for complete details regarding safety reporting for this study.

The administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Serious adverse events (see Section 5.2.2) and adverse events of special interest (see Section 5.2.3), regardless of attribution, will be recorded during the trial until the end of the special reporting period (defined as 90 days after the last dose of atezolizumab or bevacizumab or 30 days after the last dose of sunitinib [see Section 5.6]). All other adverse events will be recorded until 30 days after the last dose of atezolizumab, bevacizumab, or sunitinib or until the initiation of another anti-cancer therapy, whichever occurs first. The potential safety issues anticipated in this trial, as

well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

5.1.1 Risks Associated with Atezolizumab

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-mediated adverse events, specifically the induction or exacerbation of autoimmune conditions. As of 10 May 2015, adverse events with potentially immune-mediated causes, including rash, hypothyroidism, adrenal insufficiency, hepatitis/transaminitis, colitis, myositis, influenza-like illness, and neurologic disorders, have been observed in Study PCD4989g. A more comprehensive list of observed adverse events observed with atezolizumab is available in Section 1 and the Atezolizumab Investigator's Brochure.

Although most immune-mediated adverse events s observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo et al. 2010). Suggested workup and management guidelines for suspected immune-mediated adverse events are provided in Section 6 (Guidance for the Investigator) of the Atezolizumab Investigator's Brochure.

5.1.2 General Plan to Manage Safety Concerns

5.1.2.1 Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this trial. Results from the nonclinical toxicology studies with atezolizumab, the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, and clinical data from bevacizumab and sunitinib were taken into account. Specifically, patients at risk for study-emergent autoimmune conditions or with a prior diagnosis of autoimmune disease, patients with evidence of acute infections, and patients who have received a live-attenuated viral vaccine within 4 weeks before Day 1 are excluded from the study (see Section 4 for additional details).

5.1.2.2 Monitoring

Laboratory values must be reviewed prior to each infusion.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Appendix 1 and Appendix 2 for the list and timing of study assessments).

During the study, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

All serious adverse events and protocol-defined events of special interest (see Sections 5.2.2 and 5.2.3) will be reported in an expedited fashion (see Section 5.4). In addition, the Medical Monitor and investigators will review and evaluate observed adverse events on a regular basis.

Patients who have an ongoing study treatment–related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

5.1.3 Atezolizumab Dose Modification–General Notes

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment if they experience toxicity that is considered to be related to study drug and requires a dose to be withheld. If atezolizumab is withheld because of related adverse events for >42 days beyond when the next dose would have been given, then the patient will be discontinued from atezolizumab and will be followed up for safety and efficacy as specified in Section 4.5.12. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming atezolizumab after a hold of >42 days, the study drug may be restarted with the approval of the Medical Monitor.

If patients must be tapered off steroids used to treat adverse events, study treatment may be withheld for >42 days until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Dose interruptions for reason(s) other than adverse events, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Patients who discontinue atezolizumab either transiently or permanently (e.g., for adverse events) may continue on bevacizumab until disease progression if there is felt to be clinical benefit.

Management of atezolizumab-specific adverse events is presented in in Section 5.1.4.

See Section 4.3 for guidelines for the management of infusion-related reactions and Appendix 10 for precautions for anaphylaxis.

5.1.4 Management of Atezolizumab-Specific Adverse Events

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 determine a possible immunogenic etiology.

5.1.4.1 Immune-Mediated Reactions

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 be acutely managed with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The primary approach to Grade 1–2 immune-mediated adverse events is supportive and symptomatic care with continued treatment with atezolizumab; for higher grade immune-mediated adverse events, atezolizumab should be withheld and oral/parenteral steroids administered. Recurrent Grade 2 immune-mediated adverse events may also mandate holding atezolizumab or the use of steroids. Consideration for benefit-risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening immune-mediated adverse events.

Management of systemic immune activation is presented in Section 5.1.4.2. See the current Atezolizumab Investigator's Brochure for details on management of gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, potential pancreatic or eye toxicity and other immune-mediated adverse events. See Section 4.3.2.1 for guidelines for the management of infusion-related reactions (see Appendix 10 for precautions for anaphylaxis).

5.1.4.2 Systemic Immune Activation

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who develop a sepsis-like syndrome after administration of atezolizumab and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

5.1.5 Bevacizumab Dose and Dose Interval Modification

The bevacizumab dose will be based on the patient's weight at randomization and will remain the same throughout the study, unless there is a weight change of $>10\%$ from baseline. It is not necessary to correct dosing on the basis of ideal weight, unless warranted per institutional guidelines/standard. Management of bevacizumab may be performed according to the label. Suggested guidelines for management are summarized in Table 11. If adverse events occur that necessitate holding bevacizumab, the weight-based dose in mg/kg will remain unchanged after treatment resumes.

Patients who discontinue bevacizumab transiently or permanently for adverse events may continue on single-agent atezolizumab until disease progression if there is felt to be clinical benefit. Patients with Grade ≥ 3 toxicities attributable to bevacizumab should withhold atezolizumab until those toxicities have improved to Grade ≤ 2 (exception for Grade 3 hypertension). If bevacizumab is permanently discontinued but there is felt to be clinical benefit from atezolizumab, the latter may be continued.

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level. Patients who develop Grade 4 toxicities related to bevacizumab for >21 days should permanently discontinue bevacizumab.

The appropriate interval between the last dose of bevacizumab and major surgery is unknown. Because bevacizumab has a half-life of approximately 21 days, elective surgery should be delayed whenever possible, but if necessary, bevacizumab should be withheld for ≥ 28 days prior to the procedure. Re-initiation of bevacizumab should occur ≥ 28 days after surgery and after wounds have fully healed. Re-initiation of bevacizumab after surgery requires documented approval from the Medical Monitor.

Infusion of bevacizumab should be interrupted in patients who develop dyspnea or clinically significant hypotension. Patients who experience an NCI CTCAE Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment. If possible, a sample for ATA assessment will be collected at the time of discontinuation.

Bevacizumab infusion should be slowed to $\leq 50\%$ or interrupted for patients who experience any infusion-associated symptoms not specified above. If the infusion is interrupted, it may be resumed at $\leq 50\%$ of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.

5.1.6 Sunitinib Dose and Dose Interval Modification

Dose interruption and/or dose modification in 12.5-mg increments or decrements is recommended based on individual safety and tolerability. Modification to sunitinib

administration may be done according to the label. The starting dose of sunitinib is 50 mg, unless otherwise specified (below).

Strong CYP3A4 inhibitors such as ketoconazole may increase sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. A dose reduction for sunitinib to a minimum of 37.5 mg daily should be considered if sunitinib must be co-administered with a strong CYP3A4 inhibitor (see sections on drug interactions and clinical pharmacology from the Sutent® label).

CYP3A4 inducers such as rifampin may decrease sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. A dose increase for sunitinib to a maximum of 87.5 mg daily should be considered if sunitinib must be co-administered with a CYP3A4 inducer (see Appendix 16). If dose is increased, the patient should be monitored carefully for toxicity (see sections on drug interactions and clinical pharmacology from the Sutent label).

Sunitinib should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmics, or medicinal products that can prolong QT interval, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. QT interval prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de pointes. Torsade de pointes has been observed in $<0.1\%$ of sunitinib-exposed patients. A comprehensive list of drugs that have the potential to increase QT interval is provided in Appendix 17.

5.1.7 Recommended Guidelines for Management of Suspected Bevacizumab or Sunitinib Toxicities

Table 11 describes recommended guidelines for dose modification to sunitinib or bevacizumab for selected events.

Table 11 Bevacizumab and Sunitinib Dose Management for Adverse Events

Event	Action to Be Taken
Hypertension	
Grade 1 (asymptomatic, transient [< 24 hr] blood pressure increase by > 20 mmHg (diastolic) or to > 150/100 mmHg if previously within normal limits)	No bevacizumab or sunitinib dose modifications.
Grade 2 (recurrent or persistent [> 24 hr] or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100 mmHg if previously within normal limits)	Withhold bevacizumab or sunitinib. Start antihypertensive therapy per institutional guidelines. After blood pressure is < 150/100 mmHg, patient may continue bevacizumab or sunitinib therapy.
Grade 3	Requires more than one antihypertensive drug or more intensive therapy than previously: If not controlled to 150/100 mmHg with medication, discontinue bevacizumab or sunitinib.
Grade 4 (including hypertensive encephalopathy)	Discontinue bevacizumab or sunitinib.
Hemorrhage	
Grade 1 or 2 non-pulmonary or non-CNS events	No bevacizumab or sunitinib modifications.
Grade 3 non-pulmonary or non--brain or non-spinal cord hemorrhage	Withhold bevacizumab or sunitinib until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from bevacizumab or sunitinib.

Table 11 Bevacizumab and Sunitinib Dose Management for Adverse Events (cont.)

Event	Action to Be Taken
Hemorrhage (cont.)	
Grade 4 non-pulmonary or non-brain or non-spinal cord hemorrhage	Discontinue bevacizumab or sunitinib.
Grade 1 pulmonary or brain or spinal cord hemorrhage	Withhold bevacizumab or sunitinib until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
Grade 2, 3, or 4 pulmonary or brain or spinal cord hemorrhage	Discontinue bevacizumab or sunitinib.
Venous thromboembolic event	
Grade 1 or 2	No bevacizumab or sunitinib modifications.
Grade 3 or asymptomatic Grade 4	If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab or sunitinib should be withheld until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab or sunitinib may be resumed after 2 weeks of full-dose anticoagulation if all of the following criteria are met: • The patient must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting study treatment. • The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Symptomatic Grade 4	Discontinue bevacizumab or sunitinib.
Arterial thromboembolic event (new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab or sunitinib.
Congestive heart failure (left ventricular systolic dysfunction)	
Grade 1 or 2	No bevacizumab modifications or sunitinib.
Grade 3	Withhold bevacizumab until resolution to Grade ≤ 1; discontinue sunitinib.
Grade 4	Discontinue bevacizumab or sunitinib.

Table 11 Bevacizumab and Sunitinib Dose Management for Adverse Events (cont.)

Event	Action to Be Taken
Proteinuria	
Grade 1 (urine dipstick 1+ or urine collection 0.15 to 1.0 g/24 hr)	No bevacizumab or sunitinib modifications.
Grade 2 (urine dipstick 2+ to 3+ or urine collection >1.0 to 3.5 g/24 hr)	For 2+ dipstick, may administer bevacizumab and obtain 24-hour urine prior to next dose; no sunitinib modification. For 3+ dipstick, obtain 24-hour urine prior to administration of bevacizumab; no sunitinib modification. Withhold bevacizumab for proteinuria >2 g/24 hr and resume when proteinuria is ≤2 g/24 hr; no sunitinib modification.[a]
Grade 3 (urine dipstick 4+ or urine collection >3.5 g/24 hr)	No sunitinib modification. Withhold bevacizumab. Resume when proteinuria is ≤2 g/24 hr.[a]
Grade 4 (nephrotic syndrome)	Discontinue bevacizumab or sunitinib.
GI perforation	
Any grade	Discontinue bevacizumab or sunitinib.
Fistula	
Any grade tracheoesophageal fistula	Discontinue bevacizumab.
Grade 4 fistula (other than tracheoesophageal)	Discontinue bevacizumab.
Bowel obstruction	
Grade 1	Continue patient on study for partial obstruction not requiring medical intervention.
Grade ≥2	Discontinue bevacizumab. Withhold sunitinib for partial/complete obstruction requiring medical intervention. Patient may restart upon complete resolution.
Wound dehiscence	
Any grade (requiring medical or surgical therapy)	Discontinue bevacizumab or sunitinib.
Reversible posterior leukoencephalopathy	
Any grade (confirmed by MRI)	Discontinue bevacizumab or sunitinib.

Table 11 Bevacizumab and Sunitinib Dose Management for Adverse Events (cont.)

Event	Action to Be Taken
Fatigue/asthenia	
Grade 1 or 2	No bevacizumab or sunitinib modification
Grade 3	No bevacizumab modification; withhold sunitinib until resolves to Grade ≤ 2. Discontinue sunitinib if fatigue does not resolve within 42 days or if Grade 3 fatigue/asthenia reoccurs upon resumption
Grade 4	No bevacizumab modification; discontinue sunitinib
Hand-foot syndrome	
Grade 1 or 2	No bevacizumab modification; no sunitinib modification.
Grade 3	No bevacizumab modification; withhold sunitinib dose until resolves to Grade ≤ 2. If it resolves to Grade ≤ 1 between 7 and 42 days, resume at -1 dose level (if possible). Discontinue sunitinib if Grade 3 hand-foot syndrome does not resolve within 42 days or if recurs following resumption of sunitinib.
Stomatitis	
Grade 1 or 2	No bevacizumab modification; no sunitinib modification.
Grade 3	No bevacizumab modification; withhold sunitinib until resolves to Grade ≤ 2. If resolves in ≤ 7 days, resume sunitinib at current dose. If resolves between 7 and 42 days, resume sunitinib at -1 dose level (if possible). Discontinue sunitinib if Grade 3 stomatitis recurs following resumption of sunitinib or if does not resolve within 42 days.
Grade 4	No bevacizumab modification; discontinue sunitinib.
Hematologic toxicities (excluding anemia)	
Grade 1 or 2	No bevacizumab modification; no sunitinib modification.
Grade 3 or 4	No bevacizumab modification; withhold sunitinib until recovered to Grade ≤ 2, then resume at –1 dose level (if possible).

GI = gastrointestinal; LMWH = low molecular-weight heparin; MRI = magnetic resonance imaging.

[a] All proteinuria values are from 24-hour urine collection.

5.1.8 Sunitinib- and Bevacizumab-Related Cardiac Toxicities

Potential cardiac risks of sunitinib include risk of ejection fraction decline, which may lead to congestive heart failure and QTc interval prolongation, which may lead to ventricular arrhythmias, including Torsades de pointes. Torsade de pointes has been observed in $<0.1\%$ of sunitinib-exposed patients. These risks are described in the sunitinib label.

Patients should be carefully monitored for clinical signs and symptom of CHF while receiving sunitinib or bevacizumab, especially in patients with cardiac risk factors and/or history of coronary artery disease. Physicians are advised to weigh this risk against the potential benefits. Baseline and periodic evaluations of LVEF should also be considered while these patients are receiving sunitinib. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.

If congestive heart failure symptoms appear, sunitinib and bevacizumab should be withheld. Sunitinib dose should be interrupted or reduced in patients without clinical evidence of congestive heart failure but with ejection fraction $<$50% but $>$20% below baseline.

QT interval prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de pointes. Torsade de pointes has been observed in $<$0.1% of sunitinib-exposed patients. Sunitinib should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antiarrhythmics, or medicinal products that can prolong QT interval, or patients with relevant preexisting cardiac disease, bradycardia, or electrolyte disturbances. Concomitant administration of sunitinib with potent CYP3A4 inhibitors should be limited because of the possible increase in sunitinib plasma concentrations.

Patients who develop QTc interval prolongation $>$500 ms should undergo continuous cardiac monitoring to evaluate their QTc and this monitoring should continue until normalization of the QTc $<$460 ms and clearance by a cardiologist or equivalent physician.

In countries where additional cardiac monitoring is considered standard (e.g., France), additional cardiac monitoring will be required:

- A baseline evaluation of LVEF in those patients with cardiac risk factors and/or an abnormal baseline ECG
- ECG on Day 22 of Cycle 1 for patients randomized to the sunitinib arm

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; performing protocol-specified vital signs; and 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 5.3.5.9
- 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 drug
- 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)

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 (see 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 drug
- 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 (rated as mild, moderate, or severe, or according to NCI CTCAE

criteria; 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 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 for reporting instructions). Adverse events of special interest for this study include the following:

- The following confirmed treatment-emergent autoimmune conditions:

  Pneumonitis

  Hypoxia or dyspnea Grade ≥ 3

  Colitis

  Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, or hypothyroidism

  Vasculitis

  Hepatitis

  Transaminitis: Grade ≥ 2 (AST or ALT $> 3 \times$ ULN and bilirubin $> 2 \times$ ULN) OR AST/ALT $> 10 \times$ ULN

  Systemic lupus erythematosus

  Neurologic: Guillain-Barré syndrome, myasthenia gravis, meningoencephalitis

  Nephritis

- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response system (SIRS), systemic immune activation, or infusion reaction syndromes
- 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 5.3.5.6.
- Suspected transmission of an infectious agent by the study drug, defined as the following:

  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 test findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2.4 Selected Adverse Events

Additional data will be collected for the following selected adverse events:

- Immune-mediated adverse events, including conditions (regardless of grade) suggestive of an autoimmune disorder, such as Grade ≥3 rash or pruritus, Grade ≥3 diarrhea or Grade ≥2 colitis
- Cases of potential drug-induced liver injury that include Grade ≥ 3 asymptomatic AST/ALT/total bilirubin elevations, or Grade ≥ 2 AST/ALT/total bilirubin elevations with constitutional symptoms (Hy's law, see Section 5.3.5.6)

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 drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies).

After initiation of study drug, serious adverse events and adverse events of special interest will be reported during the trial until the end of the special reporting period (defined as 90 days after the last dose of atezolizumab or bevacizumab or 30 days after the last dose of sunitinib). All other adverse events will be reported until 30 days after the last dose of atezolizumab, bevacizumab, or sunitinib or until the initiation of another anti-cancer therapy, whichever occurs first. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see 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 Adverse Events

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

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity. Table 12 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 12 Adverse Event Severity Grading Scale

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 one's self, 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 the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 13):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug 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

Table 13 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug based on facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	Adverse events will be considered related, unless they fulfill the criteria as specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after Cycle 1, Day 1).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

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 Diagnosis versus Signs and Symptoms

For adverse events, 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.

5.3.5.2 Infusion-Related Reactions

An exception to the above is symptoms that occur during or within 24 hours after an atezolizumab infusion. These may be part of an acute infusion reaction and should not be recorded under the diagnosis of "infusion-related reaction." Rather, these symptoms should be recorded as separate adverse events on the AE eCRF. Serious symptoms should be reported as one serious adverse event on the AE eCRF with the most medically significant sign or symptom as the primary event term. Additional signs and symptoms should be reported in the Additional Case Details section of the AE eCRF.

5.3.5.3 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring 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. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events 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 separately 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

For oncology trials, 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 Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ 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 $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value 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 5.3.5.1) 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).

5.3.5.7 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).

5.3.5.8 Deaths

Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributable by the investigator solely to the progression of RCC should be recorded only on the Study Discontinuation eCRF. All other deaths during study treatment, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4).

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. The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. 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.

During survival follow-up, deaths attributed to progression of RCC should be recorded only on the Survival eCRF.

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," "worsening," or "exacerbation").

5.3.5.10 Worsening of Renal Cell Carcinoma

The term disease progression (i.e., worsening and/or progression of RCC) should not be recorded as an adverse event. The underlying symptoms should be captured as adverse events and assessed accordingly for seriousness, severity, and causality. Data for disease progression will be captured as efficacy assessment data only.

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST criteria. In rare cases, the determination of clinical

progression will be based on symptomatic deterioration. However, every effort should be made to document progression with use of objective criteria.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient 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.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Hospitalization to perform 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 condition

  The patient has not suffered an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization for outpatient care outside of normal clinic operating hours that is required per protocol or per local standard of care

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 drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, 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).

5.3.5.13 Adverse Events in Individuals Not Enrolled in the Study

If an adverse event inadvertently occurs in an individual not enrolled in the study (e.g., during administration of study drug), the Adverse Event Form provided to investigators should be completed and submitted to the Sponsor or its designee, either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators.

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 trial. 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 drug:

- 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 for All Sites

Medical Monitor: [redacted]
Telephone No.:
Mobile Telephone No.:

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 Monitor, 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 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 Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

The Serious Adverse Event / Adverse Event of Special Interest Reporting 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 with use of the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of atezolizumab or bevacizumab and 30 days after the last dose of sunitinib. All other adverse events will be reported until 30 days after the last dose of atezolizumab, bevacizumab, or sunitinib or until the initiation of another anti-cancer therapy, whichever occurs first. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6). 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.

In the event that the EDC system is unavailable, the Serious Adverse Event / Adverse Event of Special Interest Reporting 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 with use of 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 post-study adverse events 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 to immediately inform the investigator if they become pregnant during the study or within 6 months after the last dose of atezolizumab or bevacizumab or within 30 days after the last dose of sunitinib. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug 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 the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting 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 pregnancy), either by faxing or by scanning and emailing the form with use of 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.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of bevacizumab or within 30 days after the last dose of sunitinib. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (because 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).

