Official Title: **A Phase II, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study of MOXR0916 in Combination With Atezolizumab Versus Atezolizumab Alone in Patients With Untreated Locally Advanced or Metastatic Urothelial Carcinoma Who Are Ineligible for Cisplatin-Based Therapy**

NCT Number: NCT03029832

Document Date: Protocol Version 3: 29 Sep 2017

PROTOCOL

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF MOXR0916 IN COMBINATION WITH ATEZOLIZUMAB VERSUS ATEZOLIZUMAB ALONE IN PATIENTS WITH UNTREATED LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA WHO ARE INELIGIBLE FOR CISPLATIN-BASED THERAPY**
PROTOCOL NUMBER:	GO39590/ NCT03029832
VERSION NUMBER:	3
EUDRACT NUMBER:	2016-004165-58
IND NUMBER:	132240
TEST PRODUCTS:	MOXR0916 (RO7021608) MPDL3280A (RO5541267)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 14 October 2016
DATES AMENDED:	Version 2: 8 December 2016 Version 3: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	29-Sep-2017 15:06:33

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Protocol GO39590 has been amended to reflect the Sponsor's decision to halt accrual due to enrollment challenges in the context of overall clinical development considerations for MOXR0916. As only 5 patients were enrolled, this trial will not meet its scientific objectives. Hence, study procedures that are not required for safety management or assessment of clinical benefit will be streamlined or modified as follows to minimize burden to currently enrolled patients:

- The study blinding will not be maintained, and placebo infusions will not be administered. Patients assigned to placebo may continue study treatment with atezolizumab alone. Patients assigned to the MOXR0916 arm may continue study treatment with the combination of atezolizumab and MOXR0916 or with atezolizumab alone based on a discussion of benefit and risk with the treating investigator (Sections 3.1.1, 4.2, 4.3, and Appendix 1).
- Given that enrollment has been prematurely halted and the study will no longer be blinded, the Internal Monitoring Committee may recommend modification or suspension of its activities and modify its charter accordingly (Section 3.1.2).
- The imaging modality (e.g., CT vs. MRI scan, contrast-enhanced vs. non-contrast) and the frequency of tumor assessments will be determined by the investigator based on the patient's disease characteristics and local institutional standards (Section 4.5.5 and Appendix 1). As such, the requirement that patients with contrast allergy undergo non-contrast CT scans or MRI scans rather than receive corticosteroid premedication for contrast-enhanced CT imaging has been removed (Section 4.4.3).
- Follow-up tumor assessments for patients who discontinue study treatment for reasons other than disease progression are no longer required (Section 4.5.5 and Appendix 1).
- Data to support response assessment per immune-modified RECIST will not be captured in eCRFs (Section 4.5.5).
- Blood samples for whole genome sequencing will not be collected (Appendix 1).
- Autoantibody testing will not be performed (Appendix 1).
- Blood samples for biomarker (plasma, serum, PBMC), pharmacokinetic (serum), or immunogenicity/anti-therapeutic antibody (serum) evaluation will not be collected (Section 4.5.6.2).
- Patient-reported outcomes (MDASI and EQ-5D-5L) will not be collected (Section 4.5 and Appendix 1).
- Optional biopsies should not be performed (Section 3.1.1 and Appendix 1).
- Survival and anti-cancer therapy follow-up will not be performed (Section 4.6.2 and Appendix 1).

In addition, the protocol has been amended to incorporate safety updates and revised

toxicity management guidelines, in alignment with recent Dear Investigator Letters (April 2017, June 2017) and the annual update to the Atezolizumab Investigator's Brochure (Version 10):

- Guidance on the management of hypophysitis has been included (Section 5.1.5, Table 9).
- Guidance on the management of immune-related myocarditis has been added (Section 5.1.5, Table 10).

In addition, the following changes have been made:

- The Sponsor's discretion in granting exceptions to post-trial access conditions has been clarified (Section 4.3.4).
- The reporting of the term "sudden death" has been updated to also require the presumed cause of death (Section 5.3.5.8).
- Event reporting for hospitalization has been clarified (Section 5.3.5.11).
- The process for reviewing and handling protocol deviations has been updated per internal standard operating procedures (Section 9.2).

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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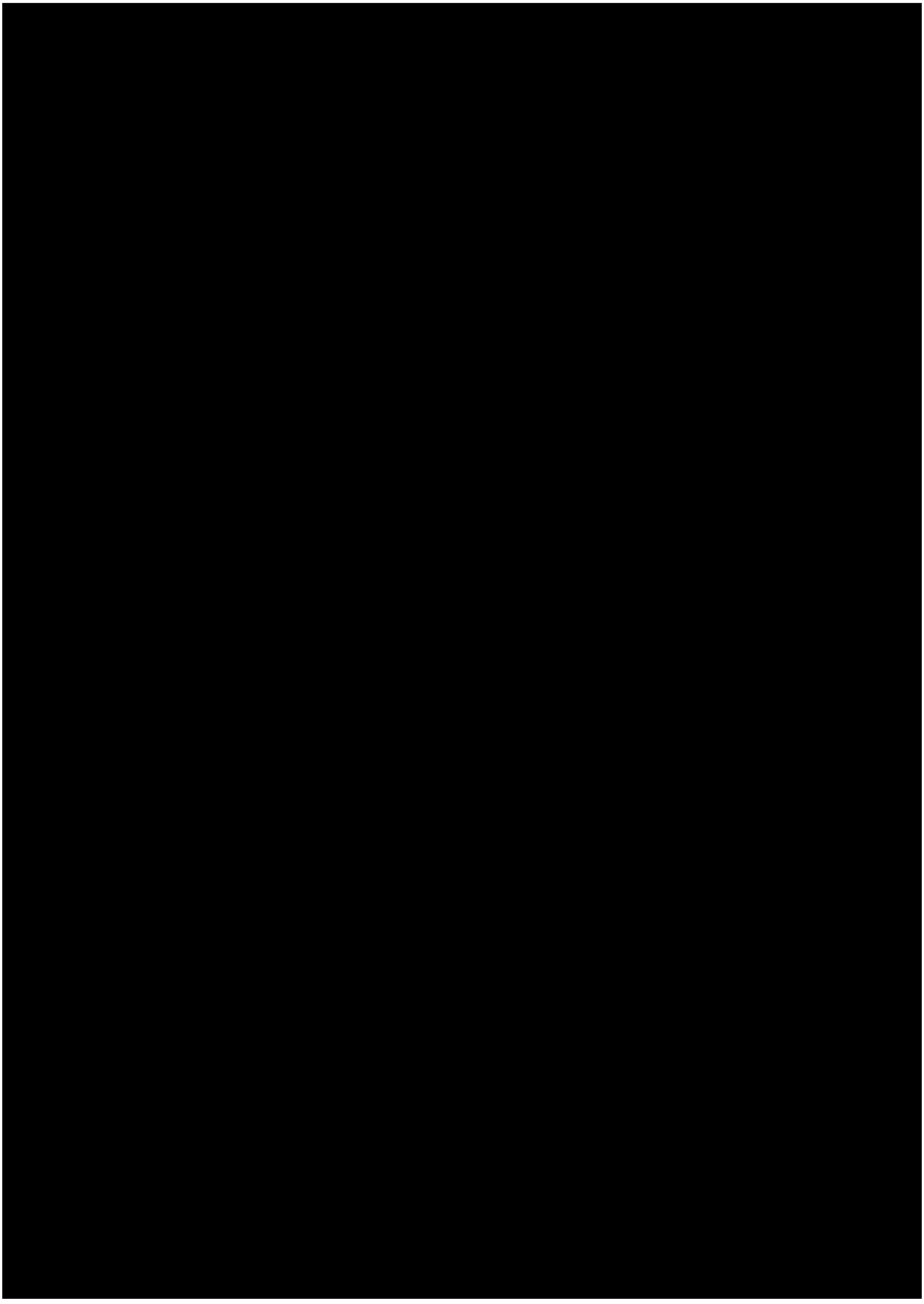