5.4.3.4 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug 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 drug or trial-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. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy or fetal outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

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 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the special reporting period (defined as 90 days after the last dose of atezolizumab or bevacizumab and 30 days after the last dose of sunitinib), if the event is believed to be related to prior study drug treatment. All other adverse events will be reported until 30 days after the last dose of atezolizumab, bevacizumab, or sunitinib or until the initiation of another anti-cancer therapy, whichever occurs first.

The investigator should report these events directly to Roche or its designee, by either faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of 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 with use of the following reference documents:

- The Atezolizumab Investigator's Brochure

- The Bevacizumab Investigator's Brochure
- Local prescribing information for sunitinib

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

This is a randomized, Phase III, open-label study designed to evaluate the safety and efficacy of atezolizumab + bevacizumab as compared with sunitinib.

Analysis populations are defined as follows:

- The ITT population is defined as all randomized patients whether or not the assigned study treatment was received.
- The PD-L1–selected population is defined as patients in the ITT population whose PD-L1 status is IC1/2/3 at the time of randomization
- The measurable disease population is defined as patients in the ITT population with measurable disease at baseline.
- The DOR-evaluable population is defined as patients with objective response.
- The PRO-evaluable population is defined as patients with a non-missing baseline PRO assessment.
- The safety-evaluable population is defined as patients who received any amount of any component of the study treatments.

All analyses will be performed for patients in the PD-L1–selected population and the ITT population, unless specified otherwise.

6.1 DETERMINATION OF SAMPLE SIZE

This study will randomize approximately 900 patients, including a minimum of approximately 351 patients with a PD-L1 IHC IC score of 1/2/3.

6.1.1 Type I Error Control

The type I error (α) for this study is 0.05 (two-sided). There are two co-primary efficacy endpoints for this study: PFS by investigator assessment per RECIST v1.1 and OS. To control the overall type I error rate (Bretz et al. 2009) at $\alpha = 0.05$ (two-sided) while accounting for two co-primary endpoints, α will be split between PFS ($\alpha = 0.04$) and OS ($\alpha = 0.01$). Because type I error will be controlled accounting for two co-primary endpoints, the study will be considered a positive study if statistical significance is achieved for either of the co-primary endpoints.

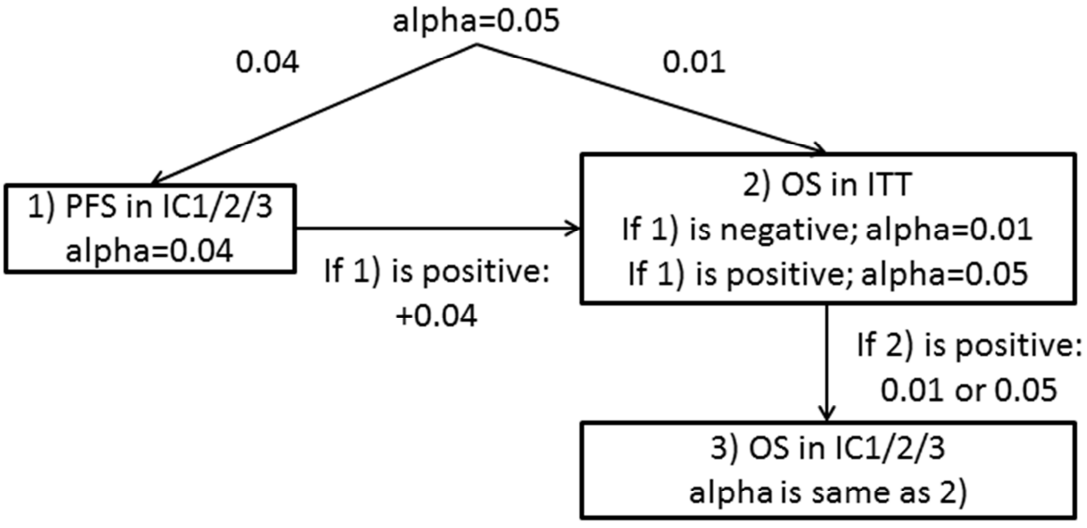
Formal treatment comparisons will be performed in a hierarchical fashion in which α may be recycled (Burman et al. 2009) as follows:

1. PFS in the PD-L1–selected population will be evaluated at $\alpha = 0.04$ (two-sided).
2. If PFS results in the PD-L1–selected population are statistically significant at $\alpha = 0.04$, then $\alpha = 0.04$ will be recycled to OS in the ITT population, and OS in the ITT population will be evaluated at $\alpha = 0.05$ (two-sided). If PFS results in the PD-L1–selected population are not statistically significant at $\alpha = 0.04$, then no recycling of α will occur, and OS in the ITT population will be evaluated at $\alpha = 0.01$ (two-sided).
3. OS will be compared between treatment arms in a hierarchical fashion as follows. If OS results in the ITT population are statistically significant at the appropriate α level, then OS in the PD-L1–selected population will be evaluated at same α-level as for OS in the ITT population. If OS results in the ITT population are not statistically significant, formal treatment comparison of OS in the PD-L1–selected population will not be performed.

Interim analyses of OS and the final analysis of OS will be based on the α allocated to the comparison of OS, as described above. Statistical significance at interim analyses of OS will be evaluated as described in Section 6.9.2.

The PFS and OS analysis hierarchy and α allocation including possible α recycling are shown in Figure 5.

Figure 5 PFS and OS Analysis Hierarchy, Alpha Allocation and Alpha Recycling



IC = tumor-infiltrating immune cell; ITT = intent to treat; PFS = progression-free survival; OS = overall survival.

6.1.2 Co-Primary Endpoint: Progression-Free Survival in the PD-L1–Selected Population

The analysis of the co-primary endpoint of PFS will take place when approximately 228 PFS events in the PD-L1–selected population (65% of the estimated 351 PD-L1–population) as defined for the primary analysis of PFS (see Section 6.4.1) have occurred based on the following assumptions:

- Two-sided, stratified log-rank test
- $\alpha = 0.04$ (two-sided)
- Approximately 88% power
- Median PFS for the sunitinib arm of 11 months and estimated median PFS in the atezolizumab + bevacizumab arm of 17 months (corresponding to HR of 0.65)
- 5% annual loss to follow-up for PFS
- No interim analysis

Accrual is projected to occur over 20 months, assuming a ramp-up period of 9 months.

On the basis of these assumptions, the required number of PFS events in the PD-L1–selected population is projected to occur at Month 34 from the time the first patient is randomized. Also on the basis of these assumptions, it is projected that an observed HR of 0.76 or lower will result in a statistically significant difference between treatment arms (i.e., an HR of 0.76 will be the minimally detectable difference for the analysis; this corresponds to an improvement of 3.5 months in median PFS from 11 months in the sunitinib arm to 14.5 months in the atezolizumab + bevacizumab arm).

6.1.3 Co-Primary Endpoint: Overall Survival in the ITT Population

The final analysis of the co-primary endpoint of OS will take place at the later of the time points when the required number of events has occurred in the PD-L1–selected population and in the ITT population, where the required number of events is as follows:

- 639 OS events in the ITT population (71% of the estimated 900 patients)
- 246 OS events in the PD-L1–selected population (70% of the estimated 351 patients)

The number of events required for the final OS analysis in these populations is based on the following assumptions:

- Two-sided, stratified log-rank test
- $\alpha = 0.01$ (two-sided)
- 1% annual loss to follow-up for OS
- For the ITT population:

  85% power

  Median OS in the control arm of 24 months

Estimated median OS in the atezolizumab + bevacizumab arm of 32 months (an increase of 8 months, corresponding to an HR of 0.75

- For the PD-L1–selected population:

  53% power

  Median OS in the control arm of 24 months

  Estimated median OS in the atezolizumab + bevacizumab arm of 33.8 months (an increase of 9.8 months, corresponding to an HR of 0.71)

On the basis of these assumptions, the required number of OS events for the final analysis of OS in both the PD-L1–selected population and the ITT population is projected to occur at Month 63 from the time the first patient is randomized.

At the final OS analysis, on the basis of these assumptions, it is projected that an observed OS HR of 0.83 or lower in the ITT population will result in a statistically significant difference between treatment arms (i.e., the minimally detectable difference at the analysis; this corresponds to an improvement of 4.9 months in median OS, from 24 months in the control arm to 28.9 months in the atezolizumab + bevacizumab arm).

Also at the final OS analysis, on the basis of these assumptions, it is projected that an observed OS HR of 0.72 or lower in the PD-L1–selected population will result in a statistically significant difference between treatment arms (i.e., an HR of 0.72 will be the minimally detectable difference at the analysis; this corresponds to an improvement of 9.5 months in median OS, from 24 months in the control arm to 33.5 months in the atezolizumab + bevacizumab arm).

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol deviations including major deviations of inclusion/exclusion criteria, and reasons for discontinuation from the study will be summarized by treatment arm for the PD-L1–selected population and the ITT population. Study treatment administration and reasons for discontinuation from the study treatment will be summarized by treatment arm for all treated patients and for treated patients in the PD-L1–selected population.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables such as age, sex, race/ethnicity, stratification factors (liver metastases, MSKCC [Motzer] score, PD-L1 status), and baseline characteristics (e.g., weight, primary tumor characteristics [Fuhrman grade, histology {clear cell; sarcomatoid}, etc.], time since initial diagnosis, time since metastatic diagnosis, site[s] of metastatic disease, number of metastatic site[s], and KPS) will be summarized by treatment arm for the ITT population and for the PD-L1–selected population. Continuous variables will be summarized using means, standard deviations, medians, and ranges. Categorical variables will be summarized by proportions.

The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

6.4 EFFICACY ANALYSES

The efficacy analyses will include patients with an IHC score of IC1/2/3 (PD-L1–selected population) and all randomized patients grouped according to the treatment assigned at randomization on the basis of the ITT principle.

6.4.1 Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints are investigator-assessed PFS per RECIST v1.1 and OS. Because type I error will be controlled accounting for two co-primary endpoints, the study will be considered a positive study if statistical significance is achieved for either of the co-primary endpoints.

PFS will be analyzed in the PD-L1–selected population and OS will be analyzed first in the ITT population; additional analyses of OS will be performed in a hierarchical fashion (see Section 6.1.1).

PFS is defined as the time from randomization to disease progression, as determined by the investigator per RECIST v1.1 (see Appendix 3), or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. Data for patients with no post-baseline tumor assessments will be censored at the randomization date + 1 day.

For United States registrational purposes, the co-primary efficacy endpoint of PFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits.

OS is defined as the time from randomization to death due to any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization + 1 day.

The following analyses will be performed for both PFS endpoints described above and OS. PFS and OS will be compared between treatment arms with use of the stratified log-rank test. The HR will be estimated using a stratified Cox proportional hazards model. The 95% CI for the HR will be provided. The stratification factors will be the same as the randomization stratification factors: presence of liver metastasis (yes/no); tumor PD-L1 status (IC0 vs. IC1/2/3); and the MSKCC (Motzer) score (0, 1–2, ≥3). The stratification factors will be obtained from the IxRS at the time of randomization. Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate the median PFS and OS for each treatment arm, and Kaplan-Meier

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

The following analyses will be performed for both PFS endpoints described above and (as applicable) for OS:

- Analyses described in Section 6.8.1 (Analyses at Landmark Time Points)
- Analyses described in Section 6.8.2 (Subgroup Analyses)
- Secondary endpoint of PFS by IRC assessment, PD-L1–selected population and ITT population, based on RECIST v1.1
- Secondary endpoint of PFS by investigator assessment in the ITT population, based on RECIST v1.1

6.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

The following secondary efficacy endpoints will be analyzed in the PD-L1–selected population and the ITT population:

- OS (PD-L1–selected population)
- PFS by IRC assessment (RECIST v1.1)
- ORR by investigator assessment (ORR-evaluable population, RECIST v1.1 [see Appendix 3])
- DOR by investigator assessment (DOR-evaluable population, RECIST v1.1)
- ORR by IRC assessment (ORR-evaluable population, RECIST v1.1)
- DOR by IRC assessment (DOR-evaluable population, RECIST v1.1)
- PFS by investigator assessment (modified RECIST [see Appendix 4])
- ORR by investigator assessment (ORR-evaluable population, modified RECIST)
- DOR by investigator assessment (DOR-evaluable population, modified RECIST)
- PFS by investigator assessment (ITT population, RECIST v1.1)
- PFS by investigator (patients with sarcomatoid histology, RECIST v1.1)
- OS (patients with sarcomatoid histology)
- Change from baseline in symptom interference from the MDASI Part II (PRO-evaluable population)

6.4.2.1 Progression-Free Survival

Progression-Free Survival by Modified RECIST

PFS by modified RECIST is defined as the time from randomization to disease progression as determined by the investigator per modified RECIST (see Appendix 4) or death from any cause, whichever occurs first. A patient is considered to have disease progression by modified RECIST if either of the following conditions were met:

- Modified RECIST criteria for progression were met at a tumor assessment and no subsequent tumor assessment was performed.
- Modified RECIST criteria for progression were met at a tumor assessment and at the subsequent tumor assessment the criteria for confirmed progression by modified RECIST were also met.

For patients who meet criterion (a), the date of progression is the date of the tumor assessment that met the criteria for modified RECIST. For patients who meet criterion (b), the date of progression is the date of the tumor assessment at which the modified RECIST criteria for progression were first met.

Patients who do not meet either of the above criteria are not considered to have had disease progression by modified RECIST. For example, a patient who had a tumor assessment for which the criteria for progression by modified RECIST criteria were met, but at the subsequent tumor assessment the criteria for confirmed progression by modified RECIST were not met, would not be considered to have had progression by modified RECIST on the basis of those two tumor assessments. The determination of whether such a patient subsequently met the criteria for progression by modified RECIST would be based only on additional subsequent tumor assessments performed after the two tumor assessments described in this example.

Data for patients who have not experienced disease progression by modified RECIST or death will be censored at the last tumor assessment date. Data for patients with no post-baseline tumor assessments will be censored at the randomization date + 1 day.

Analysis of Progression-Free Survival as Secondary Endpoints

Methods for comparison of PFS between treatment arms for the secondary endpoints of PFS will be the same as the methods for treatment comparisons for the co-primary efficacy endpoint of PFS.

6.4.2.2 Objective Response Rate

An objective response is defined as either a CR or PR (confirmation not required) based on RECIST v1.1. Patients not meeting this criterion, including patients without any post-baseline tumor assessments, will be considered non-responders.

ORR is defined as the proportion of patients who had an objective response among patients with measurable disease at baseline. Confirmed response rate will also be

evaluated, defined as patients with CR or PR at two consecutive tumor assessments at least 28 days apart.

ORR will be compared between treatment arms with use of the stratified Cochran-Mantel-Haenszel test. The stratification factors will be the same as those described in the analysis of the primary endpoint of PFS. An estimate of ORR will be calculated for each treatment arm, and its 95% CI will be calculated using the Clopper-Pearson method. The difference in ORR between treatment arms will be calculated, and its 95% CI will be calculated using the normal approximation to the binomial distribution.

6.4.2.3 Duration of Response

Duration of response is defined for patients who had an objective response as the time from the first occurrence of response (CR or PR) to disease progression or death, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of CR or PR, data for DOR will be censored at the date of the first occurrence of CR or PR + 1 day.

DOR is based on a non-randomized subset of patients (those who achieved an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes only. Methods for comparison of DOR between treatment arms will be the same as the methods for treatment comparison for the co-primary efficacy endpoint of PFS.

6.4.2.4 Change from Baseline in Symptoms Interference

See Section 6.7 for a description of this endpoint and analysis methods to be used.

6.4.3 Handling of Missing Data

For PFS, patients without a date of disease progression will be analyzed as censored observations on the date of last tumor assessment. If no post-baseline tumor assessment is available, PFS will be censored at the date of randomization + 1 day. In the analysis of PFS for United States registrational purposes, data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits (see Section 6.4.1).

For objective response, patients without any post-baseline assessment will be considered non-responders.

For OS, patients who are not reported as having died will be analyzed as censored observations on the date they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization + 1 day.

For PRO measures (MDASI and BFI), subscales with less than 50% of the items completed will be considered missing.

6.5 SAFETY ANALYSES

Safety analyses will be performed for the safety-evaluable population; selected safety analyses will be performed for safety-evaluable patients in the PD-L1–selected population. Patients will be grouped according to the treatment actually received. Exposure to study treatment will be summarized by treatment arm.

Safety will be evaluated through summaries of adverse events, changes in laboratory test results, changes in vital signs, and immunogenicity as measured by ATA, and will be presented by treatment arm.

Verbatim descriptions of adverse events will be mapped to MedDRA terms. Treatment-emergent events (defined as events occurring on or after the first dose of atezolizumab or bevacizumab or sunitinib) will be summarized by MedDRA term, appropriate MedDRA levels, and NCI CTCAE v4.0 grade. For each patient, the maximum severity reported will be used in the summaries. Adverse events will be summarized regardless of relationship to study drug as assessed by the investigator. All adverse events, adverse events leading to withdrawal of study drug, adverse events leading to dose reduction or interruption, Grade ≥ 3 adverse events, serious adverse events, and adverse events of special interest will be summarized. Deaths and cause of death will be summarized.

Changes in NCI CTCAE grade for laboratory tests will be tabulated by treatment arm. Changes in selected vital signs will be summarized. ATA results will be summarized and listed by patient and cycle.

6.6 PHARMACOKINETIC ANALYSES

Atezolizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized for each cycle at which pharmacokinetics are to be measured (C_{max} will be reported for Day 1 of Cycle 1 only; C_{min} will be evaluated at Day 1 of Cycles 1, 2, 4, 8 and every eight cycles thereafter; Day 22 of Cycles 1, 2, and 4; and at study termination).

Bevacizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized for each cycle at which pharmacokinetics are to be measured (C_{max} will be reported for Day 1 of Cycles 1 and 2; C_{min} will be evaluated at Day 1 of Cycles 1, 2, and study termination).

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

Additional PK and pharmacodynamic analyses will be conducted as appropriate.

6.7 PATIENT-REPORTED OUTCOME ANALYSES

6.7.1 MDASI, and BFI, and FKSI-19

Scoring for the MDASI and BFI questionnaires will be based on their corresponding user manuals (Cleeland 2009). For MDASI and BFI scales with more than 50% of the constituent items completed, a prorated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered missing.

The impact of symptoms on patients' functioning will be compared between treatment arms as a change from baseline on the interference items in the MDASI Part II.

The severity of symptoms captured in the MDASI and the BFI will be summarized using descriptive analyses including summary statistics and change from baseline at each assessment by treatment arm.

6.7.2 Health Economic Data

Health economic data, as assessed by the EQ-5D, will be evaluated for patients with a baseline assessment and at least one post-baseline EQ-5D assessment that generated a score. Scores at baseline and change from baseline scores for each timepoint will be quantified using descriptive statistics.

The results from the health economic data analysis will be reported separately from the Clinical Study Report.

6.8 EXPLORATORY ANALYSES

6.8.1 Analyses at Landmark Time Points

The PFS and OS rates at various timepoints (i.e., every 6 months after randomization) will be estimated by the Kaplan-Meier methodology for each treatment arm and the 95% CI will be calculated using Greenwood's formula.

6.8.2 Subgroup Analyses

To assess the consistency of study results in subgroups defined by demographic and baseline characteristics, PFS, ORR, and OS in these subgroups will be examined. Summaries of PFS and OS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of the median, will be produced separately for each level of the categorical variables. ORR will be summarized for each level of the categorical variables.

PFS and ORR will be summarized in patients with tumor Fuhrman Grade 4 or sarcomatoid histology (defined by investigator-assessed conventional histopathology)

6.8.3 Biomarker Analyses

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

6.9 INTERIM ANALYSES

6.9.1 Progression-Free Survival

There are no planned interim analyses of the co-primary endpoint of PFS.

6.9.2 Overall Survival

A total of four analyses of OS will be performed, including three interim analyses and one final analysis. The α level for OS testing is 0.05 given that the co-primary endpoint of PFS was met in the study (see Section 6.1.1). The boundary for statistical significance at each interim analysis and the final analysis will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming function (Lan and DeMets 1983) to maintain the overall type 1 error rate (Hung et al. 2007; Glimm et al. 2009) at 0.05 level. The O'Brien-Fleming (OBF) boundary for statistical significance is provided in Table 14. The OS endpoint will be considered positive in the ITT population if statistical significance is achieved for any of the three OS interim analyses or the final analysis.

Table 14 *Interim and Final OS Analyses for the ITT Population*

OS Analyses	
First interim OS (performed at time of PFS analysis) [a]	
No. of events (%) [b]	*264 (29%)*
% of final events	*41%*
Cutoff date	*Study Month 29* [c]
OBF boundary for p-value	*$p \leq 0.0009$*
Second interim OS (Time driven)	
Projected No. of events (%) [b]	*377 (41%)*
Projected % of final events	*59%*
Cutoff date	*Study Month 40* [c]
Projected OBF boundary for p-value [d]	*$p \leq 0.0067$*
Third interim OS (Event driven)	
No. of events (%) [b]	*518 (57%)*
% of final events	*81%*
Projected cutoff date	*Study Month 57* [c]
Projected OBF boundary for p-value [d]	*$p \leq 0.0233$*
Final OS (Event driven)	
No. of events (%) [b]	*639 (70%)*
% of final events	*100%*
Projected cutoff date	*Study Month 79* [c]
Projected OBF boundary for p-value [d]	*$p \leq 0.0420$*

ITT = intent-to-treat; OBF = O'Brien-Fleming; OS = overall survival; PFS = progression-free survival.

Note: The α level for OS testing is 0.05, given that the co-primary endpoint of PFS was met (see Section 6.1.1).

[a] *The first interim analysis of OS was performed at the time of the PFS primary analysis at Study Month 29, with a cut-off date of 29 September 2017, which was 5 months earlier than the initial projection of Month 34 described in Section 6.1.2 The OBF boundary for p-value is calculated based on 264 OS events observed by the cutoff date.*

[b] *The event rate is based on the actually observed ITT population with N = 915.*

[c] *Study month at which required number of events are projected to occur, where Study Month 1 is the month the first patient is enrolled.*

[d] *The projected OBF boundary for statistical significance is calculated according to the number of events shown. The actual OBF boundary will be calculated at time of analysis based on actual number of events observed.*

The first interim analysis of OS was performed at the time of the PFS primary analysis. A total of 264 deaths (29% of 915 patients in the ITT population) was observed at the first interim analysis of OS, which corresponds to 41% of the events information

required for the final analysis of OS in the ITT population. The first OS interim analysis did not pass the OBF boundary at 0.0009.

The second interim analysis of OS will be time driven and will occur approximately 11 months from the clinical cutoff of the first OS interim. [redacted] *It is projected that at the second interim OS analysis, 377 deaths (41% of 915 patients in the ITT population) will occur, corresponding to approximately 59% of the events required for the final analysis of OS in the ITT population. Statistical significance will be declared if $p \leq 0.0067$ when 377 deaths have occurred at the time of the second OS interim analysis.*

The third interim analysis of OS is event driven and remains the same as the original plan (Protocol WO29637, Version 6). The third interim analysis of OS will be performed when approximately 518 deaths (57% of 915 patients in the ITT population) have occurred, which corresponds to approximately 81% of the events information required for the final analysis of OS in the ITT population. Statistical significance will be declared if $p \leq 0.0233$ when 518 deaths have occurred at the time of the third OS interim analysis.

The final analysis of OS is event driven and remains the same as the original plan (Protocol WO29637, Version 6). The final analysis of OS will be performed when 639 deaths (70% of 915 patients in the ITT population) have occurred. Statistical significance will be declared if $p \leq 0.0420$ when 639 deaths have occurred at the time of the final OS analysis.

The interim and final analyses of OS, including analyses in both the ITT and PD-L1–selected populations, will follow the testing hierarchy described in Section 6.1.1. Specifically, for each OS interim and final analysis, OS in the PD-L1–selected population will be evaluated for statistical significance only when the OS results in the ITT population are statistically significant at the OBF boundary. The actual OBF boundary will be calculated at time of analysis based on actual number of events observed. If OS results in the ITT population are not statistically significant, formal testing of OS in the PD-L1–selected population will not be performed.

All efficacy analyses, including the interim analyses of OS, will be performed by the Sponsor.

6.9.3 Optional Interim Analysis

In addition to the planned interim analyses of OS, one additional interim analysis of OS may be performed at the discretion of the Sponsor. The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the Statistical Analysis Plan (SAP), and the SAP will be submitted to relevant health authorities prior to the conduct of the interim analysis.

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 with 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 will be sent directly to the Sponsor. The Sponsor's standard procedures will be used 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.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using 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, PRO, 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 trial.

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 trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational 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 patient-reported outcome data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 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.

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 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 FDA 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).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form 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.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. 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 allow any remaining specimens to be used for exploratory research. 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 of 1996 (HIPAA). 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 only be disclosed to third parties 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.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other 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 completion of 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.

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 trial will be sponsored F. Hoffman-La Roche. Approximately 150–180 sites worldwide will participate to enroll approximately 830 patients.

An iDMC will be in place throughout the study and will provide oversight of safety (see Section 3.1.1).

After written informed consent has been obtained, the study site will obtain the patient's screening number from the IxRS. After eligibility has been established, the patient will

be enrolled and the study site will obtain the patient's identification number from the IxRS.

The patient will be randomized by the IxRS. The IxRS will manage the inventory of atezolizumab, bevacizumab, and sunitinib (in countries where sunitinib is considered an IMP) at all sites. The IxRS will be required to randomize patients, to monitor enrollment and patient status, and to manage atezolizumab, bevacizumab, and sunitinib (where applicable) requests and shipments.

Patient data will be recorded via an EDC system with use of eCRFs.

Central laboratories, including Roche and Roche's collaborators, will be used for PD-L1 expression status determination and will provide kits for PK, pharmacogenomic, tissue, whole blood, serum, and plasma sample analyses to be conducted at central laboratories or Roche. PD-L1 evaluation will be conducted prior to randomization, and the results will be used for stratification.

Treatment decisions will be made on the basis of the local reading of ECGs obtained during the study.

Sites will provide imaging used for tumor assessment to the IRC to enable centralized, independent review of response and progression endpoints. IRC membership and procedures will be detailed in an IRC Charter.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials 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 trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials 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 trials 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

Assessment Window (Days) [a]	Screening [b] Days −28 to −1	Atezolizumab + Bevacizumab OR Sunitinib			End of Treatment ≤30 Days after Last Dose of Study Treatment [d]	Survival Follow-Up
		Cycle ≥1 Day 1	Cycle ≥1 Day 22 [c]	Day 1, Every Two Cycles		
Signed Informed Consent Form(s) [b]	x					
Review of eligibility criteria	x					
Medical, surgical, and cancer histories, including demographic information [e]	x					x Cancer treatment
HBV and HCV serology	x					
HIV testing [f]	x					
Concomitant medications [g]	x	x	x		x	
Tumor assessment [h]	x	At 12 weeks ±5 business days, then every 6 weeks ±5 business days thereafter, including Week 78 following randomization. After 78 weeks from randomization, patients will undergo tumor assessments every 12 weeks ±5 business days until treatment discontinuation.				
Complete physical examination [i]	x				x	
Limited physical examination [j]		x [j, k]				
Karnofsky performance status	x	x [k]			x	

Appendix 1
Schedule of Assessments (cont.)

Assessment Window (Days) [a]	Screening [b] Days −28 to −1	Atezolizumab + Bevacizumab OR Sunitinib			End of Treatment ≤30 Days after Last Dose of Study Treatment [d]	Survival Follow-Up
		Cycle ≥1 Day 1	Cycle ≥1 Day 22 [c]	Day 1, Every Two Cycles		
Vital signs [l]	x	x	x		x	
12-lead electrocardiogram and/or LVEF evaluation [m]	x		x		x	
Weight	x	x [n]			x	
Height	x					
Hematology [o]	x	x [k]	x		x	
Serum chemistry [p]	x	x [k]	x		x	
Coagulation panel (aPTT, INR)	x				x	
Urine dipstick (+24-hr urine if dipstick protein ≥2+) [q]	x	x			x	
Serum pregnancy test [r]	x [r]			x [r]		
TSH, free T3, free T4 [s]	x			x [s]	x	
Ferritin [s]	x			x	x	
C-reactive protein and auto-antibody testing [t]	x			x [u]	x	
Serum sample for ATA assessment [v]		x [v]			x	

Appendix 1
Schedule of Assessments (cont.)

Assessment Window (Days) [a]	Screening [b] Days −28 to −1	Atezolizumab + Bevacizumab OR Sunitinib			End of Treatment ≤30 Days after Last Dose of Study Treatment [d]	Survival Follow-Up
		Cycle ≥1 Day 1	Cycle ≥1 Day 22 [c]	Day 1, Every Two Cycles		
Atezolizumab PK serum sample [w]		x	x		x	
Bevacizumab PK serum sample [w]		x				
TBNK blood sample [x]		x				
Plasma, serum, and whole blood for biomarkers [y]		x	x		x	
DNA for RCR (optional) [z]		x				
Adverse events		x	x		x	x [d]
Atezolizumab infusion [aa]		x [z]	x			
Bevacizumab infusion [aa]		x [z]	x			
Sunitinib dispensing [c]		x [c]				
Tumor tissue specimen or at least 15 unstained slides [bb]	x					
Tumor tissue at progression [cc]						
MDASI [dd]		x	x		x	x

Appendix 1
Schedule of Assessments (cont.)

Assessment Window (Days) [a]	Screening [b] Days −28 to −1	Atezolizumab + Bevacizumab OR Sunitinib			End of Treatment ≤30 Days after Last Dose of Study Treatment [d]	Survival Follow-Up
		Cycle ≥1 Day 1	Cycle ≥1 Day 22 [c]	Day 1, Every Two Cycles		
BFI [dd]		x	x		x	x
EQ-5D [dd]		x	x		x	x
FKSI-19 [dd]		x	x		x	x
Anti-neoplastic agent use [ee]						x

ATA = anti–therapeutic antibody; BFI = Brief Fatigue Inventory; C = cycle; CA = cancer antigen; CMV = cytomegalovirus; CRP = C-reactive protein; CT = computed tomography; ePRO = electronic patient-reported outcome; EQ-5D = EuroQoL 5 Dimensions; FKSI-19 = Functional Assessment of Cancer Therapy Kidney Symptom Index-19; irRC = immune-related response criteria; MDASI = M.D. Anderson Symptom Inventory; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic; PSA = prostate-specific antigen; RCR = Roche Clinical Repository; RECIST = Response Evaluation Criteria in Solid Tumors; TBNK = T, B, and natural killer; TSH = thyroid-stimulating hormone.

Note: Assessments scheduled on the days of study treatment should be performed before the infusion or dosing unless otherwise noted. Each cycle is 42 days in length.

[a] The first dosing date (Cycle 1, Day 1) should occur within 5 business days from randomization. All visits and infusions may be administered with a window of ±3 days.

[b] Written informed consent is required for performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to randomization may be used for screening assessments, rather than repeating such tests. Screening local laboratory assessments obtained ≤96 hours prior to Cycle 1, Day 1 do not have to be repeated for Cycle 1. Test results should be reviewed prior to administration of study treatment. If re-screening is required, then then HBV, HCV, HIV, CRP, and autoantibody testing from initial screening may be acceptable for screening assessment if <60 days from Cycle 1, Day 1.

[c] Sunitinib is taken by mouth once a day on Days 1–28 of each cycle. For patients taking sunitinib, the Day 22 visits are required for the first year of the study only.

[d] Patients will be asked to return to the clinic ≤30 days after the last dose of study treatment for an end of treatment visit. After the last administration of study treatment, serious adverse events (see [Section 5.2.2] and adverse events of special interest [see Section 5.2.3], regardless of attribution, will be recorded until the end of the special reporting period (defined as 90 days after the last dose of

atezolizumab or bevacizumab or 30 days after the last dose of sunitinib). After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6). All other adverse events will be recorded until 30 days after the last dose of atezolizumab, bevacizumab or sunitinib, or until initiation of another anti-cancer therapy, whichever occurs first. Patients will be contacted at 30 days after the last dose of study treatment to determine if any new adverse events have occurred. Ongoing adverse events thought to be related to study treatment will be followed until resolution of the adverse event, until an alternate cause has been identified, the patient is lost to follow up, the patient withdraws consent, or it is determined that the study treatment or participation is not the cause of the adverse event. Scans performed within 6 weeks prior to the end of treatment visit do not need to be repeated. The Sponsor should be notified if the investigator feels any serious adverse event occurring after the end of the adverse event reporting period is related to prior study drug treatment.

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

[f] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical trial.

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

[h] All measurable and evaluable lesions should be assessed and documented using physical examination and image-based evaluation. Screening assessments should include CT scans with oral and intravenous contrast of the chest, abdomen, and pelvis, and a brain scan (CT or MRI). Bone scans and CT scan of neck should also be performed if clinically indicated. CT or MRI scans must be used to measure lesions selected for response assessment. Disease status will be assessed using RECIST v1.1 and modified RECIST criteria (see Appendix 3 and Appendix 4). The same radiographic procedure used to define measurable lesions at baseline must be used throughout the study for each patient. Results must be reviewed by the investigator before dosing at the next cycle. Tumor assessments will occur at baseline, at 12 weeks ±5 business days, then every 6 weeks ±5 business days thereafter including Week 78 following randomization. After 78 weeks from randomization, patients will undergo tumor assessments every 12 weeks ±5 business days until treatment discontinuation, or as clinically indicated. Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments as if they were on the protocol schedule until the patient dies, experiences disease progression per RECIST v1.1 and modified RECIST, withdraws consent, or until the study closes, whichever occurs first. For patients who will be permitted to continue study treatment beyond radiographic disease progression per RECIST v1.1, tumor assessment will be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 6 weeks. If the scan frequency is every 12 weeks (see above), the follow-up scan must be performed at every 12 weeks (± 5 business days), or earlier if clinically indicated, until loss of clinical benefit described in Section 4.6.2 or treatment discontinuation, whichever is later.

[i] A complete physical examination at screening and the end of treatment visit should include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Changes in

abnormalities noted at baseline should be recorded at the end of treatment visit. New or worsened abnormalities should be recorded as adverse events if appropriate.

[j] A limited physical examination will be performed at other visits to assess changes from baseline abnormalities and any new abnormalities and to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as adverse events if appropriate.

[k] Karnofsky performance status, limited physical examination may be obtained ≤96 hours prior to Day 1 of each cycle. Local laboratory safety assessments may be obtained ≤96 hours prior to Day 1 and 22 of each cycle.

[l] Vital signs include heart rate, respiratory rate, blood pressures, and temperature. For the first atezolizumab infusion, the patient's vital signs should be determined within 60 minutes before, during (every 15 [±5] minutes), and 30 (±10) minutes and 2 hours (±15 minutes) after the infusion. For subsequent atezolizumab infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated, and 1 hour (±10 minutes) after the infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. For patients randomized to Arm A, observation should be for at least 2 hours after the first administration of the combination and for at least 1 hour for subsequent infusions.

[m] Twelve-lead ECGs are required as part of the screening assessment and at the end of treatment visit. ECGs will be reviewed by the investigator to determine patient eligibility at screening. Baseline evaluation of LVEF should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease. In countries where additional cardiac monitoring is considered standard (e.g., France), additional cardiac monitoring including a 1) baseline evaluation of LVEF in those patients with cardiac risk factors and/or an abnormal baseline ECG and 2) for patients randomized to the sunitinib arm, a surveillance ECG on Day 22 of Cycle 1 will be required.

[n] The dose of bevacizumab will be based on the patient's weight (in kilograms) measured ≤14 days prior to baseline (Cycle 1, Day 1) and will remain the same throughout the study unless there is a weight change of >10% from baseline.

[o] 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.

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

[q] Urine dipstick includes specific gravity, pH, glucose, protein, ketones, and blood. Urine dipstick and 24-hour urine collection may be performed up to 7 days before Cycle 1, Day 1. Screening urine tests performed up to 7 days before Cycle 1, Day 1 do not need to be repeated for Cycle 1. Spot urine protein/creatinine ratio will not be used for this study.

[r] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to Cycle 1, Day 1, every two cycles during the study treatment, and as clinically indicated thereafter. In countries (e.g., United Kingdom) where urine pregnancy testing is considered a standard, urine pregnancy testing may

substitute for serum pregnancy testing.

[s] TSH, free T3, free T4, and serum ferritin, should be evaluated every two cycles (starting at Cycle 2).

[t] Includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody. If rescreening is required, auto-antibody testing may be performed within 60 days of Cycle 1, Day 1.

[u] C-reactive protein and autoantibodies On Day 1 of Cycle 3 and every other cycle thereafter.

[v] See Appendix 2 for details of the ATA sampling schedule.

[w] See Appendix 2 for details of the PK sampling schedule.

[x] See Appendix 2 for details of the TBNK collection schedule.

[y] See Appendix 2 for details of the pharmacodynamic sampling schedule.

[z] This is an optional sample and requires the patient to sign an RCR consent. If sample is not taken during the Cycle 1, Day 1 visit, then the sample may be obtained at any other visit.

[aa] The initial dose of atezolizumab will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. The initial dose of bevacizumab will be delivered over 90 (±15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (±10) minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. For patients randomized to Arm A, atezolizumab will be administered first followed by bevacizumab, with a minimum of 5 minutes between dosing. In the absence of unacceptable toxicity, patients may continue study treatment until there is evidence of disease progression or lack of clinical benefit.

[bb] Tumor tissue (archival <24 months or fresh) specimen may be obtained from prior tumor excision or biopsy performed during the course of the patient's illness.

[cc] Tumor specimens are required at the time of disease progression per RECIST v1.1 (for patients in both treatment arms), preferably of a progression metastatic lesion, unless the location of the tumor renders the biopsy clinically unsafe or infeasible, or is prohibited by institution or country. Optional tumor biopsies may be obtained at other timepoints at the investigator's discretion.

[dd] The ePRO questionnaires (MDASI, BFI, FSKI-19, and EQ-5D) will be completed by the patients on Days 1 and 22 of each cycle and at the end-of-treatment visit, and will be completed by patients at 6, 12, 24, and 36 weeks after the end-of-treatment visit. In addition, the BFI ePRO questionnaire will be collected weekly during the first 12 weeks. Assessments on days when the patient does not come to the clinic (e.g., Days 8, 15, 29, 36) will be completed by the patient at home. All ePRO questionnaires while on study treatments are required to be administered prior to administration of study treatment and/or prior to any other study assessment(s) to ensure that the validity of the instrument is not compromised and to ensure that data quality meets regulatory requirements.

[ee] During survival follow-up, the following information regarding all subsequent anti-neoplastic agents upon treatment discontinuation will be collected: line of therapy, date of first dose of agent, date of last dose of agent (or if ongoing), patient's best response, and date of disease progression.

Appendix 2
Anti-Therapeutic Antibody, TBNK, Biomarker, and Pharmacokinetic Sampling Schedule

Study Visit	Time	Sample
Cycle 1, Day 1	Predose	Atezolizumab ATA Bevacizumab ATA Atezolizumab pharmacokinetics Bevacizumab pharmacokinetics TBNK Biomarkers [a]
	30 (±10) minutes after end of infusion [c]	Atezolizumab pharmacokinetics Bevacizumab pharmacokinetics
Cycle 1, Day 22	Predose	Biomarkers [b] Atezolizumab pharmacokinetics
Cycles 2, 3, 4, and 8, and every eight cycles thereafter Day 1 (±3 days)	Predose	Atezolizumab ATA (Cycles 2, 4, and 8, and every eight cycles thereafter) Bevacizumab ATA (Cycle 3 only) Atezolizumab pharmacokinetics (Cycles 2, 4, and 8 and every eight cycles thereafter) Bevacizumab pharmacokinetics (Cycle 3 only) Biomarkers [b] (Cycle 2 only)
	30 (± 10) minutes after end of infusion	Bevacizumab pharmacokinetics (Cycle 3 only)
Cycles 2 and 4, Day 22 (±3 days)	Predose	Atezolizumab pharmacokinetics Biomarker (Cycle 2 only) [b]
At time of fresh biopsy (during treatment or at progression)		TBNK Biomarkers [b, d]
End of treatment visit	At visit	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [b] Bevacizumab ATA Bevacizumab pharmacokinetics
120 (±30) days after last dose of atezolizumab [e]	At visit	Atezolizumab ATA Atezolizumab pharmacokinetics Bevacizumab ATA Bevacizumab pharmacokinetics

Appendix 2
Anti-Therapeutic Antibody, TBNK, Biomarker, and Pharmacokinetic Sampling Schedule (cont'd)

ATA = anti-therapeutic antibody; TBNK = T, B, and natural killer.