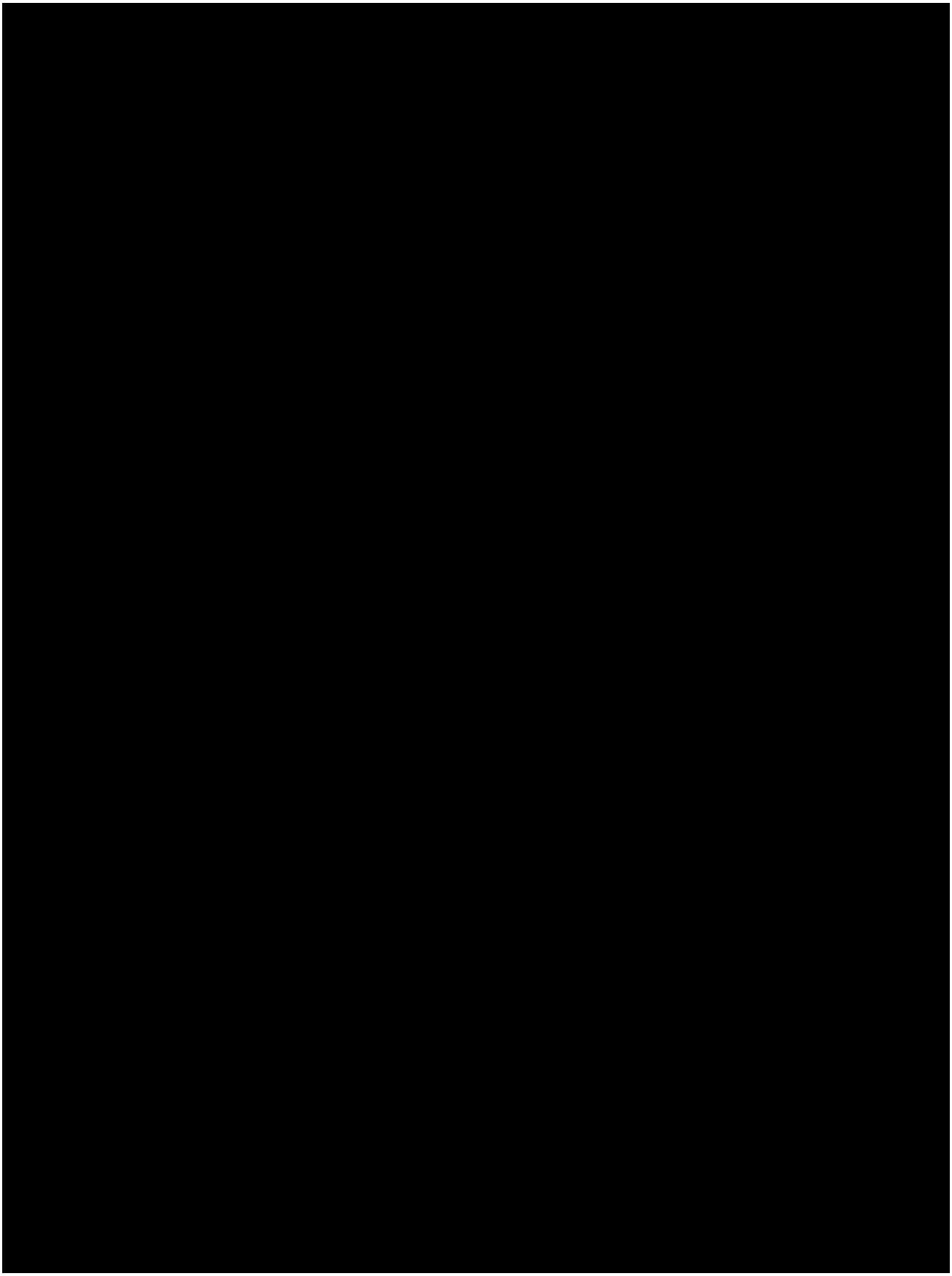

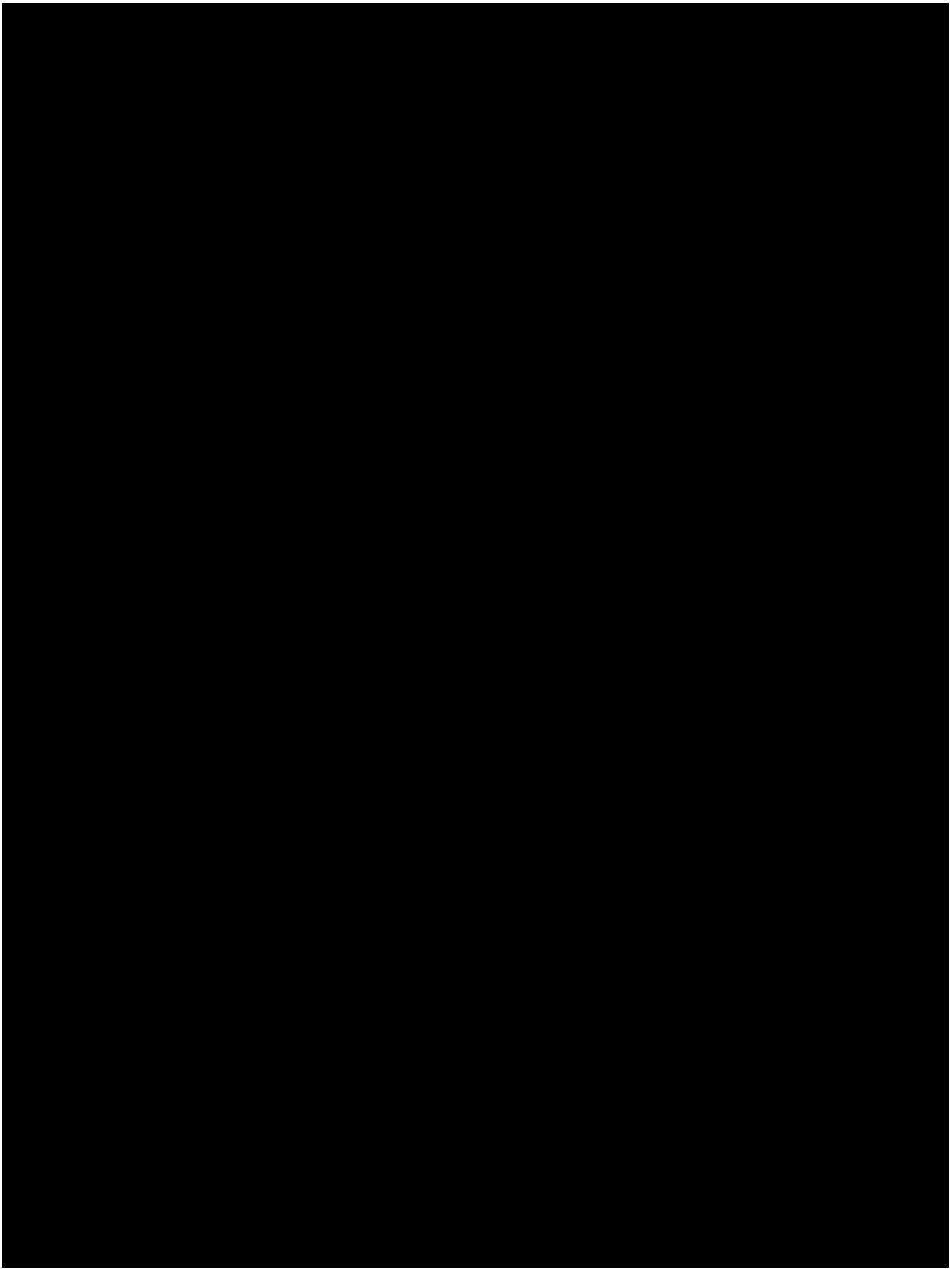

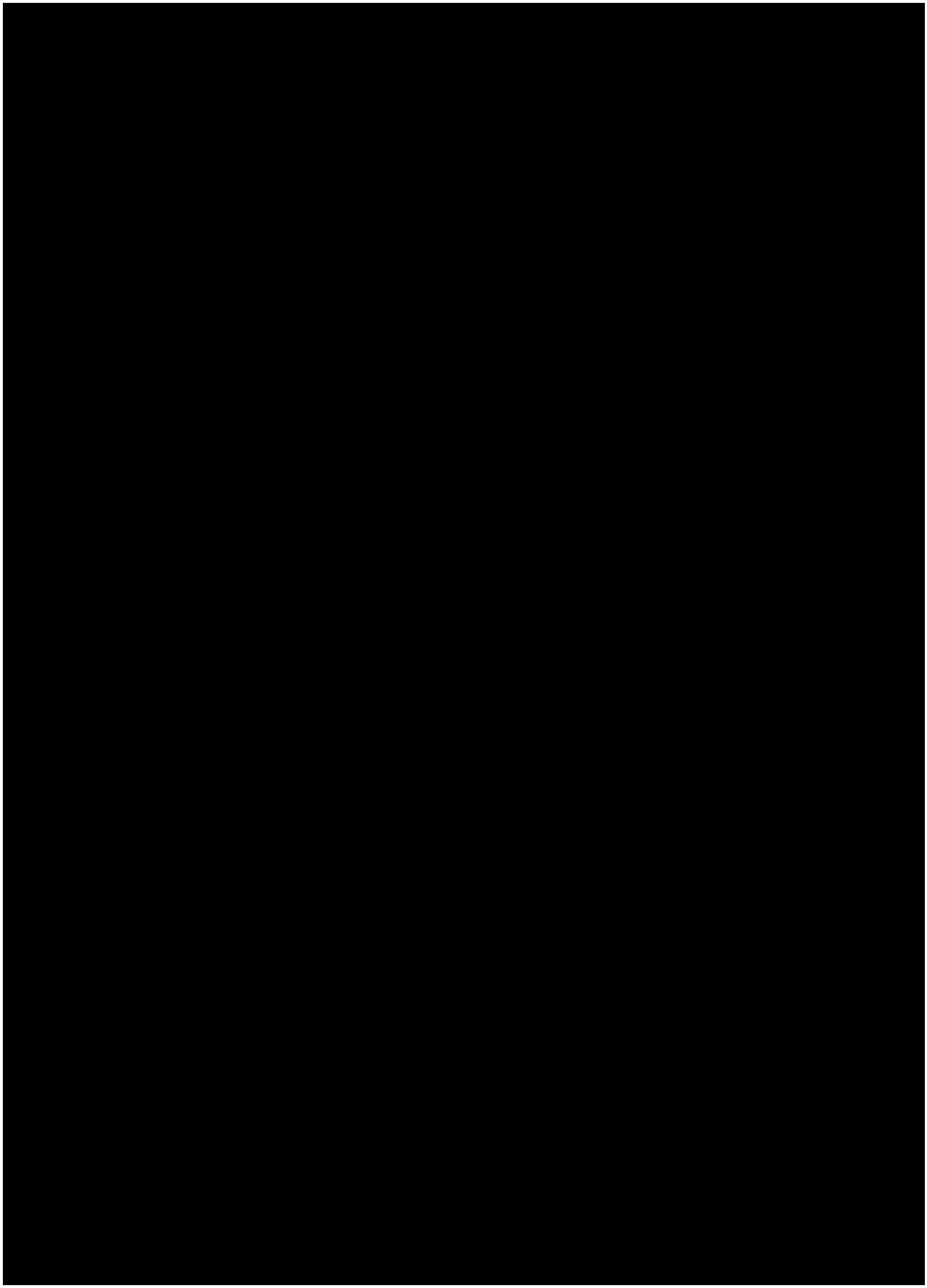

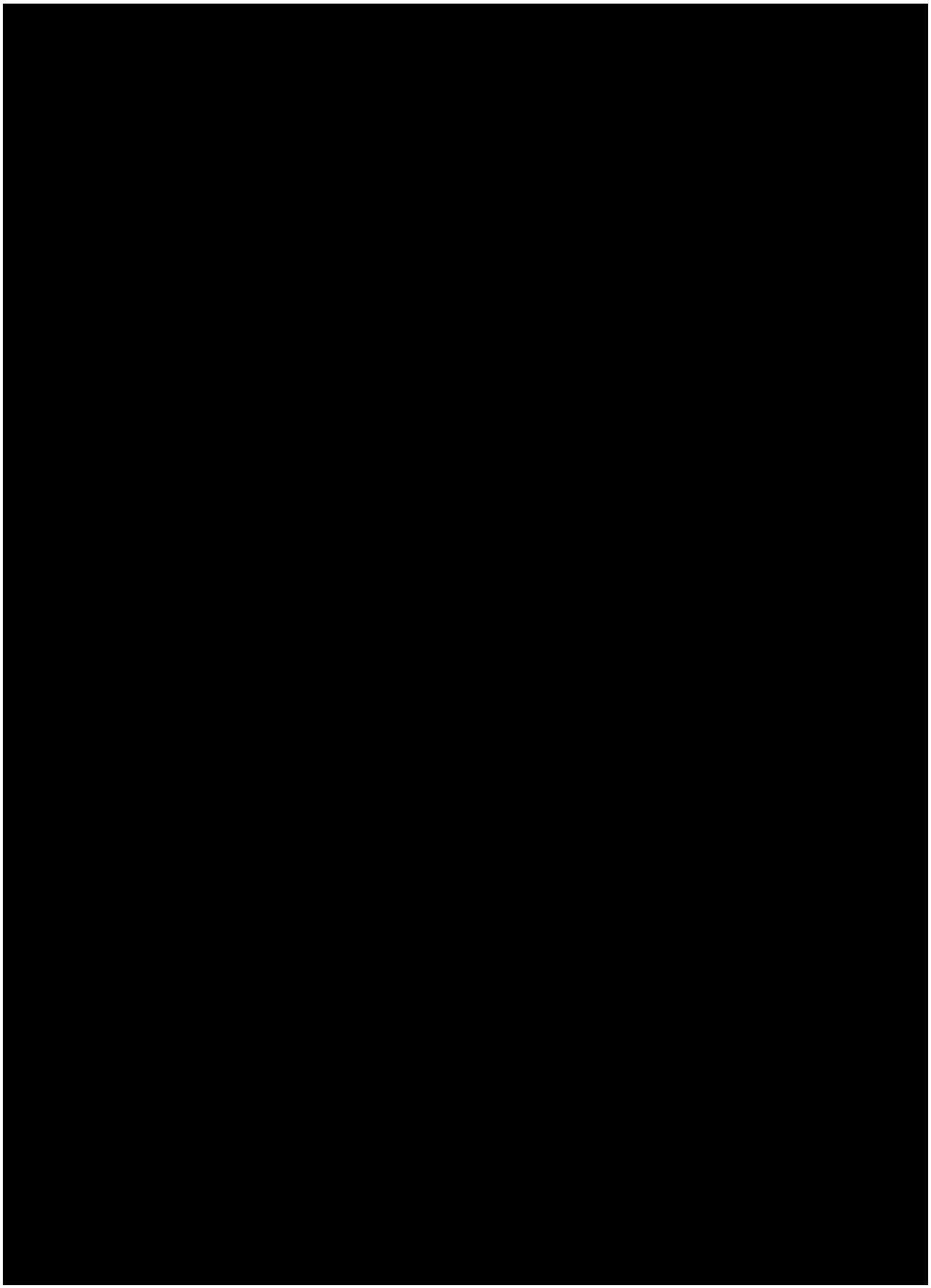

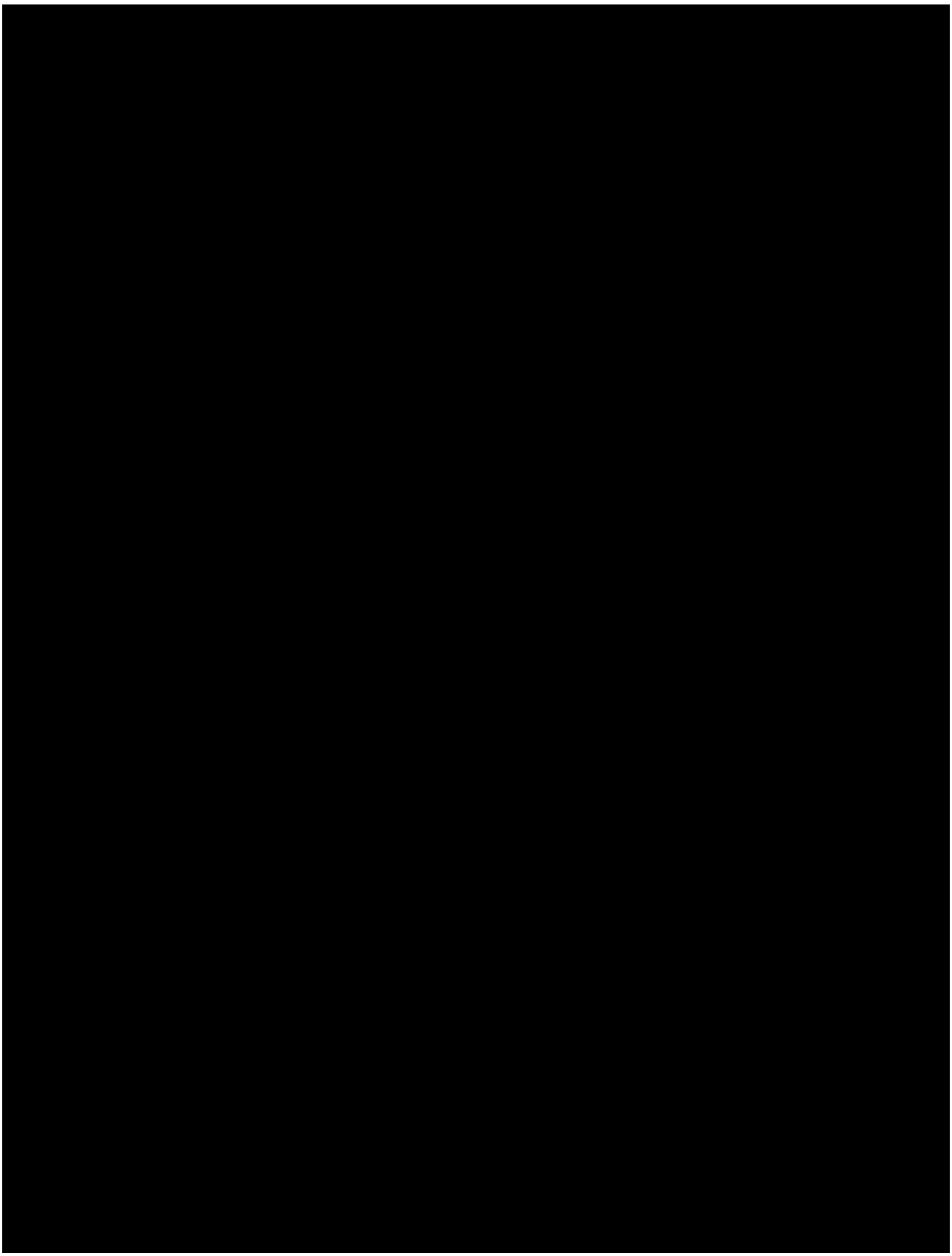

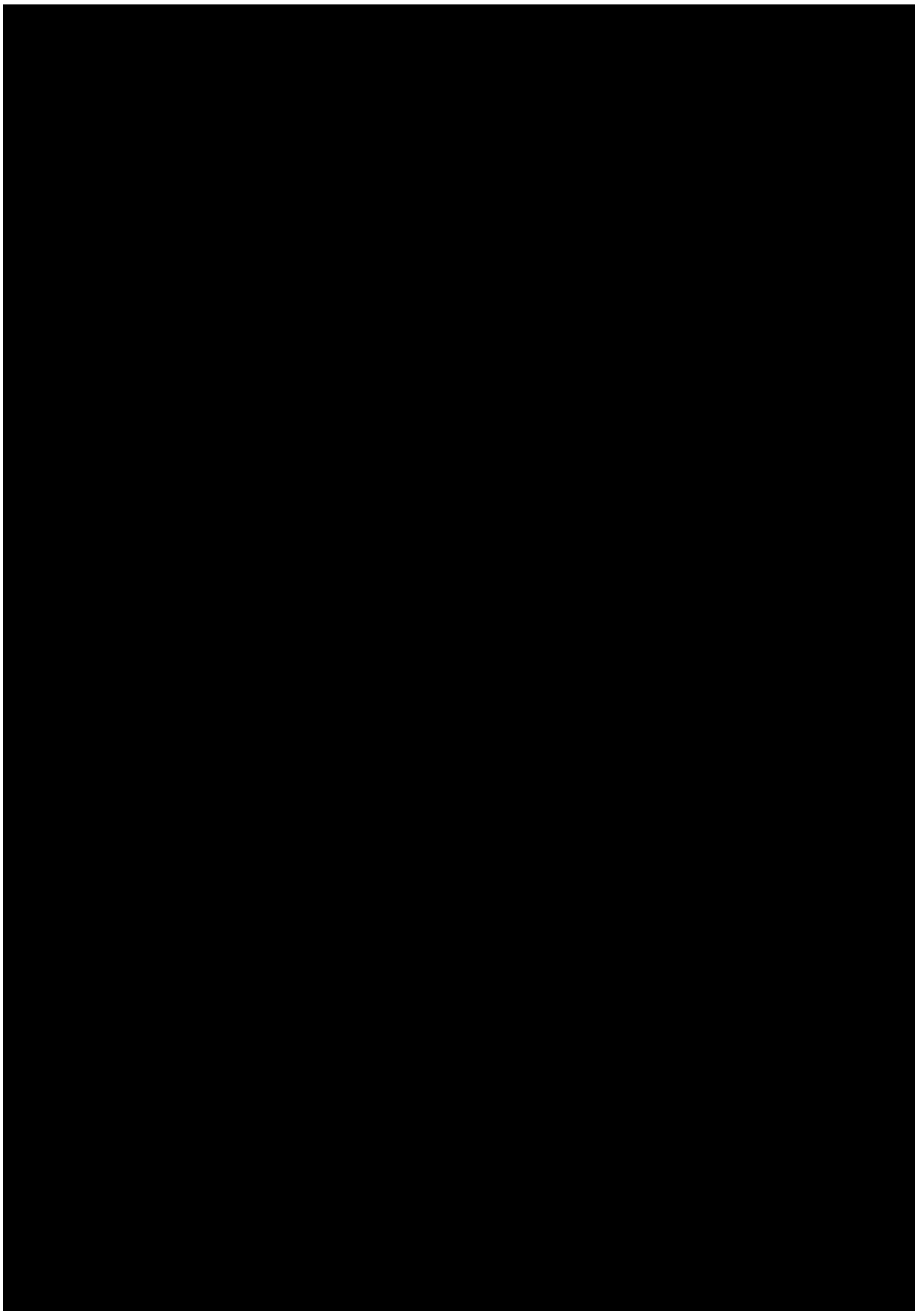