Note: Plasma, serum, and whole blood collected for pharmacodynamic biomarkers.

[a] Plasma, serum, and whole blood collected for pharmacodynamic biomarkers.

[b] Plasma and serum for biomarkers.

[c] For patients receiving both atezolizumab and bevacizumab (Arm A only), both postdose pharmacokinetic samples (for atezolizumab and bevacizumab) are to be drawn 30 minutes after the second (bevacizumab) infusion.

[d] Biomarker samples at the time of biopsy do not have to be collected if the biopsy visit occurs ≤ 3 days before or after another protocol-defined biomarker sample collection timepoint.

[e] Not required if the patient is lost to follow-up, withdraws request, or the study closes.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Version 1.1

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 [1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, 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). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Version 1.1 (cont'd)

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of Lesions

All measurements should be recorded in metric notation, with use of calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks prior to Cycle 1, Day 1.

Method of Assessment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, because CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, because the same lesion may appear to have a different size with use of a new modality.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Version 1.1 (cont'd)

Ultrasound. Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is $>$10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but additionally, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention because they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of

acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Version 1.1 (cont'd)

- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met because a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While patients are in the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on the CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes because they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Version 1.1 (cont'd)

Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. Although some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- Non-CR/Non-PD: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression based on the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely based on change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered

to have had overall PD at that point. Although it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

When the patient has bone lesions at baseline. When a bone scan is the sole indicator of progression, progression in bone will be defined as when at least two or more new lesions are seen on bone scan compared with screening. In situations where the scan findings are suggestive of a flare reaction or apparent new lesion(s) that may represent trauma, these results must be confirmed with other imaging modalities such as MRI or fine-cut CT to constitute progression. Only a single new bone lesion on bone scan is required for progression if the lesion can be correlated on CT or MRI.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

New osteoblastic bone lesions identified on plain films, CT, or MRI will not be considered progression in an otherwise stable or responding subject if, in the opinion of the physician, the osteoblastic lesion appears to be healing or a response to therapy.

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Version 1.1 (cont'd)

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease because stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a

convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" because the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point

(because disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1–Table 3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 4
Modified Response Evaluation Criteria in Solid Tumors

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment. In this protocol, patients will be permitted to continue study treatment even after modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria for progressive disease are met if the risk/benefit ratio is judged to be favorable.

Modified RECIST is derived from RECIST, Version 1.1 conventions [1, 2, 3] and immune-related response criteria [3, 4, 5] (irRC).

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1) Eur J Cancer 2009;45:228–47.

[2] Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-L1 antibody in cancer. N Engl J Med 2012;366:2443–54.

[3] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immunetherapy activity in solid tumors: immune-related response criteria Clin Can Res 2009;15:7412–20.

[4] Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab. J Immunother Can 2014;2:17.

[5] Nishino M, Giobbie-Hurder A, Gargano M et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Can Res 2013;19:3936–43.

Appendix 4
Modified Response Evaluation Criteria in Solid Tumors (cont.)

MODIFIED RECIST AND RECIST, VERSION 1.1: SUMMARY OF CHANGES

	RECIST v1.1	Modified RECIST
New lesions after baseline	Define progression.	New measurable lesions are added into the total tumor burden and followed.
Non-target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of ≥20% increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease; may be confirmed by a consecutive assessment ≥4 weeks from the date first documented

RECIST = Response Evaluation Criteria in Solid Tumors.

Definitions of Measurable/non-Measurable Lesions

All measurable and non-measurable lesions should be assessed at screening and at the protocol-specified tumor assessment timepoints. Additional assessments may be performed, as clinically indicated for suspicion of progression. The investigator will evaluate response to treatment with use of modified RECIST.

Measurable Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)

10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, 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). At baseline and follow-up, only the short axis will be measured and followed.

Appendix 4
Modified Response Evaluation Criteria in Solid Tumors (cont.)

Non-Measurable Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter $<$10 mm or pathological lymph nodes with short axis $\geq$10 but $<$15 mm), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions

Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment

Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Appendix 4
Modified Response Evaluation Criteria in Solid Tumors (cont.)

Tumor Response Evaluation
Definitions of Target/Non-Target Lesions
Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is $>$10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance, the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention because they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$10 mm but $<$15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$10 mm are considered non-pathological and should not be recorded or followed.

Lesions irradiated within 3 weeks prior to Cycle 1, Day 1 may not be counted as target lesions.

Appendix 4
Modified Response Evaluation Criteria in Solid Tumors (cont.)

Non-Target Lesions

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required.

It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

After baseline, changes in non-target lesions will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions) and will not be used to assess progressive disease.

Calculation of Sum of the Diameters

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumor burden.

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Sum of the Diameters at Tumor Assessment: For every on-study tumor assessment collected per protocol or as clinically indicated, the sum of the diameters at tumor assessment will be calculated using tumor imaging scans. All target lesions and all new measurable lesions that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment with use of modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Lymph nodes that shrink to $<$10 mm short axis are considered normal.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.

Appendix 4
Modified Response Evaluation Criteria in Solid Tumors (cont.)

Note: The appearance of new measurable lesions is factored into the overall tumor burden but *does not automatically qualify as progressive disease* until the sum of the diameters increases by ≥20% when compared with the sum of the diameters at nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the diameters while in the study.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and all new measurable lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Impact of New Lesions on Modified RECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumor response.

Evaluation of Best Overall Response with Use of Modified RECIST

Timepoint Response

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Appendix 4
Modified Response Evaluation Criteria in Solid Tumors (cont.)

Table 1 Modified RECIST Timepoint Response Definitions

% Change in Sum of the Diameters (Including Measurable New Lesions When Present)	Target Lesion Definition	Non-Target Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Overall Modified RECIST Timepoint Response
-100% [a]	CR	CR	No	No	CR
-100% [a]	CR	Non-CR or not all evaluated	No	No	PR
$\leq -30\%$	PR	Any	Yes or No	Yes or No	PR
$> -30\%$ to $< +20\%$	SD	Any	Yes or No	Yes or No	SD
Not all evaluated	Not evaluated	Any	Yes or No	Yes or No	NE
$\geq \pm 20\%$	PD	Any	Yes or No	Yes or No	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met because a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm in order to meet the definition of CR.

Best Overall Response: All Timepoints

The best overall response is determined once all the data for the patient are known.

The best overall response according to modified RECIST is interpreted as described below:

CR: Complete disappearance of all tumor lesions (target and non-target) and no new measurable or unmeasurable lesions, confirmed by a consecutive assessment ≥ 4 weeks from the date first documented. All lymph nodes short axes must be < 10 mm.

PR: Decrease in the sum of the diameters of all target and all new measurable lesions $\geq 30\%$ relative to baseline, in the absence of CR, confirmed by a consecutive assessment ≥ 4 weeks from the date first documented.

SD: Criteria for CR, PR, and PD are not met.

Appendix 4
Modified Response Evaluation Criteria in Solid Tumors (cont.)

PD: Increase in the sum of the diameters of all target and all new measurable lesions ≥ 20% relative to the nadir, which may be confirmed by a consecutive assessment ≥ 4 weeks from the date first documented as follows:

> The confirmatory assessment shows an additional measurable increase in tumor burden as measured by the sum of the diameters of all target and all new measurable lesions.

This protocol allows patients to continue to receive study treatment even after confirmed radiographic PD per modified RECIST and patients may achieve a best overall response of PR or CR based on tumor regression achieved at any time prior to study treatment discontinuation.

Appendix 5
Karnofsky Performance Score

The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

KARNOFSKY PERFORMANCE STATUS SCALE
DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Appendix 6
Preexisting Autoimmune Diseases

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be patients 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 autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone or Type I diabetes mellitus on a stable dose of insulin 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). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

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

Appendix 7
New York Heart Association Functional Classification

The **New York Heart Association (NYHA) Functional Classification** provides a simple way of classifying the extent of heart failure. It places patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain:

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity (e.g., shortness of breath when walking, climbing stairs etc.)
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity (e.g., walking short distances [20–100 m]). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Appendix 8
Biopsy Procedure

Tumor Biopsies

Patients with archival tissue collected >24 months prior to Cycle 1, Day 1 must undergo fresh tumor biopsy to meet eligibility requirements unless the site of tumor renders a biopsy medically unsafe or not feasible. Biopsies must be obtained in a manner that minimizes risk. Tumor samples will be obtained to verify that viable tumor cells are present and examine expression of programmed death–ligand 1 (PD-L1) in addition to other biomarkers.

Biopsies will be taken only if there is no intervening condition (e.g., thrombocytopenia or neutropenia) that, in the opinion of the investigator, increases the likelihood of procedural complications to an unacceptable level. Bevacizumab should be not administered until ≥3 days following the procedure and evidence of adequate wound healing is observed.

For patients undergoing needle biopsies of deep-seated (e.g., liver) lesions, hemoglobin and hematocrit will be checked at the time of biopsy and prior to starting bevacizumab or sooner as clinically indicated. For patients who have a <2-unit decrease in hemoglobin or a <6% decrease in hematocrit following the biopsy, bevacizumab may be started with appropriate clinical monitoring. For patients who have a ≥2- but <3-unit decrease in hemoglobin or a ≥6% but <9% decrease in hematocrit, bevacizumab may be started at the discretion of the investigator after discussion with the Medical Monitor. Patients who have a ≥3-unit decrease in hemoglobin or a ≥9% decrease in hematocrit should be evaluated (e.g., by means of computed tomography [CT] scan or ultrasound), and bevacizumab may be started once the levels improve at the discretion of the investigator and after discussion with the Medical Monitor.

If a patient undergoes a medically indicated procedure any time during the course of the study that has the likelihood of yielding tumor tissue, any remaining samples or a portion of the sample not necessary for medical diagnosis may be obtained for exploratory analysis. Patients must have provided specific consent on the Optional Research Informed Consent Form to allow discarded samples from routine care to be obtained.

Refer to the laboratory manual for additional details on laboratory assessments and sample handling.

Appendix 9
MSKCC (Motzer) Criteria

Risk factors:

1. Karnofsky performance status score < 80
2. Corrected serum calcium > 10 mg/dL
3. LDH level > 1.5 times the upper limit of normal
4. Hemoglobin level $<$ lower limit of normal
5. Time from nephrectomy to systemic therapy ≤ 12 months [a]

- Patient also has this risk factor if:

  Initially diagnosed with metastatic disease

  No nephrectomy

Risk stratification:

1. Low: 0 risk factors
2. Intermediate: 1–2 risk factors
3. High: ≥ 3 risk factors

MSKCC = Memorial Sloan Kettering Cancer Center.

Note: The raw MSKCC score (0–5) should be reported in the eCRF.

[a] For study purposes, systemic therapy will be designated as the date of initial study screening.

Corrected calcium = serum calcium (mg/dL) + 0.8 (4 − serum albumin (g/dL))

Calcium (mg/dL) = calcium (mmol/L) × 4

Albumin (g/dL) × 10 = albumin (g/L)

Appendix 10
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet
- 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 drug infusion, the following procedures should be performed:

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observations.

Appendix 11
M.D. Anderson Symptom Inventory

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours***. Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	NOT PRESENT 0	1	2	3	4	5	6	7	8	9	AS BAD AS YOU CAN IMAGINE 10
1. Your **pain** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
2. Your **fatigue (tiredness)** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
3. Your **nausea** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
4. Your **disturbed sleep** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
5. Your feelings of being **distressed (upset)** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
6. Your **shortness of breath** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
7. Your problem with **remembering things** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
8 Your problem with **lack of appetite** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
9. Your feeling **drowsy (sleepy)** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
10. Your having a **dry mouth** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
11. Your feeling **sad** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
12. Your **vomiting** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
13. Your **numbness or tingling** at its WORST?	O	O	O	O	O	O	O	O	O	O	O

Appendix 11
M.D. Anderson Symptom Inventory (cont'd)

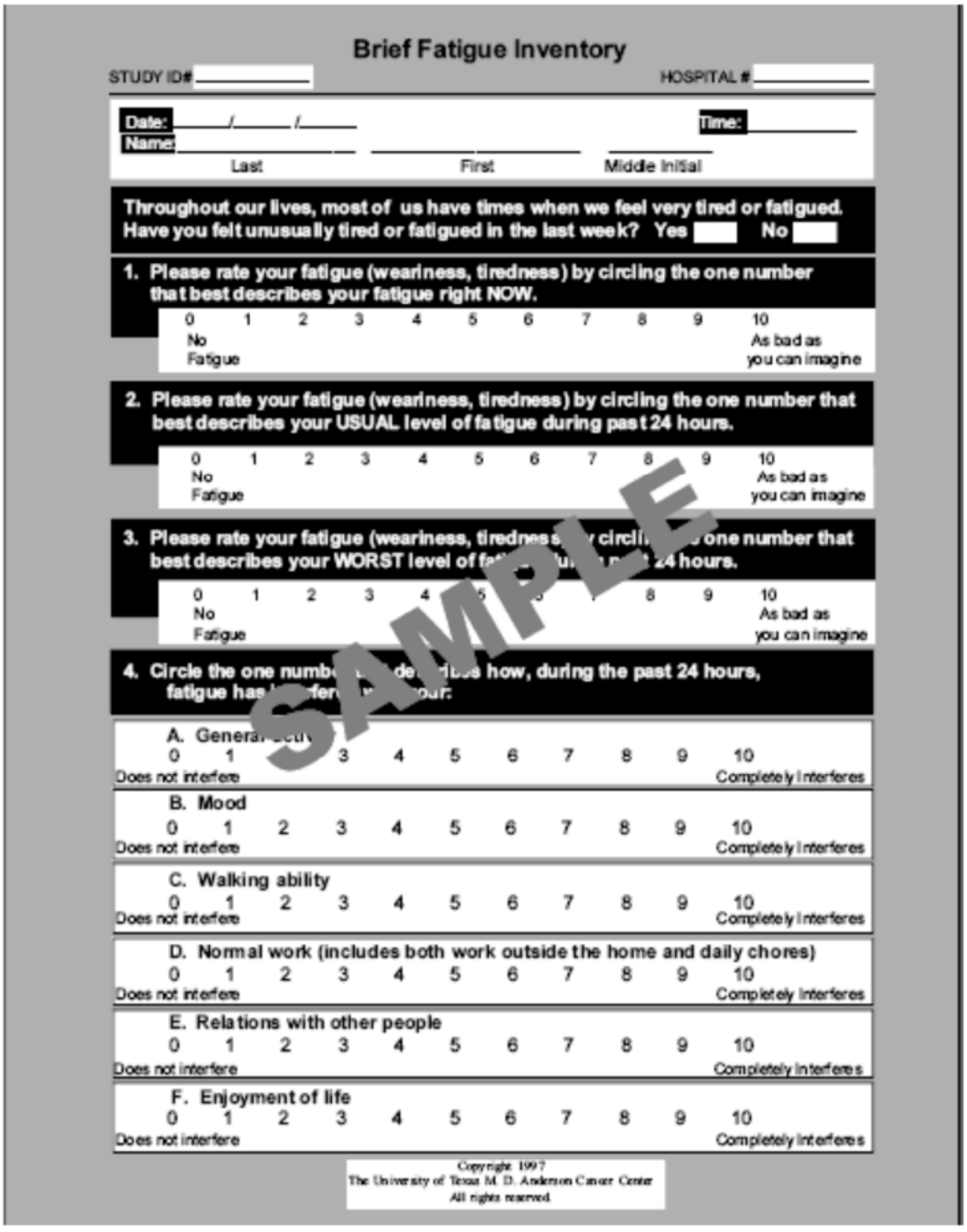
	NOT PRESENT 0	1	2	3	4	5	6	7	8	9	AS BAD AS YOU CAN IMAGINE 10
14. Your **rash or skin change** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
15. Your **headache** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
16. Your **mouth / throat sores** at its WORST?	O	O	O	O	O	O	O	O	O	O	O

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***:

	DID NOT INTERFERE 0	1	2	3	4	5	6	7	8	9	INTERFERED COMPLETELY 10
17. **General activity?**	O	O	O	O	O	O	O	O	O	O	O
18. **Mood?**	O	O	O	O	O	O	O	O	O	O	O
19. **Work (including work around the house)?**	O	O	O	O	O	O	O	O	O	O	O
20. **Relations with other people?**	O	O	O	O	O	O	O	O	O	O	O
21. **Walking?**	O	O	O	O	O	O	O	O	O	O	O
22. **Enjoyment of life?**	O	O	O	O	O	O	O	O	O	O	O
23. Your **diarrhea** at its WORST?	O	O	O	O	O	O	O	O	O	O	O

Appendix 12
Brief Fatigue Inventory



Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL # _____

Date: ____/____/____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

B. Mood
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

C. Walking ability
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

F. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

Appendix 13
National Comprehensive Cancer Network Functional Assessment of Cancer Therapy Kidney Symptom Index-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
	H1	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
	GP3	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
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Appendix 14
EQ-5D-3L Health Questionnaire

Health Questionnaire

English version for the UK
(validated for Ireland)

Appendix 14
EQ-5D-3L Health Questionnaire (cont.)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some 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 with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

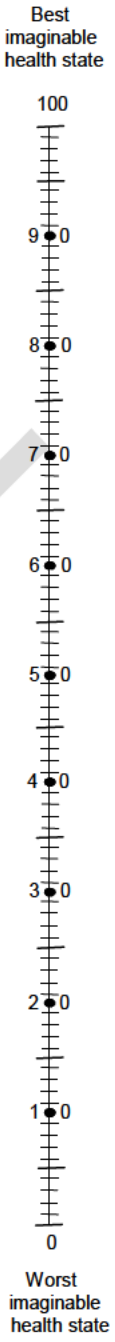
I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

Appendix 14
EQ-5D-3L Health Questionnaire (cont.)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 15
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 immunohistochemical 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 noncohesion 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 eCRF as 1) any component, 2) >20% component, or 3) predominant sarcomatoid component.

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 16
Common CYP3A4 Inducers

Carbamezepine

Dexamethasone

Ethosuximide

Glucocorticoids

Griseofulvin

Phenytoin

Primidone

Progesterone

Rifabutin

Rifampin

Nafcillin

Nelfinavir

Nevirapine

Oxcarbazepine

Phenobarbital

Phenylbutazone

Appendix 17
Common Drugs Which May Increase QTc Interval

Alfuzosin	Disopyramide	Lapatinib
Amantadine	Dofetilide	Levofloxacin
Amiodarone	Dolasetron	Levomethadyl Lithium
Amisulpride	Domperidone	Mesoridazine
Amitriptyline	Doxepin	Methadone
Amoxapine	Dronedarone	Metronidazole
Anagrelide	Droperidol	Mifepristone
Apomorphine	Eribulin	Mirabegron
Aripiprazole	Erythromycin	Mirtazapine
Arsenic trioxide	Escitalopram	Remeron
Astemizole	Famotidine	Moexipril/HCTZ
Atazanavir	Felbamate	Moxifloxacin
Azithromycin	Fingolimod	Nelfinavir
Bedaquiline	Flecainide	Nicardipine
Bepridil	Fluconazole	Nilotinib
Bortezomib	Fluoxetine	Norfloxacin
Bosutinib	Foscarnet	Nortriptyline
Chloral hydrate	Fosphenytoin	Ofloxacin
Chloroquine	Furosemide	Olanzapine
Chlorpromazine	Galantamine	Ondansetron
Ciprofloxacin	Gatifloxacin	Oxytocin
Cisapride	Gemifloxacin	Paliperidone
Citalopram	Granisetron	
Clarithromycin	Halofantrine	
Clomipramine	Haloperidol	
Clozapine	Hydrochlorothiazide	
Cocaine	Ibutilide	
Crizotinib	Iloperidone	
Dabrafenib	Imipramine (melipramine)	
Dasatinib	Indapamide	
Desipramine	Isradipine	
Dexmedetomidine	Itraconazole	
Dihydroartemisinin+piperaquine	Ivabradine	
Diphenhydramine	Ketoconazole	

STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH BEVACIZUMAB VERSUS SUNITINIB IN PATIENTS WITH UNTREATED ADVANCED RENAL CELL CARCINOMA**

PROTOCOL NUMBER: WO29637

STUDY DRUG: Atezolizumab (MPDL3280A)

VERSION NUMBER: 2

IND NUMBER: 119039

EUDRACT NUMBER: 2014-004684-20

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted]

DATE FINAL: Version 1: 21 March 2017

DATE(S) AMENDED: Version 2: See electronic date stamp below.

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

Name	Reason for Signing	Date and Time (UTC)
[redacted]	Company Signatory	04-Apr-2018 17:22:21

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

The Statistical Analysis Plan (SAP), Version 2, for Protocol WO29637 has been amended [redacted]. Changes to the SAP along with the rationale are summarized below:

- Section 2.4.2.2 (Co-Primary Endpoint of Overall Survival): An additional overall survival (OS) interim analysis, including updated alpha adjustment of the sequential testing of the OS interim analyses, [redacted] for the IMmotion151 study. The overall type 1 error of OS analyses is controlled at 5% per pre-specified O'Brien-Fleming boundary, where the 5% alpha is determined given the co-primary endpoint of progression-free survival (PFS) was met. A total of four analyses of OS will be performed according to the new analysis plan, including three interim analyses and one final analysis. The first OS interim was performed at the PFS primary analysis. The second OS interim analysis has now been added to the original interim analyses plan. The third interim and final OS analyses remain unchanged in terms of the event rate that will trigger the analyses, as per the original SAP, Version 1.

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

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1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study WO29637 (IMmotion151): a Phase III, multicenter, randomized, open-label study designed to evaluate the efficacy and safety of atezolizumab + bevacizumab versus sunitinib in patients with inoperable, locally advanced, or metastatic renal cell carcinoma (RCC) who have not received prior systemic active or experimental therapy, either in the adjuvant or metastatic setting.

2. STUDY DESIGN

Approximately 900 patients, including a minimum of approximately 351 patients with a programmed death–ligand 1 (PD-L1) immunohistochemistry (IHC) of tumor-infiltrating immune cell (IC) score of 1/2/3 (PD-L1–selected population; see protocol for the definition), were planned for enrollment at approximately 150–180 centers globally. Planned enrollment included a maximum of approximately 180 patients (20%) with a Memorial Sloan Kettering Cancer Center (MSKCC [Motzer]) score of 0 (good risk).

Patients will be randomized in a 1:1 ratio to one of two treatment arms:

- Arm A (experimental arm): Atezolizumab 1200 mg intravenous (IV) infusions every 3 weeks (q3w; dosed in 6-week cycles) + bevacizumab 15 mg/kg q3w (dosed in 6-week cycles)
- Arm B (control arm): Sunitinib 50 mg/day orally for 4 weeks, followed by 2 weeks of rest (dosed in 6-week cycles)

The co-primary efficacy endpoints are investigator-assessed progression-free survival (PFS) with use of the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) and overall survival (OS).

2.1 PROTOCOL SYNOPSIS

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

2.2 OUTCOME MEASURES

See the Protocol Synopsis in Appendix 1 for definitions of the outcome measures.

2.3 DETERMINATION OF SAMPLE SIZE

Approximately 900 patients, including a minimum of approximately 351 patients with a PD-L1 IHC IC score of 1/2/3 were planned for enrollment. Sample size calculations as shown in the protocol were based on the planned enrollment.

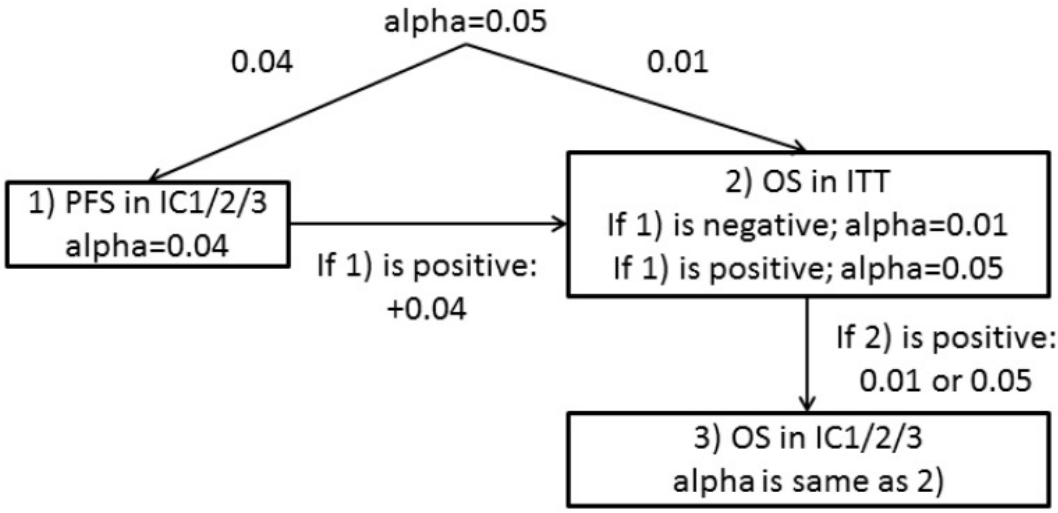
At the time of this SAP finalization, enrollment in the study had been completed 17 months after first patient randomized. A total of 915 patients were randomized, of

which 362 patients had a PD-L1 IHC IC score of 1/2/3. The required numbers of events and projected timelines for the analyses of PFS and OS have been updated in this SAP based on the actual enrollment. No changes were made to study design assumptions for the targeted treatment benefit or type 1 error control, and the ratio of the required number of events to the total population has been maintained.

2.3.1 Type I Error Control

The type I error (α) for the entire study is 0.05 (two-sided). There are two co-primary efficacy endpoints for this study: PFS by investigator assessment per RECIST v1.1 in the PD-L1–selected population and OS in the intent-to-treat (ITT) population (see Section 4.1 for the definition on the study population). To control the overall type I error rate (Bretz et al. 2009) at $\alpha = 0.05$ while accounting for two co-primary endpoints, α is split between PFS ($\alpha = 0.04$) and OS ($\alpha = 0.01$). The PFS and OS analysis hierarchy and α allocation including possible recycling are shown in Figure 1.

Figure 1 Progression-Free Survival and Overall Survival Hierarchy with Type I Error Control



IC = tumor-infiltrating immune cell; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival.

In Figure 1, formal treatment comparisons will be performed in a hierarchical fashion in which α may be recycled (Burman et al. 2009) as follows:

1. PFS by investigator assessment per RECIST v1.1 in the PD-L1–selected population will be evaluated at $\alpha = 0.04$.

   If PFS results in the PD-L1–selected population are statistically significant at $\alpha = 0.04$, then $\alpha = 0.04$ will be recycled to OS in the ITT population, and OS in the ITT population will be evaluated at $\alpha = 0.05$.

If PFS results in the PD-L1–selected population are not statistically significant at $\alpha = 0.04$, then no recycling of α will occur, and OS in the ITT population will be evaluated at $\alpha = 0.01$.

2. OS will be compared between treatment arms in a hierarchical fashion as follows:

   If OS results in the ITT population are statistically significant at the appropriate α level (either 0.01 or 0.05 that depends on step 1), then OS in the PD-L1–selected population will be evaluated at same α level as for OS in the ITT population.

   If OS results in the ITT population are not statistically significant, formal testing of OS in the PD-L1–selected population will not be performed.

   Details on the interim OS analyses and testing are described in Section 2.4.

The study will be considered as a positive study if statistical significance is achieved for either of the two co-primary endpoints, since the type I error (α) for the entire study is controlled at 0.05.

2.3.2 Co-Primary Endpoint: Progression-Free Survival by Investigator Assessment per RECIST v1.1 in the PD-L1–Selected Population

The analysis of the co-primary endpoint of PFS by investigator assessment per RECIST v1.1 in the PD-L1–selected population will take place when approximately 236 investigator-assessed PFS events have occurred in the PD-L1–selected population (65% events rate of the 362 patients in PD-L1–selected population) based on the following assumptions:

- Two-sided, stratified log-rank test
- $\alpha = 0.04$ (two-sided)
- Approximately 90% power
- Median PFS for the sunitinib arm of 11 months and estimated median PFS in the atezolizumab + bevacizumab arm of 17 months (corresponding to hazard ratio [HR] of 0.65)
- 5% annual loss to follow-up for PFS
- No interim analysis

On the basis of these assumptions, it is projected that an observed HR of 0.76 or lower will result in a statistically significant difference between treatment arms (i.e., an HR of 0.76 will be the minimally detectable difference [MDD] for the analysis; this corresponds to an improvement of 3.5 months in median PFS from 11 months in the sunitinib arm to 14.5 months in the atezolizumab + bevacizumab arm).

2.3.3 Co-Primary Endpoint: Overall Survival in the Intent-to-Treat Population

The final analysis of the co-primary endpoint of OS will take place at the later of the timepoints when the required number of events has occurred in the PD-L1−selected population and in the ITT population, where the required number of events is as follows:

- ITT population: approximately 639 OS events (approximately 70% of the 915 patients)
- PD-L1−selected population: approximately 250 OS events (approximately 70% of the 362 patients)

The number of events required for the final OS analysis in these populations is based on the following assumptions:

- Two-sided, stratified log-rank test
- $\alpha = 0.01$ (two-sided)
- Median OS in the sunitinib arm of 24 months
- 1% annual loss to follow-up for OS
- For the ITT population:

  Approximately 85% power

  Estimated median OS in the atezolizumab + bevacizumab arm of 32 months (an increase of 8 months, corresponding to an HR of 0.75)
- For the PD-L1−selected population:

  Approximately 55% power

  Estimated median OS in the atezolizumab + bevacizumab arm of 33.8 months (an increase of 9.8 months, corresponding to an HR of 0.71)

ITT population OS MDD: At the final OS analysis, on the basis of these assumptions, it is projected that an observed OS HR of 0.81 or lower in the ITT population will result in a statistically significant difference between treatment arms (i.e., the MDD at the analysis; this corresponds to an improvement of 5.6 months in median OS, from 24 months in the control arm to 29.6 months in the atezolizumab + bevacizumab arm).

PD-L1−selected population OS MDD: At the final OS analysis, on the basis of these assumptions, it is projected that an observed OS HR of 0.71 or lower in the PD-L1−selected population will result in a statistically significant difference between treatment arms (i.e., an HR of 0.71 will be the MDD at the analysis; this corresponds to an improvement of 9.8 months in median OS, from 24 months in the control arm to 33.8 months in the atezolizumab + bevacizumab arm).

2.4 INTERIM AND PRIMARY ANALYSIS TIMING

2.4.1 Primary Analysis Timing

The primary analysis timing is event driven. The analysis of the co-primary endpoint of PFS by investigator assessment per RECIST v1.1 in the PD-L1–selected population will take place when approximately 236 investigator-assessed PFS events have occurred in the PD-L1–selected population. Based on the assumptions described in Section 2.3.2 and actual accrual, the required number of PFS events is projected to occur at Month 34 from the time the first patient is randomized.

The final analysis of the co-primary endpoint of OS will take place at the later of 639 OS events in ITT population and 250 OS events in PD-L1–selected population. The required number of OS events for the final analysis of OS in both the PD-L1–selected population and the ITT population is projected to occur at Month 61 from the time the first patient is randomized.

The actual number of events that occur by the data cutoff date of the primary or final analysis could potentially be higher than the required number of events.

2.4.2 Interim Analyses Timing

2.4.2.1 Co-Primary Endpoint of Progression-Free Survival

There is no planned interim analysis of the co-primary endpoint of PFS.

2.4.2.2 Co-Primary Endpoint of Overall Survival

A total of four analyses of OS will be performed, including three interim analyses and one final analysis. The α level for OS testing is 0.05 given that the co-primary endpoint of PFS was met in the study (see Section 2.3.1). The boundary for statistical significance at each interim analysis and the final analysis will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming function (Lan and DeMets 1983) to maintain the overall type 1 error rate (Hung et al. 2007; Glimm et al. 2009) at 0.05 level. The O'Brien-Fleming (OBF) boundary for statistical significance is provided in Table 1. The OS endpoint will be considered positive in the ITT population if statistical significance is achieved for any of the three OS interim analyses or the final analysis.

Table 1 *Interim and Final OS Analyses for the ITT Population*

OS Analyses	
First interim OS (performed at time of PFS analysis) [a]	
No. of events (%) [b]	*264 (29%)*
% of final events	*41%*
Cutoff date	*Study Month 29* [c]
OBF boundary for p-value	*p≤0.0009*
Second interim OS (Time driven)	
Projected No. of events (%) [b]	*377 (41%)*
Projected % of final events	*59%*
Cutoff date	*Study Month 40* [c]
Projected OBF boundary for p-value [d]	*p≤0.0067*
Third interim OS (Event driven)	
No. of events (%) [b]	*518 (57%)*
% of final events	*81%*
Projected cutoff date	*Study Month 57* [c]
Projected OBF boundary for p-value [d]	*p≤0.0233*
Final OS (Event driven)	
No. of events (%) [b]	*639 (70%)*
% of final events	*100%*
Projected cutoff date	*Study Month 79* [c]
Projected OBF boundary for p-value [d]	*p≤0.0420*

ITT=intent-to-treat; OBF=O'Brien-Fleming; OS=overall survival; PFS=progression-free survival.

Note: The α level for OS testing is 0.05, given that the co-primary endpoint of PFS was met (see Section 2.3.1).

[a] *The first interim analysis of OS was performed at the time of the PFS primary analysis at Study Month 29, with a cut-off date of 29 September 2017, which was 5 months earlier than the initial projection of Month 34 described in Section 2.4.1. The OBF boundary for p-value is calculated based on 264 OS events observed by the cutoff date.*

[b] *The event rate is based on the actually observed ITT population with N=915.*

[c] *Study month at which required number of events are projected to occur, where Study Month 1 is the month the first patient is enrolled.*

[d] *The projected OBF boundary for statistical significance is calculated according to the number of events shown. The actual OBF boundary will be calculated at time of analysis based on actual number of events observed.*

The first interim analysis of OS was performed at the time of the PFS primary analysis. A total of 264 deaths (29% of 915 patients in the ITT population) was observed at the first interim analysis of OS, which corresponds to 41% of the events information required for the final

analysis of OS in the ITT population. The first OS interim analysis did not pass the OBF boundary at 0.0009.

The second interim analysis of OS will be time driven and will occur approximately 11 months from the clinical cutoff of the first OS interim. [redacted] *. It is projected that at the second interim OS analysis, 377 deaths (41% of 915 patients in the ITT population) will occur, corresponding to approximately 59% of the events information required for the final analysis of OS in the ITT population. Statistical significance will be declared if $p \leq 0.0067$ when 377 deaths have occurred at the time of the second OS interim analysis.*

The third interim analysis of OS is event driven and remains the same as the original plan (SAP, Version 1). The third interim analysis of OS will be performed when approximately 518 deaths (57% of 915 patients in the ITT population) have occurred, which corresponds to approximately 81% of the events information required for the final analysis of OS in the ITT population. Statistical significance will be declared if $p \leq 0.0233$ when 518 deaths have occurred at the time of the third OS interim analysis.

The final analysis of OS is event driven and remains the same as the original plan (SAP, Version 1). The final analysis of OS will be performed when 639 deaths (70% of 915 patients in the ITT population) have occurred. Statistical significance will be declared if $p \leq 0.0420$ when 639 deaths have occurred at the time of the final OS analysis.

The interim and final analyses of OS, including analyses in both the ITT and PD-L1–selected populations, will follow the testing hierarchy described in Section 2.3.1 . Specifically, for each OS interim and final analysis, OS in the PD-L1–selected population will be evaluated for statistical significance only when the OS results in the ITT population are statistically significant at the OBF boundary. The actual OBF boundary will be calculated at time of analysis based on actual number of events observed. If OS results in the ITT population are not statistically significant, formal testing of OS in the PD-L1–selected population will not be performed.

All efficacy analyses, including the interim analyses of OS, will be performed by the Sponsor.

2.4.2.3 Periodic Safety Monitoring

Safety data will be reviewed by the independent Data Monitoring Committee (iDMC) during the study on a periodic basis, approximately every 6 months from first patient randomized until the time of the primary analysis of PFS. See Section 3.2 for more details.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Eligible patients were randomized in a 1:1 ratio to receive either atezolizumab + bevacizumab versus sunitinib. A permuted-block randomization was applied to obtain balanced assignment to each treatment arm with respect to the following stratification factors:

- Presence of liver metastasis (yes vs. no)
- MSKCC (Motzer) score (low, intermediate, or high risk; 0, 1–2, or ≥ 3), which comprises the following five risk factors: Karnofsky performance status (KPS) < 80%, LDH > 1.5 × upper limit of normal (ULN), hemoglobin less than the lower limit of normal (LLN), corrected serum calcium > 10 mg/dL, and time from nephrectomy to systemic therapy (≤ 12 months vs. > 12 months)
- PD-L1 status: IC1/2/3 versus IC0

3.2 INDEPENDENT REVIEW FACILITY AND DATA MONITORING

An external iDMC will evaluate safety data during the study on a periodic basis, approximately every 6 months, until the time of the analysis of the co-primary efficacy endpoint of PFS according to policies and procedures detailed in an iDMC Charter. No interim efficacy analyses are planned for PFS.

Staff at an independent Data Coordinating Center (iDCC) will prepare all summaries and analyses for iDMC review. The safety summaries will include demographic data, adverse events, serious adverse events, and relevant laboratory data.

Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Following the data review, the iDMC will provide a recommendation to the Sponsor whether to continue the study, amend the protocol, or stop the study. 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 the investigators for notification of the Institutional Review Boards/Ethics Committees (IRBs/ECs).

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

Analysis populations of the study are defined as follows:

- The ITT population is defined as all randomized patients whether or not the assigned study treatment was received
- The measurable-disease population is defined as patients in the ITT population with measurable disease at baseline, as determined by investigator

- The duration of response (DOR)-evaluable population is defined as patients with objective response
- The safety-evaluable population is defined as patients who received any amount of any component of the study treatments
- Atezolizumab pharmacokinetic (PK) analyses will be based on PK observations from all patients who received atezolizumab treatment with evaluable PK samples
- Bevacizumab PK analyses will be based on PK observations from all patients who received bevacizumab treatment with evaluable PK samples
- The patient-reported outcome (PRO)-evaluable population is defined as patients with a non-missing baseline PRO assessment and ≥ 1 post-baseline PRO assessment

The PD-L1–selected population is defined as patient population whose PD-L1 status is IC1/2/3 at the time of randomization. PFS and OS outcome measures will be performed for patients in the PD-L1–selected population and the ITT population.

4.2 ANALYSIS OF STUDY CONDUCT

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

Analysis of study conduct will also be performed on the PD-L1–selected population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic variables such as age, sex, race/ethnicity, stratification factors (liver metastases, MSKCC Motzer score, PD-L1 status), and baseline characteristics (including but not limited to weight, primary tumor characteristics such as Fuhrman grade and histology of clear cell vs. sarcomatoid, time since initial diagnosis, time since metastatic diagnosis, sites of metastatic disease, number of metastatic sites, and KPS) will be summarized by treatment arm for the ITT population and for the PD-L1–selected population.

Baseline values are the last available data obtained prior to the patient receiving the first dose of study treatment on Cycle 1, Day 1. Descriptive statistics (mean, median, SD, range) will be presented for continuous variables. Frequencies and percentages will be presented for categorical variables.

4.4 EFFICACY ANALYSES

The efficacy analyses will be performed for patients in the PD-L1–selected population and the ITT population according to the treatment assigned at randomization on the basis of the ITT principle.

4.4.1 Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints are investigator-assessed PFS per RECIST v1.1 and OS. Co-primary efficacy endpoints of investigator-assessed PFS per RECIST v1.1 will be analyzed in the PD-L1–selected population, co-primary efficacy endpoints of OS will be analyzed in the ITT population, and OS in the PD-L1–selected population (secondary endpoint with α control) will be analyzed in a hierarchical fashion (see Section 2.3).

PFS is defined as the time from randomization to disease progression, as determined by the investigator per RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. Data for patients with no post-baseline tumor assessments will be censored at the randomization date plus1 day.