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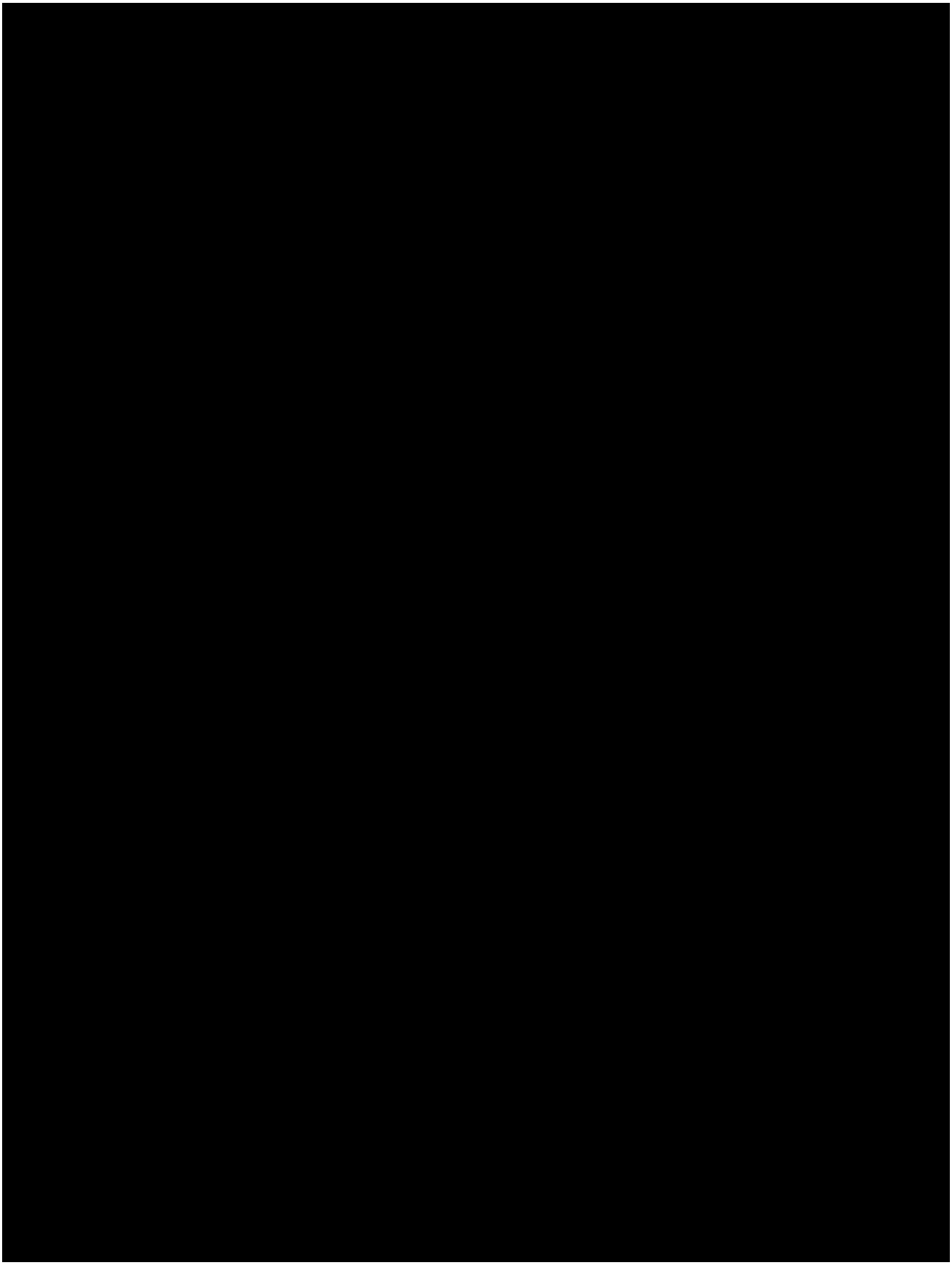

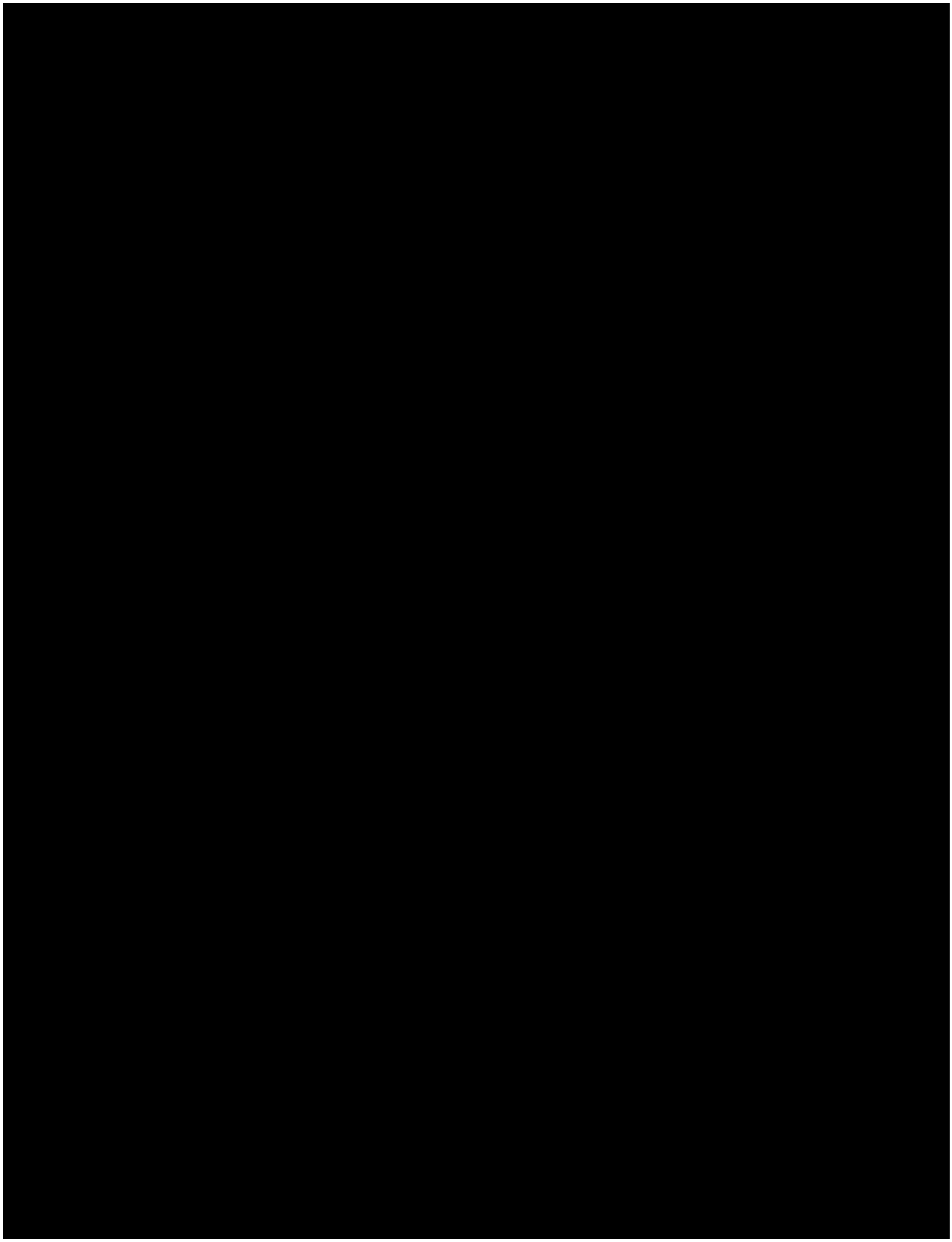

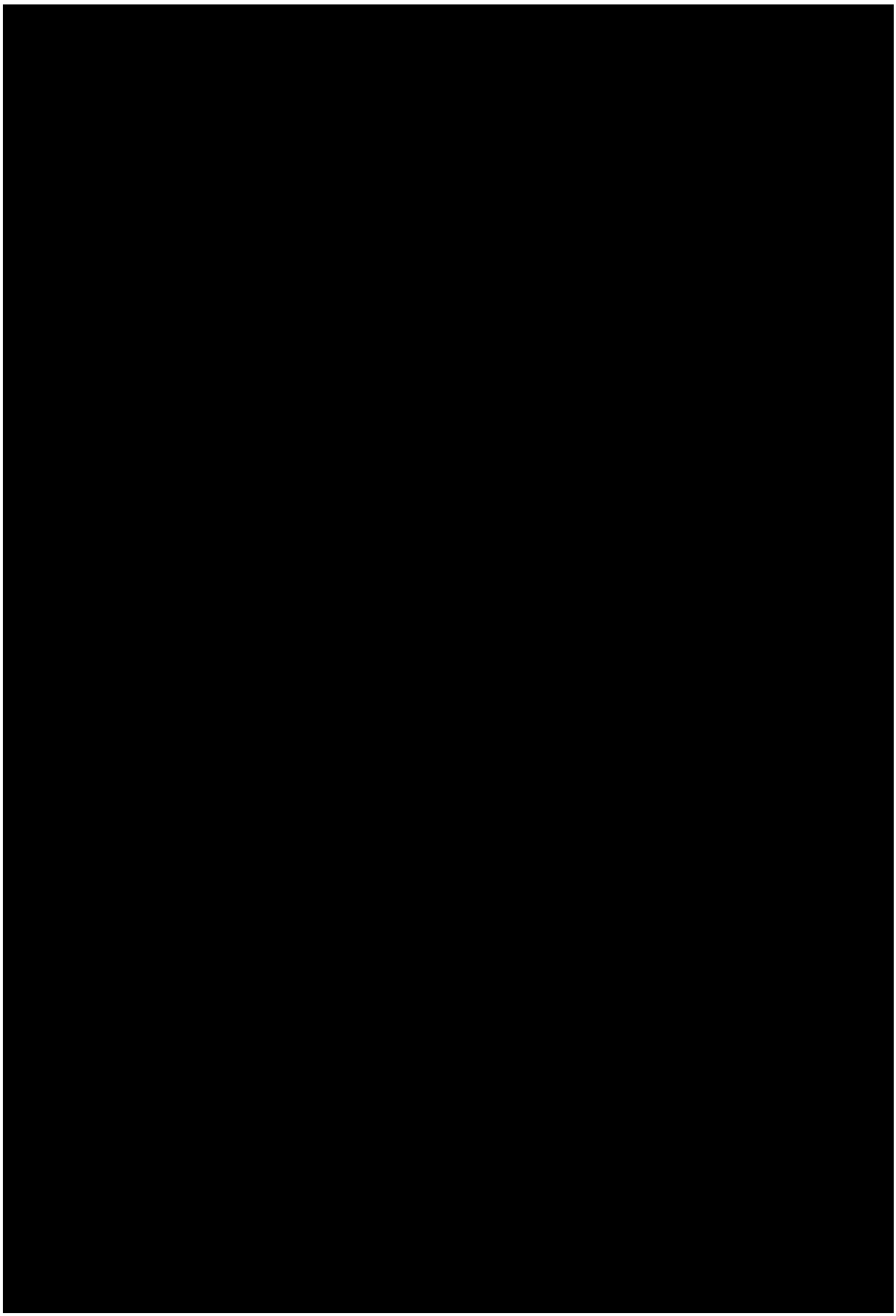

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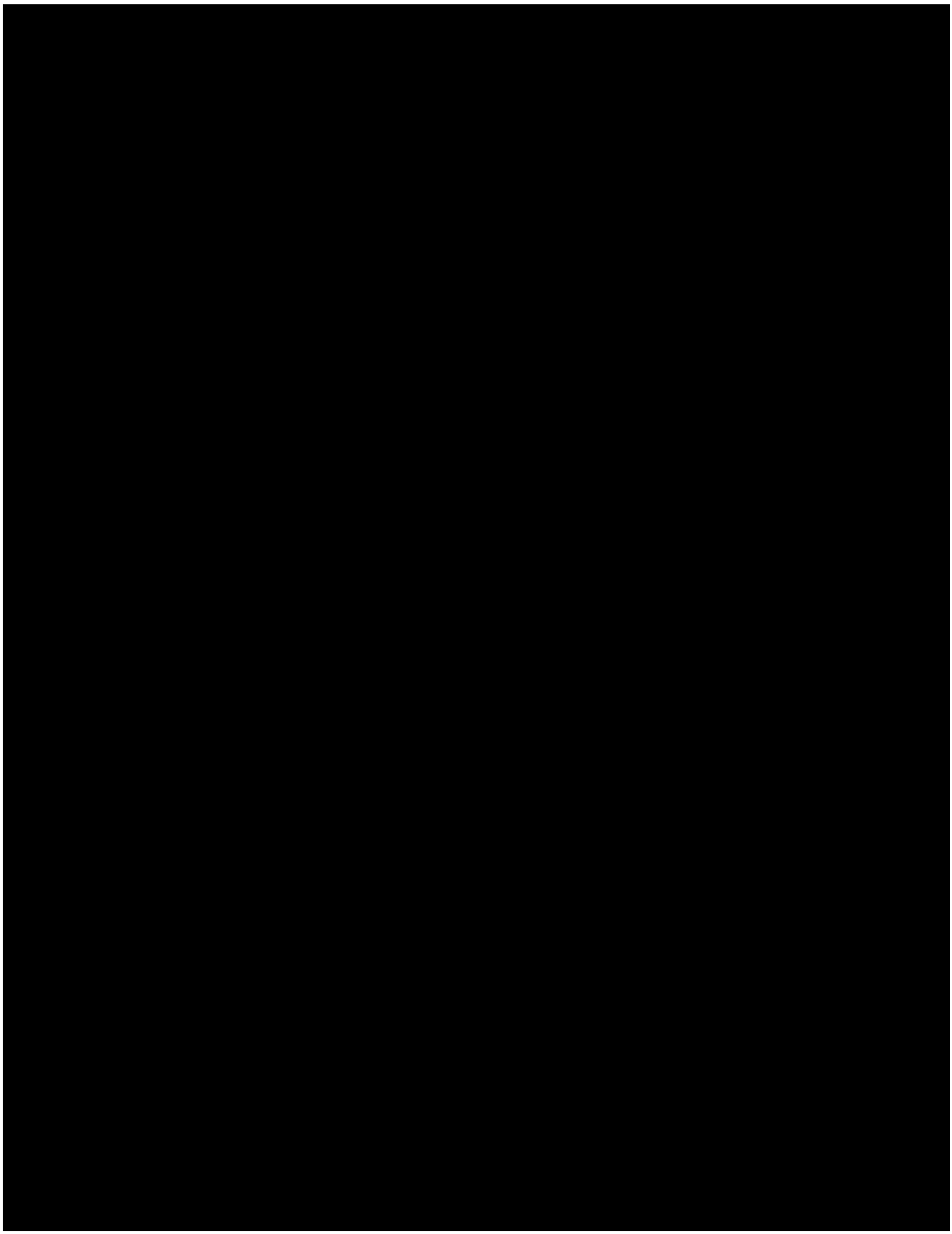