For United States registrational purposes, the co-primary efficacy endpoint of PFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits.

OS is defined as the time from randomization to death due to any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization + 1 day.

The following analyses will be performed for both PFS and OS endpoints described above. PFS and OS will be compared between treatment arms with use of the stratified log-rank test at the two-sided level of significance as described in Section 2.3. Hazard ratio will be estimated using a stratified Cox regression model with the same stratification variables used for the stratified log-rank test. The 95% CI will be provided. The randomization stratification factors are presence of liver metastasis (yes/no), tumor PD-L1 status (IC0 vs. IC1/2/3), and the MSKCC (Motzer) score (0, 1–2, $\geq$3). The stratification factors will be obtained from the interactive voice/Web response system (IxRS) at the time of randomization. Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate the median PFS and OS for each treatment arm, and Kaplan-Meier curves will be produced. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and OS for each treatment arm (Brookmeyer and Crowley 1982).

4.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- PFS by investigator assessment per RECIST v1.1 in the ITT population
- OS in the PD-L1–selected population (secondary endpoint with α control)
- PFS by Independent Review Committee (IRC) assessment per RECIST v1.1

- Objective response rate (ORR) by investigator assessment per RECIST v1.1 (ORR-evaluable population)
- DOR by investigator assessment per RECIST v1.1 (DOR-evaluable population)
- ORR by IRC assessment per RECIST v1.1 (ORR-evaluable population)
- DOR by IRC assessment per RECIST v1.1 (DOR-evaluable population)
- PFS by investigator assessment per immune-modified RECIST
- ORR by investigator assessment per immune-modified RECIST (ORR-evaluable population)
- DOR by investigator assessment per immune-modified RECIST (DOR-evaluable population)
- PFS by investigator assessment per RECIST v1.1 (patients with sarcomatoid histology defined by investigator-assessed conventional histopathology)
- OS (patients with sarcomatoid histology)
- Change from baseline in symptom interference, as measured by the M.D. Anderson Symptom Inventory (MDASI) symptom interference subscale (PRO-evaluable population)

The above secondary efficacy endpoints will be analyzed in both the PD-L1–selected population and the ITT population, if not otherwise specified. OS in the PD-L1–selected population is the only secondary endpoint with α control as described in Section 2.3. No formal hypothesis testing will be conducted for the other secondary endpoints.

4.4.2.1 Objective Response Rate

Objective response is defined as a complete response (CR) or partial response (PR) (confirmation not required) per RECIST v1.1. Patients not meeting this criterion, including patients without any post-baseline tumor assessments, will be considered non-responders. The analysis population for ORR will be measurable-disease population (defined in Section 4.1).

ORR is defined as the proportion of patients who had an objective response among the measurable-disease population. Confirmed (per RECIST v1.1) response rate will also be evaluated.

ORR will be compared between treatment arms with use of the stratified Cochran–Mantel-Haenszel test. The stratification factors will be the same as those described in the analysis of the primary endpoint of PFS. An estimate of ORR will be calculated for each treatment arm, and its 95% CI will be calculated using the Clopper–Pearson method. The difference in ORR between treatment arms will be calculated, and its 95% CI will be calculated using the normal approximation to the binomial distribution.

4.4.2.2 Duration of Response

DOR is defined for patients who had an objective response as the time from the first occurrence of response (CR or PR) to disease progression or death, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. DOR for confirmed response will also be evaluated. If no tumor assessments were performed after the date of the first occurrence of CR or PR, data for DOR will be censored at the date of the first occurrence of CR or PR plus 1 day.

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

4.4.2.3 Progression-Free Survival by Immune-Modified RECIST

PFS by immune-modified RECIST is defined as the time from randomization to disease progression as determined by the investigator per immune-modified RECIST (see Appendix 3), or death from any cause, whichever occurs first. A patient is considered to have disease progression by immune-modified RECIST if either of the following conditions were met:

a) Immune-modified RECIST criteria for progression were met at a tumor assessment and no subsequent tumor assessment was performed.

b) Immune-modified RECIST criteria for progression were met at a tumor assessment and at the subsequent tumor assessment the criteria for confirmed progression by immune-modified RECIST were also met.

For patients who meet criterion (a), the date of progression is the date of the tumor assessment that met the criteria for immune-modified RECIST. For patients who meet criterion (b), the date of progression is the date of the tumor assessment at which the immune-modified RECIST criteria for progression were first met.

Patients who do not meet either of the above criteria are not considered to have had disease progression by immune-modified RECIST. For example, a patient who had a tumor assessment for which the criteria for progression by immune-modified RECIST criteria were met, but at the subsequent tumor assessment the criteria for confirmed progression by immune-modified RECIST were not met, would not be considered to have had progression by immune-modified RECIST on the basis of those two tumor assessments. The determination of whether such a patient subsequently met the criteria for progression by immune-modified RECIST would be based only on additional subsequent tumor assessments performed after the two tumor assessments described in this example.

Data for patients who have not experienced disease progression by immune-modified RECIST or death will be censored at the last tumor assessment date. Data for patients

with no post–baseline tumor assessments will be censored at the randomization date plus 1 day.

Methods for comparison of PFS between treatment arms for the secondary endpoints of PFS (including PFS by IRC assessment per RECIST v1.1 and PFS by investigator assessment per immune-modified RECIST) will be the same as the methods for treatment comparisons for the co-primary efficacy endpoint of PFS by investigator assessment per RECIST v1.1. Kaplan–Meier methodology will be used to estimate the median PFS for each treatment arm. The Brookmeyer–Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm (Brookmeyer and Crowley 1982).

4.4.2.4 Change from Baseline in Symptom Interference

Change from baseline in symptom interference with daily living (captured by the MDASI symptom interference subscale) will be evaluated by timepoint and overall (i.e., including all on-treatment assessments) until disease progression (investigator-assessed per RECIST v1.1). Multivariate longitudinal models (e.g., mixed models) and area under the curve (AUC) methods may be used to estimate treatment effects on symptom interference as appropriate. These analyses will be performed on the PRO-evaluable population.

The MDASI symptom interference subscale comprises six items that ask patients to rate how much their symptoms interfered with general activity, mood, work, relations with other people, walking, and enjoyment of life in the last 24 hours. Each MDASI item is scored on a 0–10 scale, with 0 indicating that the patient's symptoms "did not interfere" and 10 indicating that symptoms "interfered completely" with the patient's life. The symptom interference score is calculated as a mean of the six items with a score range of 0–10, where higher scores indicate greater symptom interference with daily living. A 2-point change has been used to define a clinically meaningful change in MDASI symptom interference scores. Additional scoring details are described in Section 4.7.

4.4.3 Exploratory Efficacy Endpoints

4.4.3.1 Analyses at Landmark Timepoints of Progression-Free Survival and Overall Survival

The PFS and OS rates at various landmark timepoints include but are not limited to:

- PFS for every 6 months after randomization
- OS for every 6 months after randomization

PFS and OS rates will be estimated by the Kaplan–Meier methodology for each treatment arm and the 95% CI will be calculated using Greenwood's formula.

4.4.3.2 Subgroup Analyses

To assess the consistency of study results in subgroups defined by demographic and baseline characteristics and stratification factors, PFS, ORR, and OS in the subgroups will be examined as appropriate.

Subgroup analyses will include but not be limited to:

- PFS and ORR in patients with tumor Fuhrman Grade 4
- PFS (including PFS by IRC assessment per RECIST v1.1 and PFS by investigator assessment per immune-modified RECIST) and ORR in patients with sarcomatoid histology
- PFS and OS in MSKCC (Motzer) score subgroup of low, intermediate, or high risk (0, 1–2, or ≥ 3)

4.4.3.3 Biomarker Analyses

Exploratory prognostic, predictive, and pharmacodynamic biomarker analyses, including but not limited to subgroups defined by gene or gene expression signature expression, will be performed in archival and/or fresh tumor tissue and/or blood in an effort to understand the association of these markers with disease status and/or clinical outcomes, including ORR, PFS, and OS.

The exploratory biomarker analyses are as follows:

- Status of PD-L1, immune-, angiogenic-, and RCC biology-related and other exploratory biomarkers, as defined by but not limited to IHC or quantitative polymerase chain reaction (qPCR) in archival and/or freshly obtained tumor tissues and blood collected before, during, or after treatment with atezolizumab + bevacizumab or sunitinib, or at progression
- Status of ICs and biomarkers in biopsy specimens and blood collected at the first evidence of radiographic disease progression

The exploratory biomarker analyses will be prespecified and detailed in a separate biomarker SAP. These exploratory analyses may not be available at the time of the preparation of the Clinical Study Report and may be reported separately.

4.5 SAFETY ANALYSES

Safety analyses will be performed for the safety-evaluable population; selected safety analyses will be performed for safety-evaluable patients in the PD-L1–selected population. Patients will be grouped according to the treatment actually received. Specifically, a patient will be included in the atezolizumab + bevacizumab arm in safety analyses if the patient receives any amount of atezolizumab or bevacizumab, regardless of the initial treatment assignment by IxRS.

4.5.1 Exposure to Study Medication

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

4.5.2 Adverse Events

Verbatim description of adverse events will be mapped to MedDRA thesaurus terms. Adverse events will be graded by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

Treatment-emergent adverse events (defined as adverse events occurring on or after the first dose of study drug until the earliest of initiation of a non-protocol, anti-cancer therapy or clinical cutoff date) will be summarized by MedDRA term, appropriate MedDRA levels, NCI CTCAE v4.0 grade, and by treatment arm. Multiple occurrences of the same event will be counted once at the maximum grade. Adverse events, serious adverse events, treatment-related serious adverse events, severe adverse events (Grade ≥ 3), treatment-related severe adverse events, adverse events of special interest, immune-mediated adverse events (defined as adverse events requiring the use of systemic corticosteroids), and adverse events leading to study drug discontinuation or interruption will be summarized.

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

4.5.3 Laboratory Data

Laboratory data will be classified according to NCI CTCAE v4.0 and will be summarized descriptively by treatment arm. Shift tables from baseline to worst value during the study post-baseline will be presented. Baseline is defined as the measurement obtained on Cycle 1, Day 1 prior to first dose of study drug.

4.5.4 Vital Signs

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

4.5.5 Anti-Therapeutic Antibody

Incidence of anti-therapeutic antibodies (ATAs) against atezolizumab and bevacizumab will be summarized. The analyses of pharmacokinetics, key efficacy, and safety by ATA status may be conducted to explore the potential impact of immunogenicity.

4.6 PHARMACOKINETIC ANALYSES

Atezolizumab serum concentration data (minimum serum concentration [C_{min}] and maximum serum concentration [C_{max}]) will be tabulated and summarized for each cycle at which pharmacokinetics are to be measured (C_{max} will be reported for Day 1 of Cycle

1 only; C_{min} will be evaluated at Day 1 of Cycles 1, 2, 4, 8, and every eight cycles thereafter; Day 22 of Cycles 1, 2, and 4; and at study termination).

Bevacizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized for each cycle at which pharmacokinetics are to be measured (C_{max} will be reported for Day 1 of Cycles 1 and 2; C_{min} will be evaluated at Day 1 of Cycles 1, 2, and study termination).

Descriptive statistics will include means, medians, ranges, and SDs, as appropriate. Additional PK and pharmacodynamic analyses will be conducted as appropriate.

4.7 PATIENT-REPORTED OUTCOME ANALYSES

The PRO objectives are to evaluate patient-reported symptom severity, interference, tolerability, and overall health associated with atezolizumab plus bevacizumab versus sunitinib. PRO questionnaires (MDASI, Brief Fatigue Inventory [BFI], Functional Assessment of Cancer Therapy–Kidney Symptom Index-19 [FKSI-19], EuroQoL 5 Dimension 3 Levels [EQ-5D-3L]) will be scored on the basis of their corresponding user manuals (Cleeland 2009a, 2010b; Cella 2014; Van Reenen and Oppe 2015). For the MDASI, BFI, and FKSI-19, if more than 50% of the constituent items were completed, prorated scores will be computed consistent with the scoring manuals and validation papers. If less than 50% of the items in a subscale were completed, the subscale will be considered missing.

Completion rate for each PRO measure will be calculated and summarized at each assessment point, overall and by treatment. The PRO completion rate is defined as the number of questionnaires received divided by the number of questionnaires expected (i.e., the number of subjects still in the study).

Descriptive analyses will include summary statistics (e.g., mean, SD, median, interquartile range [IQR], minimum, maximum) for continuous PRO scale scores at each timepoint and score change from baseline to each timepoint, including disease progression and treatment discontinuation. Descriptive analyses will be performed on the PRO-evaluable population for all subscales of the MDASI, BFI, and FKSI-19, as well as the EQ-5D-3L visual analogue scale (VAS).

Key PROs include treatment- and disease-related symptoms, tolerability, interference, and overall quality of life: pain, fatigue, distress, lack of appetite, numbness or tingling, rash, headache, mouth/throat sores, diarrhea, symptom interference with enjoyment of life and functioning more broadly (MDASI); level of bother with treatment side effects and function/well-being (FKSI-19), fatigue interference (BFI), and overall health state (EQ-5D-3L VAS). Multivariate longitudinal models (e.g., mixed models) may be used to evaluate treatment effects on key PROs by timepoint and overall as appropriate.

Cumulative incidence of key patient-reported symptoms (as measured by the MDASI) will be compared between treatment arms.

The proportion of patients who experienced clinically meaningful deterioration in symptom severity and interference (MDASI) and overall health (EQ-5D-3L VAS) will be compared between treatments. Though multiple meaningful change estimates have been reported, we will use a 2-point change (increase) in MDASI scores and a 7-point change in EQ-5D-3L VAS scores as the primary thresholds for clinically meaningful change.

Time to deterioration (or improvement) in key treatment- and disease-related symptoms and functional impact (listed above) will be compared between treatments. Each time to deterioration endpoint is defined as the time from the date of randomization to the date of first clinically meaningful change in PRO score. Cox proportional hazards models will be used to estimate HRs and corresponding 95% CIs. Time to deterioration analyses will be performed on the ITT population.

As appropriate, additional exploratory analyses may be conducted to further examine the relationships among changes in symptom severity, interference, overall quality of life, disease progression, PFS, and OS.

4.7.1 Health Economic Data

Health economic data, as assessed by the EQ-5D-3L, will be evaluated for patients with a baseline assessment and at least one post-baseline EQ-5D-3L assessment that generated a score. For the EQ-5D-3L health state profiles, descriptive statistics summarizing the proportions of patients who reported having "no," "some," or "extreme" problems at each timepoint will be reported. A single summary index from the EQ-5D-3L health states will be utilized in this study for economic modeling.

The results from the health economic data analysis will be reported separately from the Clinical Study Report.

4.8 MISSING DATA

Refer to previous sections for details on how missing data are handled for each endpoint.

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Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH BEVACIZUMAB VERSUS SUNITINIB IN PATIENTS WITH UNTREATED ADVANCED RENAL CELL CARCINOMA**
PROTOCOL NUMBER:	WO29637
VERSION NUMBER:	7
EUDRACT NUMBER:	2014-004684-20
IND NUMBER:	119039
TEST PRODUCT:	Atezolizumab (RO5541267)
PHASE:	Phase III
INDICATION:	Renal cell carcinoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Analyses of the following objectives will be performed for the population of patients with inoperable, locally advanced, or metastatic renal cell carcinoma (RCC), unless otherwise indicated. Where specified, a comparison of the treatment arms will be performed in the patient population defined according to tumor programmed death–ligand 1 (PD-L1) expression as evaluated by immunohistochemistry (IHC).

Efficacy Objectives

The primary and secondary efficacy objectives will be evaluated in the PD-L1–selected population (tumor-infiltrating immune cell [IC]1/2/3) as well as in the intent-to-treat (ITT) population (includes all IC scores).

The primary efficacy objective of the study is as follows:

- To evaluate the efficacy of atezolizumab + bevacizumab compared with sunitinib as measured by the co-primary endpoints of investigator-assessed progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and overall survival (OS).

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by Independent Review Committee (IRC)–assessed PFS according to RECIST v1.1
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by investigator-assessed objective response rate (ORR) (complete + partial response rates) per RECIST v1.1
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by investigator-assessed duration of response (DOR) among patients with an objective response per RECIST v1.1

Appendix 1
Protocol Synopsis (cont.)

- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by IRC-assessed ORR and DOR according to RECIST v1.1
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib as measured by investigator-assessed PFS, DOR, and ORR per modified RECIST
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib among patients with sarcomatoid histology (defined by investigator-assessed conventional histopathology) as measured by investigator assessed PFS per RECIST v1.1 and OS
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib on symptom interference as measured by the M.D. Anderson Symptom Inventory [MDASI Part II])

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab + bevacizumab versus sunitinib
- To evaluate the incidence of anti-therapeutic antibodies (ATAs) against atezolizumab and to explore the potential relationship of immunogenicity response with pharmacokinetics, safety, and efficacy

Pharmacokinetic Objectives

The pharmacokinetic objectives for this study are as follows:

- To characterize the pharmacokinetics of atezolizumab when administered in combination with bevacizumab
- To characterize the pharmacokinetics of bevacizumab when administered in combination with atezolizumab

Patient-Reported Outcome Objectives

The additional patient-reported outcome (PRO) objectives of the study are as follows:

- To assess symptom severity associated with atezolizumab + bevacizumab versus sunitinib in patients with RCC as measured by the MDASI and Brief Fatigue Inventory (BFI)
- To document patients' perspective regarding the tolerability of the treatments (from the treatment side-effects subscale from the Functional Assessment of Cancer Therapy Kidney Symptom Index [FKSI-19])
- To obtain general measures of health as measured by the EuroQoL 5 Dimensions (EQ-5D) questionnaire for health economic modeling of atezolizumab + bevacizumab versus sunitinib in patients with RCC

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the relationship between the expression of other candidate predictive immune, angiogenic, or hypoxia biomarkers, as defined by IHC or quantitative polymerase chain reaction (qPCR), and efficacy as defined by PFS and ORR
- To evaluate the efficacy of atezolizumab + bevacizumab versus sunitinib among patients with tumor Fuhrman Grade 4 or sarcomatoid histology (defined by investigator-assessed conventional histopathology) as measured by PFS and ORR
- To assess immune-mediated predictive and prognostic exploratory biomarkers in tumor tissue and blood from archival specimens, fresh biopsy specimens, or specimens obtained during the study and their association with disease status and/or efficacy as defined by PFS and ORR

Appendix 1
Protocol Synopsis (cont.)

Study Design

Description of Study

This is a Phase III, multicenter, randomized, open-label study designed to evaluate the efficacy and safety of atezolizumab + bevacizumab versus sunitinib in patients with inoperable, locally advanced, or metastatic RCC who have not received prior systemic active or experimental therapy, either in the adjuvant or metastatic setting.

Number of Patients

The study will enroll approximately 900 patients, including a minimum of 351 patients with a PD-L1 IHC of IC score of 1/2/3 (PD-L1–selected population), at approximately 150–180 centers globally. A maximum of approximately 180 patients *(20%)* with a Memorial Sloan Kettering Cancer Center (MSKCC [Motzer]) score of 0 (good risk) will be enrolled.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Unresectable advanced or metastatic RCC with clear-cell histology and/or component of sarcomatoid carcinoma

  Renal cell carcinoma with any component of high-grade malignant spindle cells consistent with sarcomatoid histology is eligible. (See the protocol for further guidelines regarding defining sarcomatoid histology.)
- Evaluable MSKCC risk score (i.e., "Motzer" score)

  All MSKCC risk scores are included

  Patients with good risk MSKCC (risk score 0) will comprise no more than 20% of the study population
- Definitive diagnosis of RCC on the basis of a representative, formalin-fixed, paraffin-embedded tumor specimen accompanied by an associated pathology report collected within 24 months prior to Cycle 1, Day 1 available at the study site that allows determination of PD-L1 expression status (IC) (required prior to randomization)

  The archival specimen must contain adequate viable tumor tissue to establish PD-L1 expression status by a central laboratory prior to randomization.

  The specimen may consist of a tissue block (preferred) or at least 15 unstained, serial sections.

  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 embedded into a single paraffin block should be submitted for evaluation. Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

  If the archival tissue was acquired $>$ 24 months prior to Cycle 1, Day 1, the patient may still be eligible provided the patient is willing to consent to and undergo a pre-treatment core or excisional biopsy of the tumor. If the location of the tumor renders the tumor biopsy medically unsafe, eligibility may be provided with Medical Monitor approval. A local analysis to confirm the diagnosis of RCC is required.
- Measurable disease, as defined by RECIST v1.1
- Age $\geq$ 18 years
- Karnofsky performance status $\geq$ 70
- Ability and capacity to comply with study and follow-up procedures

Appendix 1
Protocol Synopsis (cont.)

- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 28 calendar 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 $\geq$ 2500 cells/μL

  Lymphocyte count $\geq$ 300 cells/μL

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

  Hemoglobin $\geq$ 9.0 g/dL

  AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ ULN, with the following exceptions:

  Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN

  Patients with documented liver or bone metastases: alkaline phosphatase $\leq 5 \times$ 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, unless on a stable dose of warfarin

  Serum albumin $>$ 2.5 g/dL

  Creatinine clearance $\geq$ 30 mL/min (Cockcroft-Gault formula or based on 24-hour urine collection)

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 6 months after the last dose of atezolizumab and bevacizumab or 30 days after the last dose of sunitinib.

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

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

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

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<$ 1% per year during the treatment period and for at least 6 months after the last dose of bevacizumab or 30 days after the last dose of sunitinib. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for the duration of the pregnancy to avoid exposing the embryo.

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

- Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:

  Evaluable or measurable disease outside the CNS

  Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla or spinal cord)

  No history of intracranial or spinal cord hemorrhage

  No evidence of significant vasogenic edema

  No ongoing requirement for corticosteroids as therapy for CNS disease

  No stereotactic radiation within 14 days

  No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to enrollment [or randomization], if all other criteria are met.

Exclusion Criteria

Disease-Specific Exclusions

- Prior treatment with active or experimental systemic agents, including treatment in the neoadjuvant or adjuvant setting. Prior treatment with placebo in adjuvant setting is allowed.
- Radiotherapy for RCC within 14 calendar days prior to Cycle 1, Day 1
- Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated at least 14 days prior to Cycle 1, Day 1.
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)
- Uncontrolled hypercalcemia ($>$ 1.5 mmol/L ionized calcium or calcium $>$ 12 mg/dL) or symptomatic hypercalcemia refractory to bisphosphonate therapy or denosumab

  Patients who are currently receiving bisphosphonate therapy without current hypercalcemia (corrected serum calcium greater than the upper limit of normal) are eligible.
- Malignancies other than RCC within 5 years prior to Cycle 1, Day 1

  Patients with localized low risk prostate cancer (defined as stage $\leq$ T2b, Gleason score $\leq$ 7, and PSA at prostate cancer diagnosis $\leq$ 20 ng/mL) treated with curative intent and without prostate-specific antigen (PSA) recurrence are eligible

  Patients with low risk prostate cancer (defined as Stage T1/T2a, Gleason score $\leq$ 6, and PSA $\leq$ 10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible

  Patients with malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death $<$ 5% at 5 years) are eligible provided they meet all of the following criteria:

  Malignancy treated with expected curative intent (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent)

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

Appendix 1
Protocol Synopsis (cont.)

General Medical Exclusions

- Life expectancy of < 12 weeks
- Current, recent (within 4 weeks of Cycle 1, Day 1), or planned participation in another experimental drug study
- Pregnant and lactating , or intending to become pregnant during the study
- Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- 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 the protocol for a more comprehensive list of autoimmune diseases)

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

  Patients with controlled Type I diabetes mellitus on a stable dose of insulin regimen may be eligible for this study.
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan; however, history of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive test for HIV
- Patients with active or chronic hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening)

  Patients with past/resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. A negative HBV DNA test must be obtained in patients with positive hepatitis B core antibody prior to Cycle 1, Day 1.
- Patients with active hepatitis C

  Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) analysis is negative for HCV RNA.
- Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of infection (including active tuberculosis) within 2 weeks prior to Cycle 1, Day 1
- Received therapeutic oral or intravenous antibiotics within 2 weeks prior to Cycle 1, Day 1

  Patients receiving routine antibiotic prophylaxis (e.g., to prevent chronic obstructive pulmonary disease exacerbation or for dental extraction) are eligible.
- Significant cardiovascular or cerebrovascular disease, such as New York Heart Association cardiac disease (Class II or greater), unstable angina, myocardial infarction or cerebrovascular events within the previous 6 months or unstable arrhythmias within the previous 3 months.

Appendix 1
Protocol Synopsis (cont.)

Patients with known coronary artery disease, arrhythmias, congestive heart failure not meeting the above criteria must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. Baseline evaluation of left ventricular ejection fraction (LVEF) should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease.

Patients with known LVEF < 50%

- Major surgical procedure other than for diagnosis within 21 days prior to Cycle 1, Day 1, or planned procedure or surgery during the study
- Prior allogeneic stem cell or solid organ transplant
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1

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

Exclusion Criteria Related to Medications

- 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 interferon α, interleukin-2) for the treatment of non-malignant conditions within 6 weeks or five half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1
- Any prior use of systemic immunostimulatory agents for the management of metastatic RCC is excluded.
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [anti–TNF] agents) within 2 weeks prior to Cycle 1, Day 1.

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) or physiologic replacement doses (i.e., prednisone 5–7.5 mg/day) for adrenal insufficiency may be enrolled in the study.

  The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for adrenal insufficiency), and mineralocorticoids (e.g., fludrocortisone) is allowed.

Bevacizumab- and Sunitinib-Specific Exclusions

- Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg)

  Anti-hypertensive therapy to maintain a systolic blood pressure < 150 mmHg and/or diastolic blood pressure < 100mmHg is permitted.
- Prior history of hypertensive crisis or hypertensive encephalopathy
- New York Heart Association Class II or greater congestive heart failure
- History of stroke or transient ischemic attack within 6 months prior to Cycle 1, Day 1

Appendix 1
Protocol Synopsis (cont.)

- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Cycle 1, Day 1
- Patients with a baseline ECG demonstrating a QTc $>$ 460 ms
- Evidence of bleeding diathesis or clinically significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (within 10 calendar days prior to Cycle 1, Day 1) use of dipyramidole, ticlopidine, clopidogrel, or cilostazol.
- Prophylactic or therapeutic use of low molecular weight heparin (e.g., enoxaparin), direct thrombin inhibitors, or warfarin are permitted, provided, where appropriate anticoagulation indices are stable. Patients should have been on a stable dose (for therapeutic use) for at least 2 weeks (or until reaching steady state level of the drug) prior to the first study treatment
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 calendar days prior to the first dose of bevacizumab
- History of abdominal or tracheoesophageal fistula or gastrointestinal perforation within 6 months prior to Cycle 1, Day 1
- Clinical signs or symptoms of gastrointestinal obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding
- Evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Proteinuria, as demonstrated by urine dipstick or $>$ 1.0 g of protein in a 24-hour urine collection

  All patients with $\geq$ 2+ protein on dipstick urinalysis at baseline must undergo a 24-hour urine collection for protein.

Length of Study

On the basis of accrual projections and projected median OS for each treatment arm, the final analysis of OS is projected to occur at Month 63 from the time the first patient is randomized.

End of Study

The end of study will occur when the number of deaths required for the final analysis of OS has been observed. On the basis of accrual projections and projected median OS for each treatment arm, the final analysis of OS is projected to occur at Month 63 from the time the first patient is randomized.

Outcome Measures

Efficacy Outcome Measures

The co-primary efficacy outcome measures are:

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator from tumor assessments based on RECIST v1.1, or death from any cause and
- OS, defined as the time from randomization to death due to any cause

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

- PFS based on IRC assessment of radiographic progression per RECIST v1.1
- ORR, defined as the proportion of patients with an objective response (either complete response or partial response, confirmation not required) as determined by investigator per RECIST v1.1

Appendix 1
Protocol Synopsis (cont.)

- Duration of response (DOR), defined as the time from the first documented response to documented disease progression as determined by the investigator per RECIST v1.1 or death due to any cause, whichever occurs first
- ORR and DOR based on IRC assessment per RECIST v1.1
- PFS, ORR, and DOR based on investigator assessment per modified RECIST criteria
- Change from baseline in symptom interference (from MDASI Part II)

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of all adverse events, including Grade ≥ 3 laboratory toxicities (grading per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0; laboratory toxicities based on local laboratory assessments), during first-line treatment
- Incidence of ATA response to atezolizumab and potential correlation with pharmacokinetics, safety, and efficacy parameters

Pharmacokinetic Outcome Measures

The pharmacokinetic outcome measures for this study are as follows:

- Maximum atezolizumab serum concentration (C_{max}) after infusion on Cycle 1, Day 1
- Minimum atezolizumab serum concentration (C_{min}) prior to the infusion on Day 1 of Cycles 1, 2, 4, 8 and every eight cycles thereafter; Day 22 of Cycles 1, 2, and 4; and at study termination
- Bevacizumab C_{max} after infusion on Day 1 of Cycles 1 and 2
- Bevacizumab C_{min} prior to the infusion on Day 1 of Cycles 1 and 2 and at study termination

Patient-Reported Outcome Measures

The other PRO outcome measures for this study are as follows:

- Change from baseline in symptom severity as measured by the MDASI and BFI
- Change from baseline in treatment side effects subscale (from FKSI-19)

In addition, health status will be collected the EuroQoL 5 Dimensions (EQ-5D) questionnaire to derive utilizes for health economic modeling.

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Status of PD-L1, immune-, angiogenic-, and RCC-related and other exploratory biomarkers in archival and/or freshly obtained tumor tissues and blood collected before, during, or after treatment with atezolizumab+bevacizumab or sunitinib or at progression
- PFS and ORR in patients with tumor Fuhrman Grade 4 or sarcomatoid histology (defined by investigator-assessed conventional histopathology)
- Status of tumor-infiltrating immune cells and biomarkers in biopsy specimens and blood collected at the first evidence of radiographic disease progression

<u>Investigational Medicinal Products</u>

Test Product (Investigational Drugs)

Atezolizumab+bevacizumab will be dosed in 6-week cycles. Atezolizumab will be administered intravenously at a fixed dose of 1200 mg on Days 1 and 22 of each 42-day cycle. Bevacizumab will be administered intravenously at 15 mg/kg on Days 1 and 22 of each 42-day cycle.

Appendix 1
Protocol Synopsis (cont.)

Comparator

Sunitinib will be administered in 6-week cycles at 50 mg/day given orally for 4 weeks, followed by 2 weeks of rest.

Statistical Methods

Primary Analysis

The co-primary efficacy endpoints are investigator-assessed PFS per RECIST v1.1 and OS. Because type I error will be controlled accounting for two co-primary endpoints, the study will be considered a positive study if statistical significance is achieved for either of the co-primary endpoints.

PFS will be analyzed in the PD-L1–selected population and OS will be analyzed first in the ITT population; additional analyses of OS will be performed in a hierarchical fashion.

PFS is defined as the time from randomization to disease progression, as determined by the investigator per RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. Data for patients with no post-baseline tumor assessments will be censored at the randomization date + 1 day.

For United States registrational purposes, the co-primary efficacy endpoint of PFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits.

OS is defined as the time from randomization to death due to any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization + 1 day.

The following analyses will be performed for both PFS endpoints described above and OS. PFS and OS will be compared between treatment arms with use of the stratified log-rank test. The HR will be estimated using a stratified Cox proportional hazards model. The 95% CI for the HR will be provided. The stratification factors will be the same as the randomization stratification factors: presence of liver metastasis (yes/no); tumor PD-L1 status (IC0 vs. IC1/2/3); and the MSKCC (Motzer) score (0, 1–2, ≥ 3). The stratification factors will be obtained from the IxRS at the time of randomization. Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate the median PFS and OS for each treatment arm, and Kaplan-Meier curves will be produced. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and OS for each treatment arm.

The following analyses will be performed for both PFS endpoints described above and (as applicable) for OS:

- Analyses described in the protocol for landmark timepoints
- Analyses described in the protocol for subgroups
- Secondary endpoint of PFS by IRC assessment, PD-L1–selected population and ITT population, based on RECIST v1.1
- Secondary endpoint of PFS by investigator assessment in the ITT population, based on RECIST v1.1

Patient-Reported Outcome Analysis

MDASI, and BFI, and FKSI-19

Scoring for the MDASI and BFI questionnaires will be based on their corresponding user manuals. For MDASI and BFI scales with more than 50% of the constituent items completed, a prorated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered missing.

The impact of symptoms on patients' functioning will be compared between treatment arms as a change from baseline on the interference items in the MDASI Part II.

The severity of symptoms captured in the MDASI and the BFI will be summarized using descriptive analyses including summary statistics and change from baseline at each assessment by treatment arm.

Determination of Sample Size

This study will randomize approximately 900 patients, including a minimum of approximately 351 patients with a PD-L1 IHC IC score of 1/2/3.

Type I Error Control

The type I error (α) for this study is 0.05 (two-sided). There are two co-primary efficacy endpoints for this study: PFS by investigator assessment per RECIST v1.1 and OS. To control the overall type I error rate at $\alpha = 0.05$ (two-sided) while accounting for two co-primary endpoints, α will be split between PFS ($\alpha = 0.04$) and OS ($\alpha = 0.01$). Because type I error will be controlled accounting for two co-primary endpoints, the study will be considered a positive study if statistical significance is achieved for either of the co-primary endpoints.

Formal treatment comparisons will be performed in a hierarchical fashion in which α may be recycled as follows:

1. PFS in the PD-L1–selected population will be evaluated at $\alpha = 0.04$ (two-sided).
2. If PFS results in the PD-L1–selected population are statistically significant at $\alpha = 0.04$, then $\alpha = 0.04$ will be recycled to OS in the ITT population, and OS in the ITT population will be evaluated at $\alpha = 0.05$ (two-sided). If PFS results in the PD-L1–selected population are not statistically significant at $\alpha = 0.04$, then no recycling of α will occur, and OS in the ITT population will be evaluated at $\alpha = 0.01$ (two-sided).
3. OS will be compared between treatment arms in a hierarchical fashion as follows. If OS results in the ITT population are statistically significant at the appropriate α level, then OS in the PD-L1–selected population will be evaluated at same α-level as for OS in the ITT population. If OS results in the ITT population are not statistically significant, formal treatment comparison of OS in the PD-L1–selected population will not be performed.

Interim analyses of OS and the final analysis of OS will be based on the α allocated to the comparison of OS, as described above. Statistical significance at interim analyses of OS will be evaluated.

Co-Primary Endpoint: Progression-Free Survival in the PD-L1–Selected Population

The analysis of the co-primary endpoint of PFS will take place when approximately 228 PFS events in the PD-L1–selected population (65% of the estimated 351 PD-L1–population) as defined for the primary analysis of PFS have occurred based on the following assumptions:

- Two-sided, stratified log-rank test
- $\alpha = 0.04$ (two-sided)
- Approximately 88% power
- Median PFS for the sunitinib arm of 11 months and estimated median PFS in the atezolizumab + bevacizumab arm of 17 months (corresponding to HR of 0.65)
- 5% annual loss to follow-up for PFS
- No interim analysis

Accrual is projected to occur over 20months, assuming a ramp-up period of 9 months.

On the basis of these assumptions, the required number of PFS events in the PD-L1–selected population is projected to occur at Month 34 from the time the first patient is randomized. Also on the basis of these assumptions, it is projected that an observed HR of 0.76 or lower will result in a statistically significant difference between treatment arms (i.e., an HR of 0.76 will be the minimally detectable difference for the analysis; this corresponds to an improvement of

3.5 months in median PFS from 11 months in the sunitinib arm to 14.5 months in the atezolizumab+bevacizumab arm).

Co-Primary Endpoint: Overall Survival in the ITT Population

The final analysis of the co-primary endpoint of OS will take place at the later of the timepoints when the required number of events has occurred in the PD-L1–selected population and in the ITT population, where the required number of events is as follows:

- 639 OS events in the ITT population (71% of the estimated 900 patients)
- 246 OS events in the PD-L1–selected population (70% of the estimated 351 patients)

The number of events required for the final OS analysis in these populations is based on the following assumptions:

- Two-sided, stratified log-rank test
- $\alpha = 0.01$ (two-sided)
- 1% annual loss to follow-up for OS
- For the ITT population:

  85% power

  Median OS in the control arm of 24 months

  Estimated median OS in the atezolizumab+bevacizumab arm of 32 months (an increase of 8 months, corresponding to an HR of 0.75
- For the PD-L1–selected population:

  53% power

  Median OS in the control arm of 24 months

  Estimated median OS in the atezolizumab+bevacizumab arm of 33.8 months (an increase of 9.8 months, corresponding to an HR of 0.71)

On the basis of these assumptions, the required number of OS events for the final analysis of OS in both the PD-L1–selected population and the ITT population is projected to occur at Month 63 from the time the first patient is randomized.

At the final OS analysis, on the basis of these assumptions, it is projected that an observed OS HR of 0.83 or lower in the ITT population will result in a statistically significant difference between treatment arms (i.e., the minimally detectable difference at the analysis; this corresponds to an improvement of 4.9 months in median OS, from 24 months in the control arm to 28.9 months in the atezolizumab+bevacizumab arm).

Also at the final OS analysis, on the basis of these assumptions, it is projected that an observed OS HR of 0.72 or lower in the PD-L1–selected population will result in a statistically significant difference between treatment arms (i.e., an HR of 0.72 will be the minimally detectable difference at the analysis; this corresponds to an improvement of 9.5 months in median OS, from 24 months in the control arm to 33.5 months in the atezolizumab+bevacizumab arm).

Interim Analyses

Progression-Free Survival

There are no planned interim analyses of the co-primary endpoint of PFS.

Overall Survival

A total of four analyses of OS will be performed, including three interim analyses and one final analysis. The α level for OS testing is 0.05 given that the co-primary endpoint of PFS was met in the study. The boundary for statistical significance at each interim analysis and the final analysis will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming function to maintain the overall type 1 error rate at 0.05 level. The O'Brien-Fleming (OBF) boundary for statistical significance is provided. The OS endpoint will be considered

positive in the ITT population if statistical significance is achieved for any of the three OS interim analyses or the final analysis.

The first interim analysis of OS was performed at the time of the PFS primary analysis. A total of 264 deaths (29% of 915 patients in the ITT population) was observed at the first interim analysis of OS, which corresponds to 41% of the events information required for the final analysis of OS in the ITT population. The first OS interim analysis did not pass the OBF boundary at 0.0009.

The second interim analysis of OS will be time driven and will occur approximately 11 months from the clinical cutoff of the first OS interim. [redacted] *It is projected that at the second interim OS analysis, 377 deaths (41% of 915 patients in the ITT population) will occur, corresponding to approximately 59% of the events required for the final analysis of OS in the ITT population. Statistical significance will be declared if $p \leq 0.0067$ when 377 deaths have occurred at the time of the second OS interim analysis.*

The third interim analysis of OS is event driven and remains the same as the original plan (Protocol WO29637, Version 6). The third interim analysis of OS will be performed when approximately 518 deaths (57% of 915 patients in the ITT population) have occurred, which corresponds to approximately 81% of the events information required for the final analysis of OS in the ITT population. Statistical significance will be declared if $p \leq 0.0233$ when 518 deaths have occurred at the time of the third OS interim analysis.

The final analysis of OS is event driven and remains the same as the original plan (Protocol WO29637, Version 6). The final analysis of OS will be performed when 639 deaths (70% of 915 patients in the ITT population) have occurred. Statistical significance will be declared if $p \leq 0.0420$ when 639 deaths have occurred at the time of the final OS analysis.

The interim and final analyses of OS, including analyses in both the ITT and PD-L1–selected populations, will follow the testing hierarchy described in the protocol. Specifically, for each OS interim and final analysis, OS in the PD-L1–selected population will be evaluated for statistical significance only when the OS results in the ITT population are statistically significant at the OBF boundary. The actual OBF boundary will be calculated at time of analysis based on actual number of events observed. If OS results in the ITT population are not statistically significant, formal testing of OS in the PD-L1–selected population will not be performed.

All efficacy analyses, including the interim analyses of OS, will be performed by the Sponsor.

Optional Interim Analysis

In addition to the planned interim analyses of OS, one additional interim analysis of OS may be performed at the discretion of the Sponsor. The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the Statistical Analysis Plan (SAP), and the SAP will be submitted to relevant health authorities prior to the conduct of the interim analysis.