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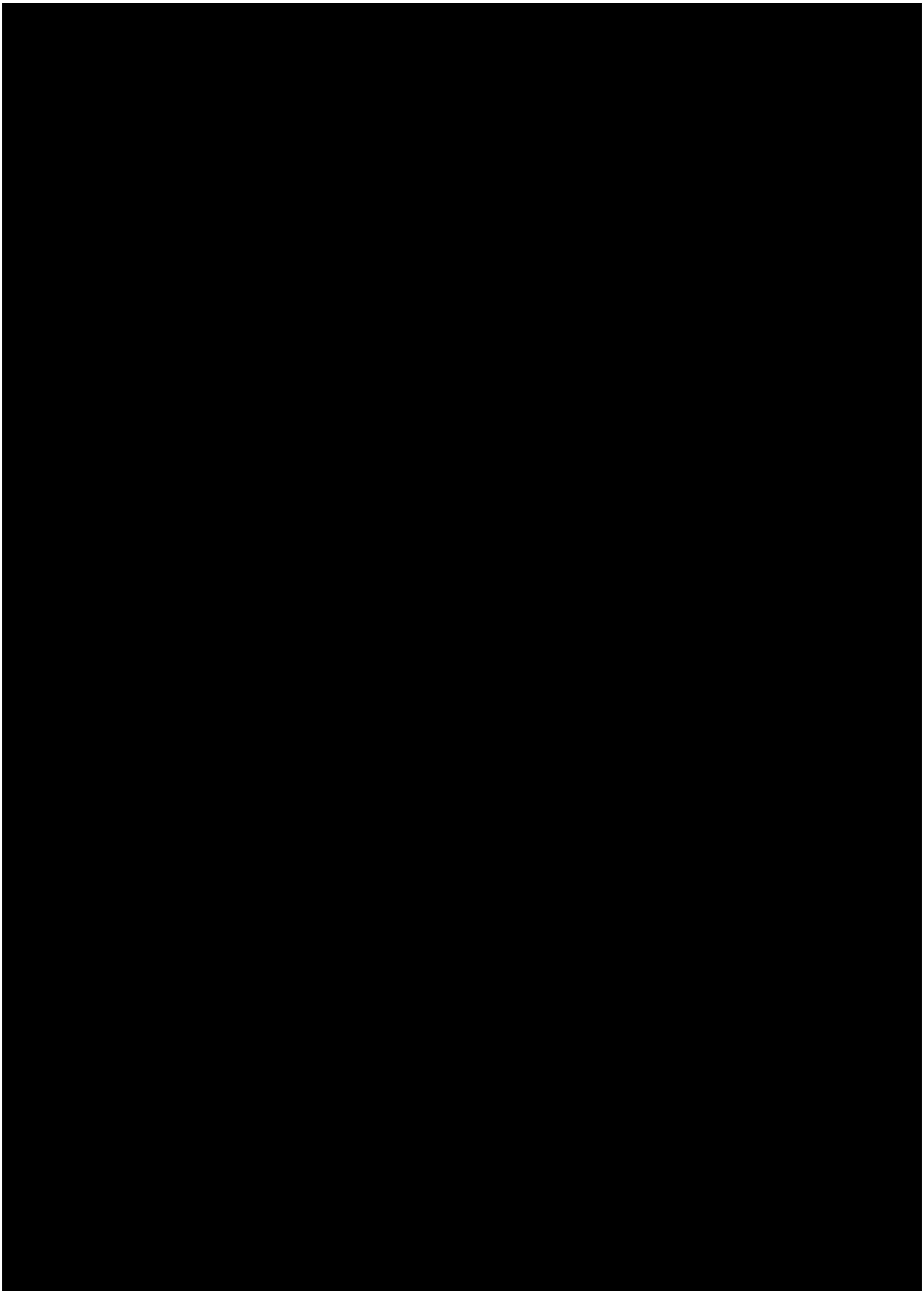

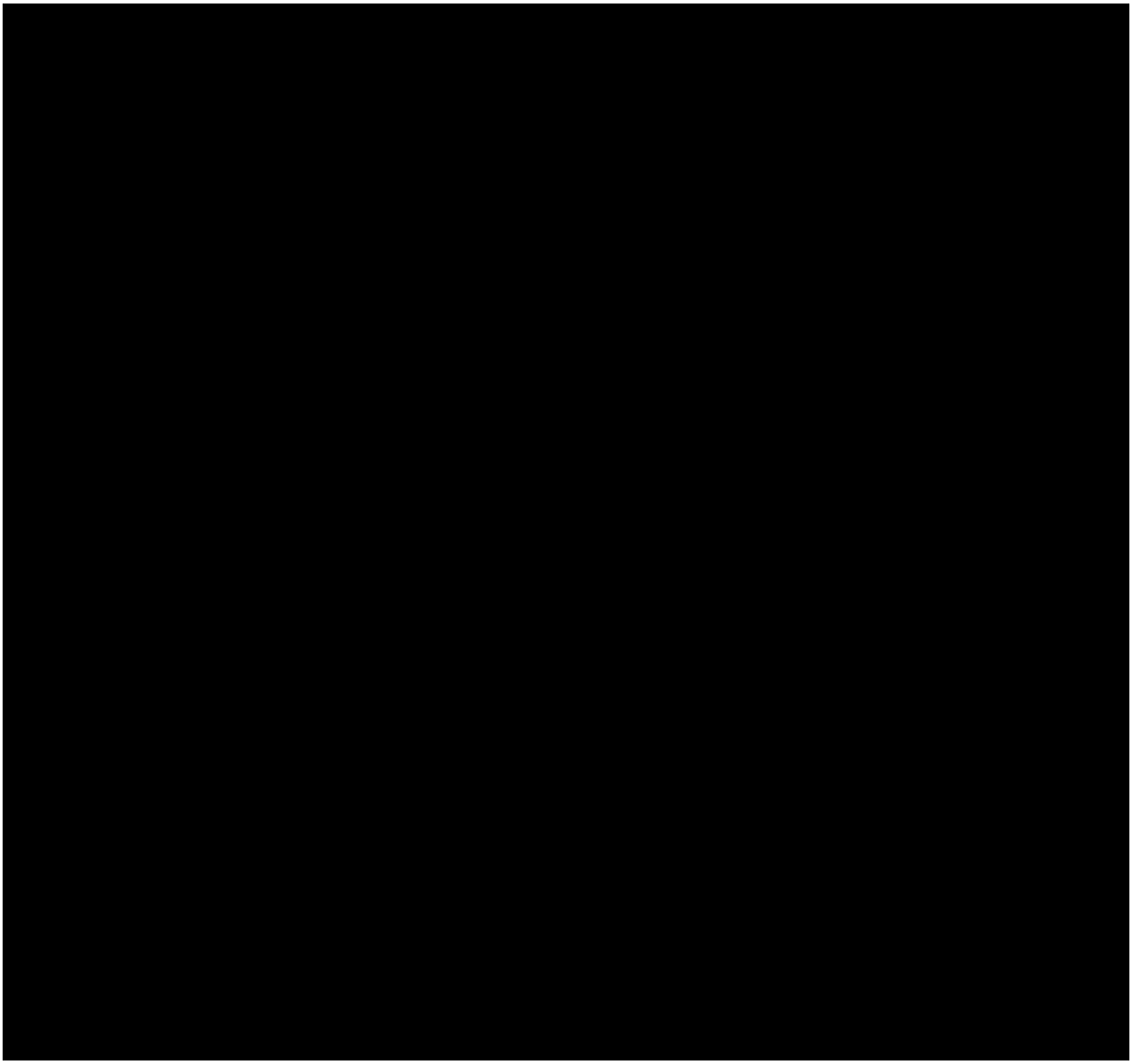

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF MOXR0916 IN COMBINATION WITH ATEZOLIZUMAB VERSUS ATEZOLIZUMAB ALONE IN PATIENTS WITH UNTREATED LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA WHO ARE INELIGIBLE FOR CISPLATIN-BASED THERAPY**
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MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	Genentech, Inc.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF MOXR0916 IN COMBINATION WITH ATEZOLIZUMAB VERSUS ATEZOLIZUMAB ALONE IN PATIENTS WITH UNTREATED LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA WHO ARE INELIGIBLE FOR CISPLATIN-BASED THERAPY**
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TEST PRODUCTS:	MOXR0916 (RO7021608) MPDL3280A (RO5541267)
PHASE:	Phase II
INDICATION:	Urothelial carcinoma
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

The Sponsor has determined that the original scientific aims of this study are no longer evaluable as a result of the Sponsor's decision to prematurely halt enrollment due to slow patient accrual. The original scientific aims of this study are described below solely for reference.

This study will evaluate the efficacy and safety of MOXR0916 plus atezolizumab compared with placebo plus atezolizumab in patients with locally advanced or metastatic urothelial carcinoma (UC) who have not received prior systemic therapy in the locally advanced or metastatic setting and who are ineligible to receive cisplatin-based therapy. The total randomized population includes the following overlapping analysis groups for assessing efficacy:

- Primary population: All patients randomized during Stage 1 of enrollment
- Programmed death-ligand 1 (PD-L1) tumor-infiltrating immune cell (IC) 2/3 population: All randomized patients with tumor PD-L1 immunohistochemistry (IHC) score of IC2/3

Specific objectives and corresponding endpoints for the study are outlined below. Unless otherwise specified, efficacy objectives will be evaluated in both analysis populations.

Primary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of MOXR0916 plus atezolizumab compared with placebo plus atezolizumab in the primary population	• PFS (defined as the time from randomization to the first occurrence of disease progression or death from any cause, whichever occurs first) as determined by the investigator according to RECIST v1.1 • OS, defined as the time from randomization to death from any cause

Secondary Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of MOXR0916 plus atezolizumab compared with placebo plus atezolizumab in the PD-L1 IC2/3 population	• PFS as determined by the investigator according to RECIST v1.1 • OS, defined as the time from randomization to death from any cause
• To evaluate the efficacy of MOXR0916 plus atezolizumab compared with placebo plus atezolizumab	• Objective response (defined as a CR or PR) on two consecutive occasions ≥ 4 weeks apart as determined by the investigator according to RECIST v1.1 • DOR, (defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first) as determined by the investigator according to RECIST v1.1 • Time to pain progression as measured by patient-reported pain severity according to the MDASI • Time to pain palliation as measured by patient-reported pain severity according to the MDASI • Time to fatigue progression as measured by patient-reported fatigue severity according to the MDASI • Proportion of patients reporting symptom interference with daily living at the time of progression according to the MDASI
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of MOXR0916 plus atezolizumab compared with placebo plus atezolizumab	• Objective response, DOR, and PFS according to immune-modified RECIST • Objective response, DOR and PFS as determined by an IRF according to RECIST v1.1 • Time to progression of patient-reported symptoms (other than pain and fatigue) as measured by the MDASI. • Change from baseline in patient-reported symptoms and symptom interference with daily living as measured by the MDASI
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of MOXR0916 plus atezolizumab compared with placebo plus atezolizumab	• Incidence of adverse events, with severity determined through use of NCI CTCAE v4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoints**
• To characterize pharmacokinetics of MOXR0916 and atezolizumab when administered in combination	• Serum concentration of MOXR0916 at specified timepoints • Serum concentration of atezolizumab at specified timepoints

Exploratory Pharmacokinetic Objective	Corresponding Endpoints
• To evaluate potential relationships between drug exposure and the efficacy and safety of MOXR0916	• Serum concentration or PK parameters for MOXR0916 and efficacy endpoints • Serum concentration or PK parameters for MOXR0916 and safety endpoints
Immunogenicity Objective	**Corresponding Endpoints**
• To evaluate the immune response to MOXR0916 and atezolizumab	• Presence of ATAs to MOXR0916 during the study relative to the presence of ATAs at baseline • Presence of ATAs to atezolizumab during the study relative to the presence of ATAs at baseline
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate potential effects of ATAs	• ATA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate candidate biomarkers that may be associated with response to MOXR0916 and atezolizumab (i.e., predictive biomarkers), progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to MOXR0916 and atezolizumab, susceptibility to developing adverse events (i.e., safety biomarkers), or that may provide evidence of MOXR0916 and atezolizumab activity (i.e. pharmacodynamic biomarkers)	• Expression of PD-L1 in tumor tissue and measures of efficacy • Tumor mutational load and measures of efficacy • Biomarkers in blood and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
Exploratory Health Status Utility Objective	**Corresponding Endpoint**
• To evaluate health status utility scores of patients treated with MOXR0916 plus atezolizumab compared with placebo plus atezolizumab	• Health status as measured using the EQ-5D-5L questionnaire for health economic modeling

ATA = anti-therapeutic antibodies; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DOR = duration of objective response; EQ-5D-5L = Euro QoL 5 Dimensions 5-Level; IC = tumor-infiltrating immune cell; IRF = independent review facility; MDASI = M. D. Anderson Symptom Inventory; NCI = National Cancer Institute; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

Study Design

Description of Study

This is a Phase II, multicenter, randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of MOXR0916 in combination with atezolizumab versus placebo and atezolizumab in patients with locally advanced or metastatic UC who have not received prior systemic therapy in the locally advanced/metastatic setting and who are ineligible to receive cisplatin-based therapy.

This study consists of a screening period, a treatment period, and a post-treatment follow-up period. Tumor specimens from patients will be prospectively tested for PD-L1 expression per IHC by a designated central laboratory prior to randomization. The IHC scores will have two categories based on expression on tumor-infiltrating immune cells (IC0/1 and IC2/3). This study will enroll up to approximately 225 patients with evaluable tissue at approximately 75 sites globally.

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

- Experimental arm: MOXR0916 plus atezolizumab
- Control arm: placebo plus atezolizumab

Randomization will be stratified by the following factors:

- PD-L1 status as centrally determined by IHC (IC0/1 or IC2/3)
- Modified Bajorin risk score (0, 1, or 2), which is derived from the Eastern Cooperative Oncology Group (ECOG) Performance Status and the presence or absence of visceral metastases (Bajorin et al. 1999)

MOXR0916/placebo and atezolizumab will be administered by intravenous (IV) infusion at fixed doses of 300 mg and 1200 mg, respectively, on Day 1 of each 21-day cycle. Patients will receive study treatment (MOXR0916/placebo plus atezolizumab) until unacceptable toxicity or loss of clinical benefit, as determined by the investigator after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). *Following unblinding by the investigator, patients assigned to the placebo arm will discontinue placebo infusions and continue atezolizumab alone. Patients assigned to the MOXR0916 arm may continue study treatment with the combination of atezolizumab and MOXR0916 or with atezolizumab alone based on a discussion of benefit and risk with the treating investigator*

Because of the possibility of pseudoprogression with atezolizumab-based therapy, radiographic progression per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 may not be indicative of true disease progression. Patients who meet RECIST v1.1 criteria for progressive disease while receiving study treatment will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in ECOG Performance Status 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
- Written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial radiographic disease progression per RECIST v1.1
- No further radiographic progression of disease at the next imaging assessment and continued demonstration of clinical benefit per the investigator.

No crossover will be allowed.

Patients will undergo tumor assessments at screening and at scheduled intervals during the study *to be determined by the investigator based on the patient's disease characteristics and*

local institutional standards.

All adverse events will be monitored and recorded for at least 90 days after the last dose of study treatment or until initiation of another systemic anti-cancer therapy, whichever occurs first. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event if the event is believed to be related to prior study treatment. Adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0.

Target Population

Patients with locally advanced or metastatic UC who have not received prior systemic therapy in the locally advanced or metastatic setting and who are ineligible to receive cisplatin-based therapy will be enrolled in this study.

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age $\geq$ 18 years
- Ability to comply with the study protocol, in the investigator's judgment
- ECOG Performance Status of $\leq$ 2
- Life expectancy $\geq$ 12 weeks
- Histologically or cytologically confirmed locally advanced (T4b, any N; or any T, N 2–3) or metastatic UC (M1, Stage IV) (also termed transitional cell carcinoma [TCC] or urothelial cell carcinoma [UCC] of the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra)

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

  Locally advanced bladder cancer must be inoperable on the basis of involvement of pelvic sidewall or adjacent viscera (clinical Stage T4b) or bulky nodal metastasis (N2–N3).
- Availability of a representative tumor specimen to enable central testing for determination of PD-L1 status and exploratory research on biomarkers

  A formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections, must be submitted along with an associated pathology report prior to study enrollment. If only 10–14 slides are available, the patient may still be eligible for the study, after discussion with and approval by the Medical Monitor.

  Submitted archival tumor tissue must be evaluated for PD-L1 expression prior to enrollment. Patients whose tumor tissue is not evaluable for PD-L1 expression are not eligible.

  If patients have multiple adequate tissue samples from procedures performed at different times during the course of their UC; priority should be given to the tissue most recently collected. Multiple samples may be submitted for a given patient, on the basis of availability; however, the requirement for a block or $\geq$ 15 unstained slides should be satisfied by a single biopsy or resection specimen. If multiple tumor specimens are submitted, patients may be eligible if at least one specimen is evaluable for PD-L1. In the event that enrollment is limited to PD-L1 selected patients, the highest PD-L1 score among the submitted samples will be used to determine eligibility.

  Transurethral resection of bladder tumor (TURBT) specimens must contain a muscle invasive component (i.e., T2 or greater) of the bladder tumor as documented in the pathology report. If the TURBT specimens do not contain a muscle invasive component, then specimens obtained at the time of cystectomy/nephroureterectomy or metastatic spread (i.e., sample from a metastatic lesion) will be required prior to randomization.

  Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, and cell pellets, pleural effusions and lavage samples are not acceptable.

Patients who do not have tissue specimens that meet eligibility requirements may undergo a biopsy prior to enrollment. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

Prior to signing the main study informed consent form, patients may sign a pre-screening consent form to specifically allow the collection and testing of archival or fresh tumor specimens.

- No prior systemic therapy for inoperable locally advanced or metastatic UC

  For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for UC, a treatment-free interval $>$ 12 months between the last treatment administration and Cycle 1, Day 1 is required in order to be considered treatment naive in the metastatic setting.

- Ineligible for cisplatin-based chemotherapy as defined by any one of the following criteria:
  - Impaired renal function (glomerular filtration rate [GFR] >30 but <60 mL/min); GFR may be assessed by calculation from serum/plasma creatinine (Cockcroft-Gault formula) or direct measurement (i.e., creatinine clearance or ethyldediaminetetra-acetate)
  - NCI CTCAE v4.0 Grade $\geq$ 2 audiometric hearing loss (25 dB at two contiguous frequencies or more severe)
  - NCI CTCAE v4.0 Grade $\geq$ 2 peripheral neuropathy (i.e., sensory alteration or paresthesias, including tingling)
  - ECOG Performance Status of 2
- Measurable disease according to RECIST v1.1

  Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.

- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - White blood cell (WBC) counts $\geq$ 2,500/μL
  - ANC $\geq$ 1500/μL (without granulocyte colony-stimulating factor support 14 days prior to Cycle 1, Day 1)
  - Lymphocyte count $\geq$ 500/μL
  - Platelet count $\geq$ 100,000/μL (without transfusion 14 days prior to Cycle 1, Day 1)
  - Hemoglobin $\geq$ 9.0 g/dL

    Patients may be transfused to meet this criterion.

    Patients with a solitary kidney or chronic kidney disease with low erythropoietin production may use erythropoietin-stimulating agents.
  - AST, ALT, and alkaline phosphatase (ALP) $\leq 3 \times$ upper limit of normal (ULN), with the following exception:

    Patients with documented liver or bone metastases: ALP $\leq 5 \times$ 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.
  - Measured or calculated creatinine clearance $\geq$ 30 mL/min (calculated using the Cockcroft-Gault formula)
  - Serum albumin $\geq$ 2.5 g/dL
  - Prothrombin time (PT)/INR and activated partial thromboplastin time (aPTT) $\leq 1.5 \times$ ULN

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

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $<1\%$ per year during the treatment period and for at least 6 months after the last dose of study treatment

  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, 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 or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  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.

<u>Exclusion Criteria</u>

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

- Pregnant or lactating, or intending to become pregnant or breast feed during the study or 6 months afterward

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina

  Patients with a known left ventricular ejection fraction (LVEF) $<40\%$ will be excluded

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF 40%–50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease
- Major surgical procedure within 4 weeks prior to initiation of study treatment or anticipation of need for a major surgical procedure during the course of the study.

  TURBT is considered a minor surgical procedure

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

- Any approved anti-cancer therapy, including chemotherapy or hormonal therapy, within 3 weeks prior to initiation of study treatment; the following exceptions are allowed:
  - Palliative radiotherapy for bone metastases or soft tissue lesions that is completed > 7 days prior to baseline imaging
  - Radiotherapy for brain metastases as stipulated below
  - Prior local intravesical chemotherapy or immunotherapy is allowed if completed at least 4 weeks prior to the initiation of study treatment
  - Hormone-replacement therapy or oral contraceptives
  - Patients should be recovered from any toxicities associated with permitted anti-cancer therapies
- Prior treatment with CD137 or OX40 agonists, anti–CTLA-4, anti–PD-1, anti–PD-L1, anti-CD-27, anti-GITR therapeutic antibody or pathway-targeting agents
- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to initiation of study treatment
- Untreated CNS metastases or active (progressing or requiring corticosteroids for symptomatic control) CNS metastases

  Patients with a history of treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:
  - Measurable disease outside the CNS
  - No ongoing requirement for corticosteroids as therapy for CNS disease, with corticosteroids discontinued for ≥ 2 weeks prior to enrollment
  - Anticonvulsants at a stable dose are allowed
  - No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to Cycle 1, Day 1
  - No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  Patients with new asymptomatic CNS metastases detected during screening 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, if all other criteria are met.
- Any history of leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX) are allowed.
- Uncontrolled tumor-related pain

  Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Malignancies other than UC within 5 years prior to Cycle 1, Day 1

  Patients with localized low-risk prostate cancer (defined as Stage ≤ pT2b, Gleason score ≤ 7, and prostate-specific antigen (PSA) at prostate cancer diagnosis ≤ 20 ng/mL) treated with curative intent and without PSA recurrence are eligible.

  Patients with pre-existing low-risk prostate cancer (defined as Stage cT1/T2a, Gleason score ≤ 7 and PSA ≤ 10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible.

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

criteria:

Malignancy treated with expected curative intent (e.g., 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

- Uncontrolled or symptomatic hypercalcemia (> 1.5 mmol/L ionized calcium or calcium > 12 mg/dL or corrected serum calcium > ULN)
- History of autoimmune disease with the following caveats:

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

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

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

  - Rash must cover < 10% of body surface area
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study with the following exceptions:

  Patients who have received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication are eligible for the study.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to initiation of study treatment
- History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan

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

  History of drug-induced pneumonitis that was asymptomatic (defined by radiographic findings only) and reversible (without any anti-inflammatory therapies) is permitted
- Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening

  Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study.
- Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test at screening

Patients who have a positive HCV antibody test are eligible for the study if a polymerase chain reaction assay is negative for HCV RNA

- Positive HIV test at screening
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Patients with recent infections that are not judged to be severe (as described above) are excluded if they have either:
  - Signs or symptoms of infection within 2 weeks prior to initiation of study treatment

    Patients with uncomplicated viral upper respiratory tract infections are eligible provided symptoms have resolved to baseline.
  - Received oral or IV antibiotics (including anti-fungal or anti-viral therapy) within 2 weeks prior to initiation of study treatment for suspected or confirmed infection

    Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease or for dental extraction) are eligible.
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks before initiation of study treatment, or anticipation of need for such a vaccine during the course of the study.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells
- Known allergy or hypersensitivity to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the MOXR0916 formulation

End of Study

The end of the study is defined as the date when the number of OS events specified for the final analysis has been observed. Additionally, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 45 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

MOXR0916 will be administered at the 300-mg dose level by IV infusion every 3 weeks.

Atezolizumab will be administered at the 1200-mg dose level by IV infusion every 3 weeks.

Comparator

MOXR0916 placebo will be administered by IV infusion every 3 weeks.

Statistical Methods

The Sponsor has determined that the original scientific aims of this study are no longer evaluable as a result of the Sponsor's decision to prematurely halt enrollment due to slow patient accrual. However, the original statistical considerations and analysis plan are retained below for reference.

Efficacy Analyses

The co-primary and secondary efficacy analyses will be conducted among all randomized patients in appropriate study populations (primary population or PD-L1 IC2/3 population) with patients grouped according to their assigned treatment (i.e., intent-to-treat [ITT]) analysis. Specifically, formal hypothesis testing of the co-primary efficacy endpoints of progression-free

survival (PFS) and overall survival (OS) will be conducted in the ITT primary patient population at significance levels of 0.005 and 0.045, respectively.

Other secondary endpoints, including PFS and OS in the PD-L1 IC2/3 subpopulation, as well as objective response rate (ORR), duration of response (DOR), and patient-reported outcome (PROs; including pain, fatigue, other symptoms, and interference scores from the M. D. Anderson Symptom Inventory [MDASI]) in both the primary patient population and in the PD-L1 IC2/3 population will also be analyzed but are not included in the formal hypothesis testing framework. Results will be presented with 95% confidence intervals unless otherwise specified.

Determination of Sample Size

The primary objective of this study is to test the hypothesis of greater treatment effect of MOXR0916 plus atezolizumab on duration of PFS and OS relative to the placebo plus atezolizumab. For the co-primary endpoints of PFS and OS in the primary patient population, at 70% event maturity (112 PFS or OS events), the trial will have 81% power to detect a PFS hazard ratio of 0.50 at a two-sided significance level of 0.005 (corresponding to an improvement from 3 to 6 months in median PFS), and 80% power to detect an OS hazard ratio of 0.58 at a two-sided significance level of 0.045 (corresponding to an improvement from 13.3 to 22.9 months in median OS). Total type I error will be controlled at a 0.05 significance level.

Notably, the trial is able to detect only very large benefits in OS. The trial will not, however, have adequate power to detect all potentially clinically meaningful differences in OS. For example, with 112 OS events, there is only 45% power to detect a hazard ratio of 0.70 (corresponding to an improvement from 13.3 to 19 months in median OS) at a two-sided significance level of 0.045. Thus, a statistically negative outcome in the co-primary OS analysis does not necessarily rule out a clinically meaningful outcome.

Additionally, with 60 PFS events in the PD-L1 IC2/3 population (corresponding to 75% event maturity), there is 77% power to detect a HR of 0.50 at a two-sided significance level of 0.05. The upper bound of the two-sided 95% CI for the HR will be 0.83.

Interim Analyses

There will be no interim efficacy analyses prior to the primary PFS analysis in the primary population. Interim efficacy analyses for OS will be conducted.

An Internal Monitoring Committee (IMC) will convene approximately every 6 months during enrollment to review available safety data and to make recommendations regarding study conduct to ensure the safety of patients enrolled on the study. In the absence of significant safety concerns or other extenuating circumstances, accrual will continue in the study while the reviews are being conducted. Pending review of accumulating safety data, the IMC may choose to meet more frequently, if necessary. On the basis of these interim safety results, however, the IMC may recommend to continue, modify, or terminate the study. However, as the IMC will review only safety data, it cannot undertake decisions to halt the trial based on early efficacy or futility.

The members, roles, responsibilities and communication processes of the IMC will be outlined in a separate charter.

There will be no interim efficacy analyses prior to the primary PFS analysis in the primary population. Following the primary PFS analysis, however, the Sponsor may choose to conduct up to two additional interim efficacy analyses for OS. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADCC	antibody-dependent cell-mediated cytotoxicity
ALP	alkaline phosphatase
aPTT	activated partial thromboplastin
ATA	anti-therapeutic antibody
CNS	central nervous system
CRO	contract research organization
CRS	Cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DMC	Data Monitoring Committee
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D-5L	European Quality-of-Life 5-Dimension Questionnaire
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GC	gemcitabine and cisplatin
GFR	glomerular filtration rate
HBcAb	antibody against hepatitis B core antigen
HBsAb	antibody against hepatitis B surface antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
IC	tumor-infiltrating immune cell
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRF	independent review facilty
ITT	intent-to-treat

Abbreviation	Definition
IV	intravenous
LOQ	lower limit of quantification
LPLV	last patient, last visit
MAS	macrophage activation syndrome
MDASI	M. D. Anderson Symptom Inventory
MTD	maximum tolerated dose
MVAC	methotrexate, vinblastine, doxorubicin, and cisplatin
NCI	National Cancer Institute
NGS	next generation sequencing
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PET	positron emission tomography
PFS	progression-free survival
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PK	pharmacokinetic
PRO	patient-reported outcome
PSA	prostate-specific antigen
PT	Prothrombin time
QTcF	QT interval corrected using Fridericia's formula
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SIA	systemic immune activation
TCC	transitional cell carcinoma
TURBT	transurethral resection of bladder tumor
UBC	urothelial bladder cancer
UC	urothelial carcinoma
UCC	urothelial cell carcinoma
ULN	upper limit of normal
WBC	white blood cell
WES	whole exome sequencing
WGS	whole genome sequencing
WHO	World Health Organization

1. BACKGROUND

1.1 BACKGROUND ON UROTHELIAL CARCINOMA

Bladder cancer is the ninth most common cause of cancer with an estimated global incidence of 429,000 cases in 2012 (Ferlay et al. 2015). In the United States, the expected incidence and mortality from bladder cancer in 2016 is 76,960 and 16,390 cases, respectively (American Cancer Society 2016). The disease is 3 to 4 times more common in males than females and typically affects older patients, who have an average age of 73 years at time of diagnosis (American Cancer Society 2016).

Urothelial carcinoma (UC; also termed transitional cell carcinoma [TCC], urothelial bladder cancer [UBC], or urothelial cell carcinoma [UCC] of the urinary tract) is the predominant histologic type of cancer arising in the urinary tract. While bladder is the most frequent location, UC may also originate in the renal pelvis, ureter, or urethra.

The urothelium is exposed to potential carcinogens that are excreted in the urine or activated from precursors in the urine, and environmental exposures appear to account for most cases of UC. Smoking is the most well established risk factor for UC, accounting for about 50% of all cases. Other carcinogens have also been implicated, as the risk for developing bladder cancer is increased among workers in the dye, rubber, leather, and aluminum industries; painters; and people who live in communities with high levels of arsenic in the drinking water (American Cancer Society 2016). Consistent with the important role of chemical carcinogens in this disease, UC is associated with a high rate of somatic mutations compared with other common cancers (Alexandrov et al. 2013; Weinstein et al. 2014).

Approximately 5% of UC patients present with metastatic disease at diagnosis. In addition, approximately half of the patients with locally advanced UC progress to metastatic disease within 2 years of cystectomy. With an overall 5-year survival rate of 5.2%, patients with metastatic UC represent a persistent high unmet need (Surveillance, Epidemiology and End Results [SEER] 2016).

1.1.1 First-Line Treatment of Metastatic Urothelial Carcinoma

Cisplatin-based combination chemotherapy results in superior survival when compared with single-agent cisplatin and is the preferred initial therapy for patients with metastatic UC. Common cisplatin-based regimens include methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and gemcitabine and cisplatin (GC). A Phase III study of 405 patients showed that both regimens have comparable efficacy including similar objective response rate (ORR; 49% for GC vs. 46% for MVAC), time to progression (7 months in each arm) and overall survival (OS; 14.0 months for GC vs. 15.2 months for MVAC; von der Maase et al. 2005). Although GC resulted in fewer Grade 3 and 4 adverse events than MVAC, both regimens are associated with substantial toxicities (such as febrile neutropenia, myelosuppression, nausea, alopecia, nephropathy, and neuropathy).

Given this toxicity profile, a substantial proportion of metastatic UC patients are considered medically "unfit" or ineligible to receive cisplatin-based regimens because of baseline comorbidities (Sonpavde et al. 2014, Thompson et al. 2014). Indeed, two independent retrospective studies of medical claims in the SEER-Medicare database showed that only about 50% of patients receive treatment with any chemotherapy for first-line metastatic UC, and among these, only 36% received cisplatin-based therapy (Sonpavde et al. 2014; Galsky et al. 2015).