Appendix 2
Schedule of Assessments

Assessment Window (Days)[a]	Screening[b] Days −28 to −1	Atezolizumab + Bevacizumab OR Sunitinib			End of Treatment ≤30 Days after Last Dose of Study Treatment[d]	Survival Follow-Up
		Cycle ≥1 Day 1	Cycle ≥1 Day 22[c]	Day 1, Every Two Cycles		
Signed Informed Consent Form(s)[b]	x					
Review of eligibility criteria	x					
Medical, surgical, and cancer histories, including demographic information[e]	x					x Cancer treatment
HBV *and* HCV serology	x					
HIV testing[f]	x					
Concomitant medications[g]	x	x	x		x	
Tumor assessment[h]	x	At 12 weeks ±5 business days, then every 6 weeks ±5 business days thereafter, including Week 78 following randomization. After 78 weeks from randomization, patients will undergo tumor assessments every 12 weeks ±5 business days until treatment discontinuation.				
Complete physical examination[i]	x				x	
Limited physical examination[j]		x[j, k]				
Karnofsky performance status	x	x[k]			x	

Appendix 2
Schedule of Assessments (cont.)

Assessment Window (Days) [a]	Screening [b] Days −28 to −1	Atezolizumab + Bevacizumab OR Sunitinib			End of Treatment ≤30 Days after Last Dose of Study Treatment [d]	Survival Follow-Up
		Cycle ≥1 Day 1	Cycle ≥1 Day 22 [c]	Day 1, Every Two Cycles		
Vital signs [l]	x	x	x		x	
12-lead electrocardiogram and/or LVEF evaluation [m]	x		x		x	
Weight	x	x [n]			x	
Height	x					
Hematology [o]	x	x [k]	x		x	
Serum chemistry [p]	x	x [k]	x		x	
Coagulation panel (aPTT, INR)	x				x	
Urine dipstick (+24-hr urine if dipstick protein ≥2+) [q]	x	x			x	
Serum pregnancy test [r]	x [r]			x [r]		
TSH, free T3, free T4 [s]	x			x [s]	x	
Ferritin [s]	x			x	x	
C-reactive protein and auto-antibody testing [t]	x			x [u]	x	
Serum sample for ATA assessment [v]		x [v]			x	

Appendix 2
Schedule of Assessments (cont.)

Assessment Window (Days) [a]	Screening [b] Days −28 to −1	Atezolizumab + Bevacizumab OR Sunitinib			End of Treatment ≤30 Days after Last Dose of Study Treatment [d]	Survival Follow-Up
		Cycle ≥1 Day 1	Cycle ≥1 Day 22 [c]	Day 1, Every Two Cycles		
Atezolizumab PK serum sample [w]		x	x		x	
Bevacizumab PK serum sample [w]		x				
TBNK blood sample [x]		x				
Plasma, serum, and whole blood for biomarkers [y]		x	x		x	
DNA for RCR (optional) [z]		x				
Adverse events		x	x		x	x [d]
Atezolizumab infusion [aa]		x [z]	x			
Bevacizumab infusion [aa]		x [z]	x			
Sunitinib dispensing [c]		x [c]				
Tumor tissue specimen or at least 15 unstained slides [bb]	x					
Tumor tissue at progression [cc]						
MDASI [dd]		x	x		x	x

Appendix 2
Schedule of Assessments (cont.)

Assessment Window (Days) [a]	Screening [b] Days −28 to −1	Atezolizumab + Bevacizumab OR Sunitinib			End of Treatment ≤30 Days after Last Dose of Study Treatment [d]	Survival Follow-Up
		Cycle ≥1 Day 1	Cycle ≥1 Day 22 [c]	Day 1, Every Two Cycles		
BFI [dd]		x	x		x	x
EQ-5D [dd]		x	x		x	x
FKSI-19 [dd]		x	x		x	x
Anti-neoplastic agent use [ee]						x

ATA = anti–therapeutic antibody; BFI = Brief Fatigue Inventory; C = cycle; CA = cancer antigen; CMV = cytomegalovirus; CRP = C-reactive protein; CT = computed tomography; ePRO = electronic patient-reported outcome; EQ-5D = EuroQoL 5 Dimensions; FKSI-19 = Functional Assessment of Cancer Therapy Kidney Symptom Index-19; irRC = immune-related response criteria; MDASI = M.D. Anderson Symptom Inventory; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic; PSA = prostate-specific antigen; RCR = Roche Clinical Repository; RECIST = Response Evaluation Criteria in Solid Tumors; TBNK = T, B, and natural killer; TSH = thyroid-stimulating hormone.

Note: Assessments scheduled on the days of study treatment should be performed before the infusion or dosing unless otherwise noted. Each cycle is 42 days in length.

[a] The first dosing date (Cycle 1, Day 1) should occur within 5 $business$ days from randomization. All visits and infusions may be administered with a window of ± 3 days.

[b] Written informed consent is required for performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to randomization may be used for screening assessments, rather than repeating such tests. Screening local laboratory assessments obtained ≤ 96 hours prior to Cycle 1, Day 1 do not have to be repeated for Cycle 1. Test results should be reviewed prior to administration of study treatment. If re-screening is required, then then HBV, HCV, HIV, CRP, and autoantibody testing from initial screening may be acceptable for screening assessment if < 60 days from Cycle 1, Day 1.

[c] Sunitinib is taken by mouth once a day on Days 1–28 of each cycle. For patients taking sunitinib, the Day 22 visits are required for the first year of the study only.

Appendix 2
Schedule of Assessments (cont.)

[d] Patients will be asked to return to the clinic ≤ 30 days after the last dose of study treatment for an end of treatment visit. After the last administration of study treatment, serious adverse events (see [Section 5.2.2 of the protocol] and adverse events of special interest [see Section 5.2.3 of the protocol], regardless of attribution, will be recorded until the end of the special reporting period (defined as 90 days after the last dose of atezolizumab or bevacizumab or 30 days after the last dose of sunitinib). After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6 of the protocol). All other adverse events will be recorded until 30 days after the last dose of atezolizumab, bevacizumab or sunitinib, or until initiation of another anti-cancer therapy, whichever occurs first. Patients will be contacted at 30 days after the last dose of study treatment to determine if any new adverse events have occurred. Ongoing adverse events thought to be related to study treatment will be followed until resolution of the adverse event, until an alternate cause has been identified, the patient is lost to follow up, the patient withdraws consent, or it is determined that the study treatment or participation is not the cause of the adverse event. Scans performed within 6 weeks prior to the end of treatment visit do not need to be repeated. The Sponsor should be notified if the investigator feels any serious adverse event occurring after the end of the adverse event reporting period is related to prior study drug treatment.

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

[f] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical trial.

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

[h] All measurable and evaluable lesions should be assessed and documented using physical examination and image-based evaluation. Screening assessments should include CT scans with oral and intravenous contrast of the chest, abdomen, and pelvis, and a brain scan (CT or MRI). Bone scans and CT scan of neck should also be performed if clinically indicated. CT or MRI scans must be used to measure lesions selected for response assessment. Disease status will be assessed using RECIST v1.1 and modified RECIST criteria (see Appendix 3 and Appendix 4 of the protocol). The same radiographic procedure used to define measurable lesions at baseline must be used throughout the study for each patient. Results must be reviewed by the investigator before dosing at the next cycle. Tumor assessments will occur at baseline, at 12 weeks ± 5 business days, then every 6 weeks ± 5 business days thereafter including Week 78 following randomization. After 78 weeks from randomization, patients will undergo tumor assessments every 12 weeks ± 5 business days until treatment discontinuation, or as clinically indicated. Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments as if they were on the protocol schedule until the patient dies, experiences disease progression per RECIST v1.1 *and modified RECIST*, withdraws consent, or until the study closes, whichever occurs first. For patients who will be permitted to continue study treatment beyond radiographic disease progression per RECIST v1.1, tumor assessment will be monitored with a follow-up scan at the next scheduled tumor assessment when the scan frequency is every 6 weeks. If the scan frequency is every 12 weeks (see above), the follow-up scan must be performed at every 12 weeks (± 5 business days), or earlier if clinically indicated, until loss of clinical benefit described in Section 4.6.2 of the protocol or treatment discontinuation, whichever is later.

Appendix 2
Schedule of Assessments (cont.)

[i] A complete physical examination at screening and the end of treatment visit should include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Changes in abnormalities noted at baseline should be recorded at the end of treatment visit. New or worsened abnormalities should be recorded as adverse events if appropriate.

[j] A limited physical examination will be performed at other visits to assess changes from baseline abnormalities and any new abnormalities and to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as adverse events if appropriate.

[k] Karnofsky performance status, limited physical examination may be obtained ≤ 96 hours prior to Day 1 of each cycle. Local laboratory safety assessments may be obtained $\leq$ 96 hours prior to Day 1 and 22 of each cycle.

[l] Vital signs include heart rate, respiratory rate, blood pressures, and temperature. For the first atezolizumab infusion, the patient's vital signs should be determined within 60 minutes before, during (every 15 [$\pm$ 5] minutes), and 30 ($\pm$ 10) minutes and 2 hours ($\pm$ 15 minutes) after the infusion. For subsequent atezolizumab infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated, and 1 hour ($\pm$ 10 minutes) after the infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. For patients randomized to Arm A, observation should be for at least 2 hours after the first administration of the combination and for at least 1 hour for subsequent infusions.

[m] Twelve-lead ECGs are required as part of the screening assessment and at the end of treatment visit. ECGs will be reviewed by the investigator to determine patient eligibility at screening. Baseline evaluation of LVEF should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease. In countries where additional cardiac monitoring is considered standard (e.g., France), additional cardiac monitoring including a 1) baseline evaluation of LVEF in those patients with cardiac risk factors and/or an abnormal baseline ECG and 2) for patients randomized to the sunitinib arm, a surveillance ECG on Day 22 of Cycle 1 will be required.

[n] The dose of bevacizumab will be based on the patient's weight (in kilograms) measured $\leq$ 14 days prior to baseline (Cycle 1, Day 1) and will remain the same throughout the study unless there is a weight change of $>$ 10% from baseline.

[o] 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.

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

[q] Urine dipstick includes specific gravity, pH, glucose, protein, ketones, and blood. Urine dipstick and 24-hour urine collection may be performed up to 7 days before Cycle 1, Day 1. Screening urine tests performed up to 7 days before Cycle 1, Day 1 do not need to be repeated for Cycle 1. Spot urine protein/creatinine ratio will not be used for this study.

Appendix 2
Schedule of Assessments (cont.)

[r] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to Cycle 1, Day 1, every two cycles during the study treatment, and as clinically indicated thereafter. In countries (e.g., United Kingdom) where urine pregnancy testing is considered a standard, urine pregnancy testing may substitute for serum pregnancy testing.

[s] TSH, free T3, free T4, and serum ferritin, should be evaluated every two cycles (starting at Cycle 2).

[t] Includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody. If rescreening is required, auto-antibody testing may be performed within 60 days of Cycle 1, Day 1.

[u] C-reactive protein and autoantibodies On Day 1 of Cycle 3 and every other cycle thereafter.

[v] See Appendix 2 of the protocol for details of the ATA sampling schedule.

[w] See Appendix 2 of the protocol for details of the PK sampling schedule.

[x] See Appendix 2 of the protocol for details of the TBNK collection schedule.

[y] See Appendix 2 of the protocol for details of the pharmacodynamic sampling schedule.

[z] This is an optional sample and requires the patient to sign an RCR consent. If sample is not taken during the Cycle 1, Day 1 visit, then the sample may be obtained at any other visit.

[aa] The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. The initial dose of bevacizumab will be delivered over 90 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (± 10) minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. For patients randomized to Arm A, atezolizumab will be administered first followed by bevacizumab, with a minimum of 5 minutes between dosing. In the absence of unacceptable toxicity, patients may continue study treatment until there is evidence of disease progression or lack of clinical benefit.

[bb] Tumor tissue (archival < 24 months or fresh) specimen may be obtained from prior tumor excision or biopsy performed during the course of the patient's illness.

[cc] Tumor specimens are required at the time of disease progression per RECIST v1.1 (for patients *in both treatment arms*), preferably of a progression metastatic lesion, unless the location of the tumor renders the biopsy clinically unsafe or infeasible, or is prohibited by institution or country. Optional tumor biopsies may be obtained at other timepoints at the investigator's discretion.

[dd] The ePRO questionnaires (MDASI, BFI, FSKI-19, and EQ-5D) will be completed by the patients on Days 1 and 22 of each cycle and at the end-of-treatment visit, and will be completed by patients at 6, 12, 24, and 36 weeks after the end-of-treatment visit. In addition, the BFI ePRO questionnaire will be collected weekly during the first 12 weeks. Assessments on days when the patient does not come to the clinic (e.g., Days 8, 15, 29, 36) will be completed by the patient at home. All ePRO questionnaires while on study treatments are required to be administered prior to administration of study treatment and/or prior to any other study assessment(s) to ensure that the validity of the instrument is not compromised and to ensure that data quality meets regulatory requirements.

Appendix 2
Schedule of Assessments (cont.)

[ee] During survival follow-up, the following information regarding all subsequent anti-neoplastic agents upon treatment discontinuation will be collected: line of therapy, date of first dose of agent, date of last dose of agent (or if ongoing), patient's best response, and date of disease progression.

Appendix 2
Schedule of Assessments (cont.)

Anti-Therapeutic Antibody, TBNK, Biomarker, and Pharmacokinetic Sampling Schedule		
Study Visit	Time	Sample
Cycle 1, Day 1	Predose	Atezolizumab ATA Bevacizumab ATA Atezolizumab pharmacokinetics Bevacizumab pharmacokinetics TBNK Biomarkers [a]
	30 (±10) minutes after end of infusion [c]	Atezolizumab pharmacokinetics Bevacizumab pharmacokinetics
Cycle 1, Day 22	Predose	Biomarkers [b] Atezolizumab pharmacokinetics
Cycles 2, 3, 4, and 8, and every eight cycles thereafter Day 1 (±3 days)	Predose	Atezolizumab ATA (Cycles 2, 4, and 8, and every eight cycles thereafter) Bevacizumab ATA (Cycle 3 only) Atezolizumab pharmacokinetics (Cycles 2, 4, and 8 and every eight cycles thereafter) Bevacizumab pharmacokinetics (Cycle 3 only) Biomarkers [b] (Cycle 2 only)
	30 (± 10) minutes after end of infusion	Bevacizumab pharmacokinetics (Cycle 3 only)
Cycles 2 and 4, Day 22 (±3 days)	Predose	Atezolizumab pharmacokinetics Biomarker (Cycle 2 only) [b]
At time of fresh biopsy (during treatment or at progression)		TBNK Biomarkers [b, d]
End of treatment visit	At visit	Atezolizumab ATA Atezolizumab pharmacokinetics Biomarkers [b] Bevacizumab ATA Bevacizumab pharmacokinetics
120 (±30) days after last dose of atezolizumab [e]	At visit	Atezolizumab ATA Atezolizumab pharmacokinetics Bevacizumab ATA Bevacizumab pharmacokinetics

Appendix 2
Schedule of Assessments (cont.)

ATA = anti-therapeutic antibody; TBNK = T, B, and natural killer.

Note: Plasma, serum, and whole blood collected for pharmacodynamic biomarkers.

[a] Plasma, serum, and whole blood collected for pharmacodynamic biomarkers.

[b] Plasma and serum for biomarkers.

[c] For patients receiving both atezolizumab and bevacizumab (Arm A only), both postdose pharmacokinetic samples (for atezolizumab and bevacizumab) are to be drawn 30 minutes after the second (bevacizumab) infusion.

[d] Biomarker samples at the time of biopsy do not have to be collected if the biopsy visit occurs $\leq$3 days before or after another protocol-defined biomarker sample collection timepoint.

[e] Not required if the patient is lost to follow-up, withdraws request, or the study closes.

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment. In this protocol, patients will be permitted to continue study treatment even after modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria for progressive disease are met if the risk/benefit ratio is judged to be favorable.

Modified RECIST is derived from RECIST, Version 1.1 conventions [1, 2, 3] and immune-related response criteria [3, 4, 5] (irRC).

Modified RECIST and RECIST, Version 1.1: Summary of Changes

	RECIST v1.1	Modified RECIST
New lesions after baseline	Define progression.	New measurable lesions are added into the total tumor burden and followed.
Non-target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of ≥ 20% increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease; may be confirmed by a consecutive assessment ≥ 4 weeks from the date first documented

RECIST = Response Evaluation Criteria in Solid Tumors.

1 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1) Eur J Cancer 2009;45:228–47.

2 Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-L1 antibody in cancer. N Engl J Med 2012;366:2443–54.

3 Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immunetherapy activity in solid tumors: immune-related response criteria Clin Can Res 2009;15:7412–20.

4 Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab. J Immunother Can 2014;2:17.

5 Nishino M, Giobbie-Hurder A, Gargano M et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Can Res 2013;19:3936–43.

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors (cont.)

Definitions of Measurable/non-Measurable Lesions

All measurable and non-measurable lesions should be assessed at screening and at the protocol-specified tumor assessment timepoints. Additional assessments may be performed, as clinically indicated for suspicion of progression. The investigator will evaluate response to treatment with use of modified RECIST.

Measurable Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)

10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

Non-Measurable Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with short axis $\geq$ 10 but $<$ 15 mm), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions

Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be

considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment

Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Tumor Response Evaluation

Definitions of Target/Non-Target Lesions

Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is $>$ 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance, the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention because they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above,

pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

Lesions irradiated within 3 weeks prior to Cycle 1, Day 1 may not be counted as target lesions.

Non-Target Lesions

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required.

It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

After baseline, changes in non-target lesions will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions) and will not be used to assess progressive disease.

Calculation of Sum of the Diameters

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumor burden.

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors (cont.)

Sum of the Diameters at Tumor Assessment: For every on-study tumor assessment collected per protocol or as clinically indicated, the sum of the diameters at tumor assessment will be calculated using tumor imaging scans. All target lesions and all new measurable lesions that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment with use of modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

Response Criteria
Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.

Note: The appearance of new measurable lesions is factored into the overall tumor burden but *does not automatically qualify as progressive disease* until the sum of the diameters increases by $\geq 20\%$ when compared with the sum of the diameters at nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the diameters while in the study.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and all new measurable lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Impact of New Lesions on Modified RECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumor response.

Evaluation of Best Overall Response with Use of Modified RECIST
Timepoint Response

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors (cont.)

Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors (cont.)

Table 1 Modified RECIST Timepoint Response Definitions

% Change in Sum of the Diameters (Including Measurable New Lesions When Present)	Target Lesion Definition	Non-Target Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Overall Modified RECIST Timepoint Response
-100% [a]	CR	CR	No	No	CR
-100% [a]	CR	Non-CR or not all evaluated	No	No	PR
$\leq -30\%$	PR	Any	Yes or No	Yes or No	PR
$> -30\%$ to $< +20\%$	SD	Any	Yes or No	Yes or No	SD
Not all evaluated	Not evaluated	Any	Yes or No	Yes or No	NE
$\geq \pm 20\%$	PD	Any	Yes or No	Yes or No	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met because a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm in order to meet the definition of CR.

Best Overall Response: All Timepoints

The best overall response is determined once all the data for the patient are known.

The best overall response according to modified RECIST is interpreted as described below:

CR: Complete disappearance of all tumor lesions (target and non-target) and no new measurable or unmeasurable lesions, confirmed by a consecutive assessment ≥ 4 weeks from the date first documented. All lymph nodes short axes must be < 10 mm.

PR: Decrease in the sum of the diameters of all target and all new measurable lesions $\geq 30\%$ relative to baseline, in the absence of CR, confirmed by a consecutive assessment ≥ 4 weeks from the date first documented.

SD: Criteria for CR, PR, and PD are not met.

Appendix 3
Modified Response Evaluation Criteria in Solid Tumors (cont.)

PD: Increase in the sum of the diameters of all target and all new measurable lesions ≥ 20% relative to the nadir, which may be confirmed by a consecutive assessment ≥ 4 weeks from the date first documented as follows:

> The confirmatory assessment shows an additional measurable increase in tumor burden as measured by the sum of the diameters of all target and all new measurable lesions.

This protocol allows patients to continue to receive study treatment even after confirmed radiographic PD per modified RECIST and patients may achieve a best overall response of PR or CR based on tumor regression achieved at any time prior to study treatment discontinuation.