A consensus-working group has defined patients who meet at least one of the following criteria as "unfit" for cisplatin-based chemotherapy based on an increased risk of cisplatin toxicity (Galsky et al. 2011):

- World Health Organization (WHO)/ Eastern Cooperative Oncology Group (ECOG) Performance Status of 2 or a Karnofsky Performance Status of 60% to 70%
- Creatinine clearance $<$60 mL/min
- A hearing loss of 25 dB at two contiguous frequencies or more severe
- Grade $\geq$2 peripheral neuropathy
- New York Heart Association Class $\geq$III heart failure

Cisplatin-ineligible patients who are otherwise candidates for chemotherapy are typically offered carboplatin-based regimens (Cathomas et al. 2015). A randomized Phase III study of 238 cis-ineligible patients with previously untreated advanced UC compared carboplatin and gemcitabine to methotrexate, carboplatin, and vincristine (De Santis et al. 2012). In this study, the confirmed ORR of the carboplatin and gemcitabine arm was 36.1% versus 21.0% for the methotrexate, carboplatin, and vincristine arm and the study demonstrated no difference in OS between the two treatment arms (median OS 9.3 vs. 8.1 months; HR$=$0.94; 95% CI: 0.72, 1.22; p$=$0.64). Notably, patients with both impaired renal function and poor performance status had especially poor outcomes and increased acute toxicity with either combination chemotherapy in the study. In a post hoc analysis, OS decreased significantly as the number of Bajorin risk factors (ECOG Performance Status of 2 or presence of visceral metastases) increased (Bajorin et al. 1999).

For patients with ECOG $\geq$2, treatment options include single-agent chemotherapy or best supportive care. Responses to single-agent chemotherapy are generally of short duration, with unclear impact on survival. Outcomes for patients not receiving any chemotherapy are extremely poor, with a median OS of only 3 months (Sonpavde et al. 2014; Galsky et al. 2015).

Given the poor treatment outcomes for the cisplatin-ineligible UC patient population, a substantial need for chemotherapy-free treatment options exists. However, although there is an increasing understanding of the molecular biology and signaling pathways that underlie bladder cancer development and progression (particularly the fibroblast growth factor receptor–, vascular endothelial growth factor–, and epidermal growth factor

receptor–/human epidermal growth factor 2–pathways), no targeted agents related to these pathways currently have a role in the treatment of UC.

1.1.2 Immunotherapy for Urothelial Carcinoma

The strategy of blocking inhibitory T-cell pathways known as immune checkpoints in order to reinvigorate anti-tumor immune responses has been validated across diverse malignancies by the therapeutic successes of targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death-1 (PD-1), and programmed death-ligand 1 (PD-L1) (Hodi et al. 2010; Robert et al. 2014; Borghaei et al. 2015; Brahmer et al. 2015; Larkin et al. 2015; Motzer et al. 2015; Robert et al. 2015; Rosenberg et al. 2016, Fehrenbacher et al. 2016).

High tumor mutational load has been associated with clinical benefit in ipilimumab-treated melanoma patients and pembrolizumab-treated non–small cell lung cancer (NSCLC) patients, demonstrating a genetic basis for response to checkpoint inhibition (Snyder et al. 2014; Rizvi et al. 2015). These results underscore the role of novel epitopes derived from mutated genes in eliciting tumor-specific T-cell responses. The observation that UC is associated with the third highest mutation rate of all studied cancers provides a strong rationale for evaluating checkpoint inhibition in this disease (Weinstein et al. 2014).

As described further below, investigation of the anti–PD-L1 checkpoint inhibitor atezolizumab has culminated in the approval in the United States for the treatment of patients with locally advanced or metastatic UC who have previously been treated with platinum-containing chemotherapy.

1.2 BACKGROUND ON ATEZOLIZUMAB

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding

to Fc・receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

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

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

1.2.1 Atezolizumab in Urothelial Cancer

Study GO29293 (IMvigor 210) is an ongoing single-arm, open-label, Phase II study evaluating atezolizumab as a single agent in two cohorts of patients with locally advanced or metastatic UC (Rosenberg et al. 2016; Balar et al. 2016; Dreicer et al. 2016). Cohort 1 enrolled first-line patients who were ineligible to receive cisplatin-based chemotherapy, and Cohort 2 enrolled patients who had progressed during or following platinum-based chemotherapy. The co-primary endpoints of the study were independent review facility (IRF)–assessed ORR according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (both cohorts) and investigator-assessed ORR according to modified RECIST criteria (Cohort 2 only).

Cohort 2 demonstrated that compared with a historical control ORR of 10%, treatment with atezolizumab resulted in a significantly improved ORR of 16% in all patients. ORR was enriched in patients with tumor-infiltrating immune cell (IC) PD-L1 immunohistochemistry (IHC) scores of 2/3, with an observed ORR of 28% and CR rate of 15%. Durable responses were observed, with seventy one percent of responses ongoing at the time of data cutoff and median duration of response not yet reached after a median follow-up of 17.5 months (Dreicer et al. 2016). Median OS was 7.9 months (CI: 6.7, 9.3) in all patients and 11.9 months (CI: 9.0, 17.9) in the IC 2/3 population. Atezolizumab was well tolerated with a low rate of treatment-related Grade 3–4 toxicities and no treatment-related Grade 5 adverse events (Dreicer et al. 2016). Results from this cohort have led to the approval of atezolizumab in the United States for the treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

In Cohort 1, ORR in all patients was 24% (CI: 16, 32) in all patients with 7% CRs. Responses were durable, with 75% of responses ongoing at the time of data cutoff, and median duration of response not reached after a median follow-up of 14.4 months. Median OS in all patients was 14.8 months (CI: 10.1, not estimable; Balar et al. 2016). Atezolizumab was well tolerated with a low rate of treatment-related Grade 3–4 toxicities

and one treatment-related Grade 5 adverse event of sepsis (Balar et al. 2016). The OS and tolerability profile observed in this Phase II study compare favorably with historical benchmarks for carboplatin-based chemotherapy and strongly support further evaluation of atezolizumab in cisplatin-ineligible patients with metastatic UC.

1.3 BACKGROUND ON MOXR0916

OX40 is a member of the TNF receptor superfamily that is transiently expressed by T cells upon engagement of the TCR. Ligation of OX40 in the context of TCR engagement provides co-stimulatory signals to $CD4^+$ and $CD8^+$ effector T cells, resulting in enhanced proliferation, survival, and effector function. Conversely, OX40 signaling leads to functional inhibition and loss of regulatory T cells. In murine tumor models, OX40 engagement by an agonist anti-OX40 antibody can promote anti-tumor T-cell responses and tumor shrinkage (Moran et al. 2013).

MOXR0916 is an agonist monoclonal antibody that targets human OX40. It is a humanized effector-competent molecule based on a human IgG1 framework and is produced in Chinese hamster ovary cells.

MOXR0916 is being investigated as a single agent and in combination with atezolizumab in patients with locally advanced or metastatic solid tumors.

Nonclinical studies that supported the entry of MOXR0916 into clinical studies are described in the MOXR0916 Investigator's Brochure. Clinical experience with MOXR0916 is summarized briefly below and discussed in more detail in the MOXR0916 Investigator's Brochure.

1.3.1 Summary of Clinical Studies with MOXR0916

Preliminary clinical data are available from two ongoing Phase I studies in patients with locally advanced or metastatic solid tumors:

- Study GO29313, evaluating single-agent MOXR0916
- Study GO29674, evaluating the combination of MOXR0916 and atezolizumab

Both GO29313 and GO29674 share the same overall structure that includes the following:

- A dose-escalation stage to evaluate safety, tolerability, and pharmacokinetics and determine the maximum tolerated dose (MTD) or maximum administered dose
- An expansion stage, that includes the following:
  - Part I: a serial biopsy cohort to explore tumor biomarkers of pharmacodynamic (PK) activity and obtain additional safety, tolerability, and PK data at multiple dose levels that mirror the dose-escalation scheme
  - Part II: multiple indication-specific cohorts enrolled at a selected dose to better characterize the preliminary efficacy of the study regimen in different cancer types

1.3.2 Clinical Pharmacokinetics and Immunogenicity

In Study GO29313, preliminary PK data (0.2 to 1200 mg of MOXR0916, every 21 days) for MOXR0916 appeared to show linear pharmacokinetics at doses of ≥160 mg. The observed data are generally consistent with the expected pharmacokinetics of an IgG1 antibody in humans.

In Study GO29674, the preliminary data for serum pharmacokinetics of MOXR0916 (0.8 to 1200 mg, every 21 days) administered in combination with 1200 mg atezolizumab appeared to be similar to available single-agent PK data of MOXR0916. Similarly, preliminary PK data suggest similar atezolizumab pharmacokinetics in combination with MOXR0916 compared with historical single-agent PK data for atezolizumab at the 1200 mg dose.

The development of anti-therapeutic antibodies (ATAs) has been observed in some patients in most dose groups. Serum MOXR0916 concentrations over time appear to be reduced in some patients who were ATA positive compared with patients who were ATA negative. At higher dose levels (≥300 mg), the effect of ATA on pharmacokinetics appeared to be limited, and serum concentrations were maintained throughout all dosing cycles. No clear relationship between detection of ATAs and adverse events or infusion reactions has been observed. However, data are limited, and no definitive conclusions can be made. Immunogenicity assessment is ongoing in both studies.

1.3.3 Clinical Safety

Overall, MOXR0916 has been well tolerated as a single agent and in combination with atezolizumab.

As of 1 July 2016, preliminary safety data are available for 164 patients with refractory solid tumors who received MOXR0916 at doses between 0.2 to 1200 mg intravenous (IV) every 21 days, including 101 patients treated at the 300 mg dose level selected for expansion. No dose limiting toxicities were observed and no maximum tolerated dose was reached. Adverse events attributed to MOXR0916 across dose levels were generally Grade 1 or 2 in maximum severity and transient or manageable (Hansen et al. 2016).

As of 12 July 2016, preliminary safety data are available for 211 patients with locally advanced or solid tumors who received MOXR0916 at doses between 0.8 and 1200 mg in combination with atezolizumab 1200 mg IV every 21 days. These include 170 patients treated at the 300-mg dose level of MOXR0916 selected for expansion, of whom 26 patients were enrolled in a dedicated UC cohort. No dose limiting toxicities were observed and no maximum tolerated dose was reached (Infante et al. 2016). The most frequently observed adverse events regardless of attribution (occurring in ≥10% of all patients) include fatigue, nausea, diarrhea, constipation, pyrexia, decreased appetite, vomiting, abdominal pain, and anemia. Adverse events attributed to the combination of

MOXR0916 and atezolizumab across dose levels were generally Grade 1 or 2 in maximum severity and transient or manageable. No disease-specific safety trends were observed in the UC expansion cohort. Overall, the preliminary data on the frequency and severity of adverse events attributed to the combination of MOXR0916 and atezolizumab in the ongoing Study GO29674 has not been distinguishable from the more thoroughly characterized toxicity profile of atezolizumab as a single agent (Atezolizumab Investigator's Brochure).

1.3.4 Clinical Efficacy

Based on ongoing indication-specific expansion cohorts in Study GO29313, MOXR0916 appears to have limited efficacy as a single agent. In Study GO29674, the combination of MOXR0916 and atezolizumab is being evaluated in ongoing expansion cohorts for patients with UC, non–small cell lung cancer, triple-negative breast cancer, renal cell carcinoma, and melanoma, with preliminary anti-tumor activity observed in each cohort. Mature response rate, duration of response (DOR), survival data, and the relationship between biomarkers and efficacy are not yet available for these ongoing cohorts. Comparative efficacy with respect to atezolizumab monotherapy cannot be determined from Study GO29674 based on the single-arm Phase I design.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The approval of atezolizumab for the second-line therapy of patients with UC marked a notable advance in a stagnant therapeutic landscape otherwise comprised of cytotoxic chemotherapy regimens. Available data from the pivotal Phase II trial IMvigor210 demonstrate that the tolerability and durability of response observed with atezolizumab are qualitatively distinct from those observed with chemotherapy. In particular, median OS in this study was 7.9 months for patients previously treated with platinum-based regimens and 14.8 months for first-line cisplatin-ineligible patients (Balar et al. 2016; Dreicer et al. 2016; Rosenberg et al. 2016). In contrast, the median OS for first-line cisplatin-ineligible UC patients treated with carboplatin/gemcitabine in a large Phase III study was 9.3 months (De Santis et al. 2012).

Nevertheless, despite the robust activity observed with PD-L1/PD-1 inhibitors across diverse malignancies, durable clinical benefit appears limited to a minority of patients. Although several published studies suggest that the expression of PD-L1 in tumors correlates with response to PD-L1/PD-1 inhibition (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016), more refined patient selection strategies to reliably identify those most likely to respond are required. In addition to improving patient selection, broadening the population eligible to benefit from checkpoint blockade through combination therapies that address intrinsic or acquired mechanisms of resistance to PD-L1/PD-1 inhibitors is an urgent priority. Resistance may occur at the level of the effector T cell, which may be downregulated by multiple co-inhibitory inputs. Resistance may also originate with other immunosuppressive cell types in the tumor microenvironment, such as regulatory

T cells, myeloid-derived suppressor cells, and tumor-associated macrophages.

OX40 is a co-stimulatory receptor expressed on antigen experienced T cells but not detected on naïve T cells. OX40 signaling, upon engagement with its ligand OX40L in the context of antigen recognition by the T-cell receptor, enhances the proliferation and survival of effector T cells and inhibits the suppressive function of regulatory T cells (Moran et al. 2013). In multiple murine syngeneic tumor models, targeting of OX40 with an agonist antibody results in co-stimulation of effector T cells, as measured by proliferation and inflammatory cytokine production, as well as reduction of regulatory T cells. This dual mechanism of action is predicted to complement the activity of PD-L1 blockade by enhancing priming of anti-tumor T-cell responses as well as reversing regulatory T cell-mediated suppression of intratumoral effector T cells. Indeed, the combination of antibodies targeting OX40 and PD-L1, has demonstrated greater anti-tumor activity in selected murine tumor models than either antibody as a single agent (see the MOXR0916 and Atezolizumab Investigator's Brochures).

OX40 expression has been detected on T cells in human tumor specimens from multiple cancer indications, including UC (Vetto et al. 1997; Ramstad et al. 2000; Petty et al. 2002, Ziai et al. 2015). Furthermore, expression levels of OX40 and PD-L1 are moderately correlated across tumor types (Genentech data on file). Hence, combination therapy targeting OX40 and PD-L1 may prove applicable to a broad population with diverse cancers including UC.

To date, the combination of the OX40 agonist MOXR0916 with the PD-L1 inhibitor atezolizumab has been evaluated in a large Phase Ib study (GO29674) that includes indication-specific expansion cohorts. The single-arm design, the uncontrolled biases in Phase I patient selection, and the size constraints of individual expansion cohorts in Study GO29674 preclude straightforward conclusions about the efficacy of the combination relative to atezolizumab monotherapy. Hence, this Phase II trial is proposed as a randomized comparison of MOXR0916/atezolizumab to placebo/atezolizumab in a defined population of patients for whom atezolizumab represents an acceptable standard of care in order to establish proof-of-concept for the combination of anti-OX40 and anti-PD-L1.

While no direct benefits have been established at this time, the available nonclinical and clinical data provide a strong rationale for investigating the potential synergistic benefit of these combinations in patients with UC. Data from the ongoing Studies GO29313 and GO29674 suggest MOXR0916 has been generally well tolerated as a single agent and in combination with atezolizumab (Hansen et al. 2016; Infante et al. 2016). To date, there are no identified risks with MOXR0916. Nevertheless, the postulated mechanisms of action of anti-OX40 are predicted to complement and enhance the immune-potentiating activity of anti−PD-L1; hence, the combination may be associated with a higher frequency and/or greater severity of immune-related adverse events than observed with anti-PD-L1 as a single agent.

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-related causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with treatment. Engagement of the OX40 co-stimulatory pathway may further increase the risk of autoimmune inflammation as well as cytokine release syndrome. Therefore, MOXR0916 may cause adverse events similar to but independently of atezolizumab, may exacerbate atezolizumab-related adverse events, or may have non-overlapping toxicities with atezolizumab.

The largest clinical experience to date with the combination of complementary modulators of adaptive immunity is derived from trials of anti-CTLA4 in combination with anti-PD-1 (Wolchok et al. 2013, Antonia et al. 2014; Hammers et al. 2014; Larkin et al. 2015; Antonia et al. 2016). Based on these data, it is anticipated that combination immune-related adverse events will be monitorable and manageable in the clinical setting, though the frequency of immune-related adverse events may be increased as compared with either single agent alone. The extensive nonclinical and clinical experience with immune checkpoint inhibitors to date has been incorporated into the design and safety management plan (see Section 5.1) of this study in order to reduce the potential risks to participating patients. Moreover, an Internal Monitoring Committee (IMC) will be established (see Section 3.1.2) to monitor cumulative safety data at regular intervals and provide recommendations on study conduct to ensure the safety of trial participants.

2. OBJECTIVES AND ENDPOINTS

The Sponsor has determined that the original scientific aims of this study are no longer evaluable as a result of the Sponsor's decision to prematurely halt enrollment due to slow patient accrual. The original scientific aims of this study are described below solely for reference.

This study will evaluate the efficacy and safety of MOXR0916 plus atezolizumab compared with placebo plus atezolizumab in patients with locally advanced or metastatic UC who have not received prior systemic therapy in the locally advanced or metastatic setting and who are ineligible to receive cisplatin-based therapy.

- The total randomized population includes the following overlapping analysis groups for assessing efficacy (see Section 3.1 and Figure 1):
- Primary population: All patients randomized during Stage 1 of enrollment (see Section 3.1.1)
- PD-L1 IC2/3 population: All randomized patients with tumor PD-L1 IHC score of IC2/3

Specific objectives and corresponding endpoints for the study are outlined below.

Unless otherwise specified, efficacy objectives will be evaluated in both analysis populations.

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of MOXR0916 plus atezolizumab compared with placebo plus atezolizumab in the primary population	• PFS (defined as the time from randomization to the first occurrence of disease progression or death from any cause, whichever occurs first) as determined by the investigator according to RECIST v1.1 • OS, defined as the time from randomization to death from any cause
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of MOXR0916 plus atezolizumab compared with placebo plus atezolizumab in the PD-L1 IC2/3 population	• PFS as determined by the investigator according to RECIST v1.1 • OS, defined as the time from randomization to death from any cause
• To evaluate the efficacy of MOXR0916 plus atezolizumab compared with placebo plus atezolizumab	• Objective response (defined as a CR or PR) on two consecutive occasions ≥ 4 weeks apart as determined by the investigator according to RECIST v1.1 • DOR, (defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first) as determined by the investigator according to RECIST v1.1 • Time to pain progression as measured by patient-reported pain severity according to the MDASI • Time to pain palliation as measured by patient-reported pain severity according to the MDASI • Time to fatigue progression as measured by patient-reported fatigue severity according to the MDASI • Proportion of patients reporting symptom interference with daily living at the time of progression according to the MDASI
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of MOXR0916 plus atezolizumab compared with placebo plus atezolizumab	• Objective response, DOR, and PFS according to immune-modified RECIST • Objective response, DOR and PFS as determined by an IRF according to RECIST v1.1 • Time to progression of patient-reported symptoms (other than pain and fatigue) as measured by the MDASI. • Change from baseline in patient-reported symptoms and symptom interference with daily living as measured by the MDASI

Table 1 Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of MOXR0916 plus atezolizumab compared with placebo plus atezolizumab	• Incidence of adverse events, with severity determined through use of NCI CTCAE v4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoints**
• To characterize pharmacokinetics of MOXR0916 and atezolizumab when administered in combination	• Serum concentration of MOXR0916 at specified timepoints • Serum concentration of atezolizumab at specified timepoints
Exploratory Pharmacokinetic Objective	**Corresponding Endpoints**
• To evaluate potential relationships between drug exposure and the efficacy and safety of MOXR0916	• Serum concentration or PK parameters for MOXR0916 and efficacy endpoints • Serum concentration or PK parameters for MOXR0916 and safety endpoints
Immunogenicity Objective	**Corresponding Endpoints**
• To evaluate the immune response to MOXR0916 and atezolizumab	• Presence of ATAs to MOXR0916 during the study relative to the presence of ATAs at baseline • Presence of ATAs to atezolizumab during the study relative to the presence of ATAs at baseline
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate potential effects of ATAs	• ATA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate candidate biomarkers that may be associated with response to MOXR0916 and atezolizumab (i.e., predictive biomarkers), progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to MOXR0916 and atezolizumab, susceptibility to developing adverse events (i.e., safety biomarkers), or that may provide evidence of MOXR0916 and atezolizumab activity (i.e. pharmacodynamic biomarkers)	• Expression of PD-L1 in tumor tissue and measures of efficacy • Tumor mutational load and measures of efficacy • Biomarkers in blood and tumor tissue (listed in Section 4.5.6) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
Exploratory Health Status Utility Objective	**Corresponding Endpoint**
• To evaluate health status utility scores of patients treated with MOXR0916 plus atezolizumab compared with placebo plus atezolizumab	• Health status as measured using the EQ-5D-5L questionnaire for health economic modeling

Table 1 Objectives and Corresponding Endpoints (cont.)

ATA = anti-therapeutic antibodies; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DOR = duration of objective response; EQ-5D-5L = Euro QoL 5 Dimensions 5-Level; IC = tumor-infiltrating immune cell; IRF = independent review facility; MDASI = M. D. Anderson Symptom Inventory; NCI = National Cancer Institute; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase II, multicenter, randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of MOXR0916 in combination with atezolizumab versus placebo and atezolizumab in patients with locally advanced or metastatic UC who have not received prior systemic therapy in the locally advanced/metastatic setting and who are ineligible to receive cisplatin-based therapy.

This study consists of a screening period, a treatment period, and a post-treatment follow-up period. Tumor specimens from patients will be prospectively tested for PD-L1 expression per IHC by a designated central laboratory prior to randomization (see Sections 4.1.1 and 4.5.6.2). The IHC scores will have two categories based on expression on tumor-infiltrating immune cells (IC0/1 and IC2/3).

[redacted]

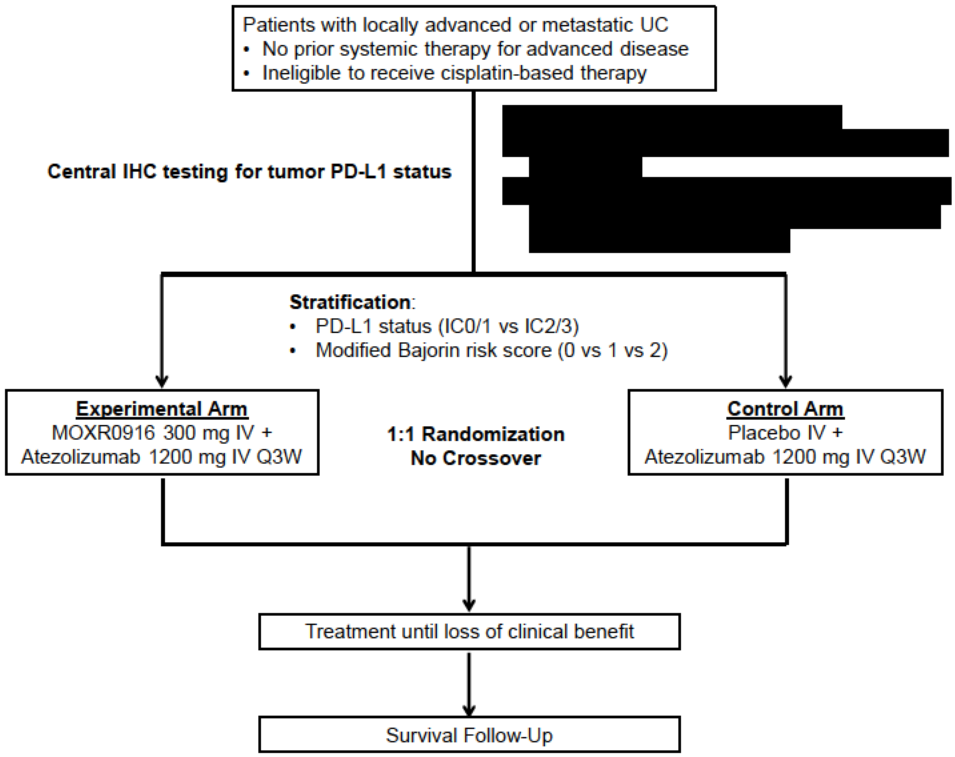
Patients will be randomized in a 1:1 ratio (experimental to control arm) to receive one of the following:

- Experimental arm: MOXR0916 plus atezolizumab
- Control arm: placebo plus atezolizumab

Randomization will be stratified by the following factors:

- PD-L1 status as centrally determined by IHC (IC0/1 or IC2/3)
- Modified Bajorin risk score (0, 1, or 2), which is derived from the ECOG Performance Status and the presence or absence of visceral metastases (Bajorin et al. 1999; see Appendix 2)

Figure 1 Study Schema



IC = tumor-infiltrating immune cell; IHC = immunohistochemistry; IV = intravenous; PD-L1 = programmed death-ligand 1; Q3W = every 3 weeks; UC = urothelial carcinoma.

MOXR0916/placebo and atezolizumab will be administered by intravenous (IV) infusion at fixed doses of 300 mg and 1200 mg, respectively, on Day 1 of each 21-day cycle. Patients will receive study treatment (MOXR0916/placebo plus atezolizumab) until unacceptable toxicity or loss of clinical benefit, as determined by the investigator after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). *Following unblinding by the investigator, patients assigned to the placebo arm will discontinue placebo infusions and continue atezolizumab alone. Patients assigned to the MOXR0916 arm may continue study treatment with the combination of atezolizumab and MOXR0916 or with atezolizumab alone based on a discussion of benefit and risk with the treating investigator.*

Because of the possibility of pseudoprogression with atezolizumab-based therapy (see Section 1.1.1), radiographic progression per RECIST v1.1 may not be indicative of true disease progression. Patients who meet RECIST v1.1 criteria for progressive disease while receiving study treatment will be permitted to continue study treatment if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator

- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of decline in ECOG Performance Status 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
- Written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial radiographic disease progression per RECIST v1.1
- No further radiographic progression of disease at the next imaging assessment and continued demonstration of clinical benefit per the investigator.

No crossover will be allowed.

Patients will undergo tumor assessments at screening and at intervals during the study *to be determined by the investigator based on the patient's disease characteristics and local institutional standards* (see Section 4.5.5 and Appendix 1).

All adverse events will be monitored and recorded for at least 90 days after the last dose of study treatment or until initiation of another systemic anti-cancer therapy, whichever occurs first (see Section 5.3.1). After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event if the event is believed to be related to prior study treatment. Adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0.

An updated schedule of activities is provided in Appendix 1.

3.1.2 Internal Monitoring Committee

This study *established* an IMC to review available safety data and to make recommendations regarding study conduct to ensure the safety of patients enrolled on the study. The IMC Chair *is* a medical oncologist who is not the Medical Monitor and is not associated with the study. Other IMC members include key study team members including the drug safety scientist, biostatistician, statistical programmer, and clinical pharmacologist. The responsibility, membership, and communication flow of the IMC is further described in the IMC charter.

For the study as originally designed, the IMC planned to review cumulative safety data approximately every 6 months, or more frequently if recommended by the IMC or Sponsor, until the study *was* unblinded for primary analysis. *However, given that enrollment has been prematurely halted (for reasons unrelated to safety) and the study will no longer be blinded, the IMC may recommend modification or suspension of its activities and modify its charter accordingly.*

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the number of OS events specified for the final analysis in Section 6.4 has been observed. Additionally, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 45 months.

3.3 RATIONALE FOR STUDY DESIGN

The study design has been streamlined subsequent to the Sponsor's decision to halt enrollment due to study accrual. For procedures and assessments that have been removed, the corresponding rationale has been deleted or modified accordingly.

3.3.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle), which is the approved dosage for atezolizumab (Tecentriq™ U.S. Package Insert).

Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg Q3W. The MTD of atezolizumab was not reached and no DLTs have been observed at any dose in Study PCD4989g. The fixed dose of 1200 mg Q3W (equivalent to an average body weight−based dose of 15 mg/kg Q3W) has been selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data as described below.

The pharmacokinetics of atezolizumab monotherapy have been characterized in patients in Study PCD4989g at doses 0.01 mg/kg to 20 mg/kg Q3W, including the fixed dose 1200 mg (equivalent to 15 mg/kg). Exposure to atezolizumab increased dose-proportionally over the dose range of 1 mg/kg to 20 mg/kg. While a subset of ATA-positive patients in Study PCD4989g receiving 0.3 to 3 mg/kg atezolizumab Q3W experienced a reduction of atezolizumab minimum serum concentration (Cmin) to below the PK assay lower limit of quantification (LOQ), patients receiving 10 to 20 mg/ kg atezolizumab, including the fixed 1200-mg dose, maintained geometric mean C_{min} that was in excess of both the LOQ and the target serum concentration of 6 mg/mL.

[redacted]

3.3.2 Rationale for MOXR0916 Dose and Schedule

The proposed regimen of MOXR0916 300 mg administered every 21 days has been selected on the basis of available clinical data from Studies GO29313 and GO29674 as

below:

- MOXR0916 has been evaluated across a wide dose range as a single agent (0.2–1200 mg) and in combination with atezolizumab (0.8–1200 mg) without DLTs or clear dose related trends in the incidence or severity or adverse events.
- The MOXR0916 dose of 300 mg administered every 21 days is expected to achieve sustained saturation of OX40 receptor in tumors throughout the dosing interval (data on file).
- Available data indicate minimal impact of ATA on exposure at doses ≥300 mg.
- The pharmacokinetics of MOXR0916 appear to be generally consistent with that of a typical IgG1, monoclonal antibody, supporting the proposed every 21-day dosing interval (see MOXR0916 Investigator's Brochure).

MOXR0916 is being evaluated at 300 mg Q3W in ongoing dose expansion cohorts in both Studies GO29313 (single agent) and GO29674 (combination with atezolizumab). Preliminary safety and PK data from these ongoing cohorts continue to support the proposed Phase II dose and schedule.

3.3.3 Rationale for Patient Population, Analysis Groups, and Enrollment Stages

Inoperable locally advanced/metastatic UC is a uniformly lethal disease with high unmet medical need. Patients who are ineligible for cisplatin-based regimens due to comorbidities have particularly poor outcomes, characterized by transient responses at the cost of significant toxicity, with available standard therapies. Even the most fit among these patients, who are eligible for carboplatin-based combinations, experience a median OS of 8–9 months (see Section 1.1.1). In contrast, Phase II data (IMvigor210, Cohort 1) for atezolizumab in previously untreated cisplatin-ineligible patients with advanced UC demonstrated favorable tolerability, DORs and a median OS of 14.8 months (Balar et al. 2016; see Section 1.2.1). These data robustly support further evaluation of atezolizumab in first-line cisplatin-ineligible UC patients.

[redacted]

[redacted]

Tumor PD-L1 status does not indicate simply the expression of the target of atezolizumab. Rather, it reflects adaptive induction of PD-L1 in response to T-cell-derived interferon-γ and hence the presence of a pre-existing anti-tumor immune response (Taube et al. 2012; Herbst et al. 2014). PD-L1 expression on tumor-infiltrating immune cells has been shown to be associated with other hallmarks of pre-existing immunity, such as high expression of effector T cell-associated and interferon-γ-associated genes (Fehrenbacher et al. 2016). [redacted]

[redacted]

3.3.4 Rationale for Control Group

3.3.4.1 Atezolizumab as a Comparator

The primary hypothesis tested by this study is whether the addition of MOXR0916 to atezolizumab enhances the clinical activity of atezolizumab in patients with cisplatin-ineligible UC. Therefore, it is appropriate to compare against atezolizumab as the active control. Moreover, as described above in Section 3.3.3), outcomes with atezolizumab compare favorably to those achieved with standard available therapies for this population.

3.3.4.2 Placebo Control

Placebo for MOXR0916 will no longer be utilized subsequent to the unblinding of the study.

3.3.5 Rationale for Stratification Factors

Patients will be stratified on the basis of PD-L1 expression and Bajorin risk model/liver metastasis.

3.3.5.1 PD-L1 expression (IC0/1 vs. IC2/3)

PD-L1 expression is prevalent in many human tumors (e.g., lung, bladder, renal, ovarian, melanoma, malignant lymphoma, multiple myeloma, and colon carcinoma), and elevated PD-L1 expression was reported to be associated with a worse prognosis in patients with several cancers, including lung cancer, renal cell carcinoma, melanoma, colorectal cancer, ovarian cancer, and others (Mu et al. 2011; Herbst et al. 2014; Powles et al. 2014).

Responses to atezolizumab have been observed in patients with mUC whose tumors demonstrate a PD-L1 IHC score of IC2/3 as well as in patients with an IHC score of IC0/1 (Dreicer et al. 2016). In Phase I and II studies of atezolizumab, higher levels of PD-L1 expression have been associated with higher response rates in patients with urothelial carcinoma. Because PD-L1 expression may impact efficacy outcomes, the randomization will be stratified by PD-L1 expression by IHC in order to minimize potential imbalances between treatment arms within levels of PD-L1 expression.

3.3.5.2 Bajorin Risk Factor Score/Liver Metastasis (0 vs. 1 vs. 2 or Liver Metastasis)

The Bajorin risk model is a prognostic model that was developed to predict OS for patients with metastatic UC who were treated with cisplatin-based chemotherapy (Bajorin et al. 1999). The model includes two pre-treatment variables: Karnofsky performance status (less than 80% vs. at least 80%) and presence/absence of visceral (lung, liver, or bone) metastases. A post hoc analysis of the EORTC Trial 30986 in cisplatin-ineligible patients, based on Bajorin risk groups (0, 1, or 2 risk factors), demonstrated that as the number of risk factors increased, OS decreased significantly (De Santis et al. 2012). Because OS is a co-primary efficacy endpoint and the Bajorin risk model identifies risk factors for OS, the randomization will be stratified by Bajorin risk score to minimize imbalances between treatment arms within levels of the Bajorin risk score.

3.3.6 Rationale for Collection of Mandatory Baseline Tumor Specimens (Archival or Pre-Treatment Biopsy)

In this study, tumor specimens from patients will be prospectively tested for PD-L1 expression by a central laboratory during the screening or pre-screening period, and

patients who are enrolled will be stratified according to tumor tissue PD-L1 expression.

3.3.7 Rationale for Treatment Beyond Radiographic Progression

Cancer immunotherapies may result in early radiographic progression (including the appearance of new lesions) that is followed by delayed tumor shrinkage consistent with the time required to mobilize an effective anti-tumor immune response (Wolchok et al. 2009). Additionally, responding tumors may appear to initially increase in size because of the influx of immune cells (Hoos et al. 2010; Pennock et al. 2012). Such unconventional "pseudoprogression" response patterns have been described in patients treated with anti-CTLA-4 (Wolchok et al. 2009) and anti-PD-L1/anti−PD-1 agents (Hodi et al. 2014). Evidence of tumor growth followed by a response was also observed in several tumor types in the atezolizumab Phase I study PCD4989g. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed ICs and no viable cancer cells.

Cisplatin-ineligible patients with metastatic UC have limited options that offer unsatisfactory survival outcomes at the cost of the toxicities associated with chemotherapy (see Section 1.1.1). Given the potential for pseudoprogression associated with atezolizumab-based therapy, and the limited efficacy and high toxicity associated with available standard therapies, selected patients may be considered for treatment beyond apparent radiographic progression per RECIST v1.1, provided the benefit-risk ratio is judged to be favorable by the investigator (see criteria in Section 3.1). Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic and biochemical data, biopsy results (if available), and clinical status.

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients with locally advanced or metastatic UC who have not received prior systemic therapy in the locally advanced or metastatic setting and who are ineligible to receive cisplatin-based therapy will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Ability to comply with the study protocol, in the investigator's judgment
- ECOG Performance Status of ≤ 2
- Life expectancy ≥ 12 weeks
- Histologically or cytologically confirmed locally advanced (T4b, any N; or any T,

N 2–3) or metastatic UC (M1, Stage IV) (also termed TCC or UCC of the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra)

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

Locally advanced bladder cancer must be inoperable on the basis of involvement of pelvic sidewall or adjacent viscera (clinical Stage T4b) or bulky nodal metastasis (N2–N3).

- Availability of a representative tumor specimen to enable central testing for determination of PD-L1 status and exploratory research on biomarkers (see Section 4.5.6.2)

  A formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections, must be submitted along with an associated pathology report prior to study enrollment. If only 10–14 slides are available, the patient may still be eligible for the study, after discussion with and approval by the Medical Monitor.

  Submitted archival tumor tissue must be evaluated for PD-L1 expression prior to enrollment. Patients whose tumor tissue is not evaluable for PD-L1 expression are not eligible.

  If patients have multiple adequate tissue samples from procedures performed at different times during the course of their UC; priority should be given to the tissue most recently collected. Multiple samples may be submitted for a given patient, on the basis of availability; however, the requirement for a block or ≥ 15 unstained slides should be satisfied by a single biopsy or resection specimen. If multiple tumor specimens are submitted, patients may be eligible if at least one specimen is evaluable for PD-L1. In the event that enrollment is limited to PD-L1 selected patients, the highest PD-L1 score among the submitted samples will be used to determine eligibility.

  Transurethral resection of bladder tumor (TURBT) specimens must contain a muscle invasive component (i.e., T2 or greater) of the bladder tumor as documented in the pathology report. If the TURBT specimens do not contain a muscle invasive component, then specimens obtained at the time of cystectomy/nephroureterectomy or metastatic spread (i.e., sample from a metastatic lesion) will be required prior to randomization.

  Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

  Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, and cell pellets, pleural effusions and lavage samples are not acceptable.

  Patients who do not have tissue specimens that meet eligibility requirements may undergo a biopsy prior to enrollment. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

Prior to signing the main study informed consent form, patients may sign a pre-screening consent form to specifically allow the collection and testing of archival or fresh tumor specimens.

Refer to Section 4.5.6 for additional information on tumor specimens collected.

- No prior systemic therapy for inoperable locally advanced or metastatic UC

  For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for UC, a treatment-free interval >12 months between the last treatment administration and Cycle 1, Day 1 is required in order to be considered treatment naive in the metastatic setting.

- Ineligible for cisplatin-based chemotherapy as defined by any one of the following criteria:
  - Impaired renal function (glomerular filtration rate [GFR] >30 but <60 mL/min); GFR may be assessed by calculation from serum/plasma creatinine (Cockcroft-Gault formula) or direct measurement (i.e., creatinine clearance or ethyldediaminetetra-acetate)
  - NCI CTCAE v4.0 Grade ≥ 2 audiometric hearing loss (25 dB at two contiguous frequencies or more severe)
  - NCI CTCAE v4.0 Grade ≥ 2 peripheral neuropathy (i.e., sensory alteration or paresthesias, including tingling)
  - ECOG Performance Status of 2
- Measurable disease according to RECIST v1.1

  Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.

- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - White blood cell (WBC) counts $\geq$ 2,500/μL
  - ANC $\geq$ 1500/μL (without granulocyte colony-stimulating factor support 14 days prior to Cycle 1, Day 1)
  - Lymphocyte count $\geq$ 500/μL
  - Platelet count $\geq$ 100,000/μL (without transfusion 14 days prior to Cycle 1, Day 1)
  - Hemoglobin $\geq$ 9.0 g/dL

    Patients may be transfused to meet this criterion.

    Patients with a solitary kidney or chronic kidney disease with low erythropoietin production may use erythropoietin-stimulating agents.
  - AST, ALT, and alkaline phosphatase (ALP) $\leq 3 \times$ upper limit of normal (ULN), with the following exception:

    Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
  - Serum bilirubin $\leq 1.5 \times$ ULN

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

- Measured or calculated creatinine clearance ≥ 30 mL/min (calculated using the Cockcroft-Gault formula)
- Serum albumin ≥ 2.5 g/dL
- Prothrombin time (PT)/INR and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN

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

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of < 1% per year during the treatment period and for at least 6 months after the last dose of study treatment

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

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

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

- 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 or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  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.

4.1.2 Exclusion Criteria

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

- Pregnant or lactating, or intending to become pregnant or breast feed during the

study or 6 months afterward

Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater, see Appendix 4), myocardial infarction, or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina

  Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF 40%–50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, and inherited liver disease
- Major surgical procedure within 4 weeks prior to initiation of study treatment or anticipation of need for a major surgical procedure during the course of the study.

  TURBT is considered a minor surgical procedure

- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Any approved anti-cancer therapy, including chemotherapy or hormonal therapy, within 3 weeks prior to initiation of study treatment; the following exceptions are allowed:
  - Palliative radiotherapy for bone metastases or soft tissue lesions that is completed > 7 days prior to baseline imaging
  - Radiotherapy for brain metastases as stipulated below
  - Prior local intravesical chemotherapy or immunotherapy is allowed if completed at least 4 weeks prior to the initiation of study treatment
  - Hormone-replacement therapy or oral contraceptives
  - Patients should be recovered from any toxicities associated with permitted anti-cancer therapies
- Prior treatment with CD137 or OX40 agonists, anti–CTLA-4, anti–PD-1, anti–PD-L1, anti-CD-27, anti-GITR therapeutic antibody or pathway-targeting agents
- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to initiation of study treatment
- Untreated CNS metastases or active (progressing or requiring corticosteroids for symptomatic control) CNS metastases

  Patients with a history of treated asymptomatic CNS metastases are eligible,

provided they meet all of the following criteria:

- Measurable disease outside the CNS
- No ongoing requirement for corticosteroids as therapy for CNS disease, with corticosteroids discontinued for ≥ 2 weeks prior to enrollment
- Anticonvulsants at a stable dose are allowed
- No stereotactic radiation within 7 days or whole-brain radiation within 14 days prior to Cycle 1, Day 1
- No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

Patients with new asymptomatic CNS metastases detected during screening 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, if all other criteria are met.

- Any history of leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX) are allowed.
- Uncontrolled tumor-related pain

  Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment.

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Malignancies other than UC within 5 years prior to Cycle 1, Day 1

  Patients with localized low-risk prostate cancer (defined as Stage ≤ pT2b, Gleason score ≤ 7, and prostate-specific antigen (PSA) at prostate cancer diagnosis ≤ 20 ng/mL) treated with curative intent and without PSA recurrence are eligible.

  Patients with pre-existing low-risk prostate cancer (defined as Stage cT1/T2a, Gleason score ≤ 7 and PSA ≤ 10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible.

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

  Malignancy treated with expected curative intent (e.g., 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

- Uncontrolled or symptomatic hypercalcemia ($>$1.5 mmol/L ionized calcium or calcium $>$12 mg/dL or corrected serum calcium $>$ULN)
- History of autoimmune disease with the following caveats:

  Patients with a history of autoimmune-related endocrinopathy (e.g., hypothyroidism) on a stable dose of replacement hormone (e.g., thyroid hormone) may be eligible for this study.

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

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

  - Rash must cover $<$10% of body surface area
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study with the following exceptions:

  Patients who have received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication are eligible for the study.

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to initiation of study treatment
- History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan

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

  History of drug-induced pneumonitis that was asymptomatic (defined by

radiographic findings only) and reversible (without any anti-inflammatory therapies) is permitted

- Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening

  Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study.

- Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test at screening

  Patients who have a positive HCV antibody test are eligible for the study if a polymerase chain reaction assay is negative for HCV RNA

- Positive HIV test at screening
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Patients with recent infections that are not judged to be severe (as described above) are excluded if they have either:

  Signs or symptoms of infection within 2 weeks prior to initiation of study treatment

  Patients with uncomplicated viral upper respiratory tract infections are eligible provided symptoms have resolved to baseline.

  Received oral or IV antibiotics (including anti-fungal or anti-viral therapy) within 2 weeks prior to initiation of study treatment for suspected or confirmed infection

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

- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks before initiation of study treatment, or anticipation of need for such a vaccine during the course of the study.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to biopharmaceutical agents produced in Chinese hamster ovary cells
- Known allergy or hypersensitivity to any component of the atezolizumab formulation
- Known allergy or hypersensitivity to any component of the MOXR0916 formulation

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient (including determination of tumor PD-L1 status by central testing), the study site will obtain the patient's identification number and treatment assignment from the interactive voice or web-based response system (IxRS).

Patients will be randomized to one of two treatment arms: MOXR0916 plus atezolizumab or placebo plus atezolizumab. Randomization will occur in a 1:1 ratio using a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- PD-L1 expression in ICs by IHC (IC0/1 or IC2/3)
- Modified Bajorin risk factors (see Appendix 2)

Following unblinding by the investigator (Section 4.2.3), patients assigned to the placebo arm will discontinue placebo infusions and continue atezolizumab alone. Patients assigned to the MOXR0916 arm may continue study treatment with the combination of atezolizumab and MOXR0916 or with atezolizumab alone based on a discussion of benefit and risk with the treating investigator.

4.2.2 Blinding

Under the original study design, the Sponsor and its agents (with the exception of the IxRS service provider, laboratory personnel performing PK or biomarker analyses, and the IMC members) *were to* be blinded to treatment assignment until the primary analysis. Study site personnel and patients *were to* be blinded to treatment assignment throughout the study. *Subsequent to the decision to halt enrollment, subjects will be unblinded as outlined below.*

4.2.3 Unblinding

Because this trial will not meet its study objectives following the Sponsor's decision to halt accrual, blinding as a method to minimize bias in study conduct or interpretation is no longer necessary. The investigator will break the treatment code by contacting the IxRS. Investigators are encouraged to consult with the Medical Monitor prior to performing emergency unblinding. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event). Unblinding should not result in the withdrawal of patients from the study.

4.3 STUDY TREATMENT

The investigational medicinal products (IMP) for this study are MOXR0916, placebo, and atezolizumab.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 MOXR0916 and Placebo

Placebo will no longer be supplied by the Sponsor.

MOXR0916 will be supplied by the Sponsor as a sterile liquid in either of the following two configurations:

- A single-use, 15-mL glass vial containing approximately 10 mL (200 mg) of MOXR0916 solution.
- A single-use, 6-mL glass vial containing approximately 5 mL (300 mg) of MOXR0916 solution.

For information on the formulation, packaging, and handling of MOXR0916, *see* the pharmacy manual and MOXR0916 Investigator's Brochure.

4.3.1.2 Atezolizumab

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

For information on the formulation, packaging and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure

4.3.2 Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.

Administration of MOXR0916 and atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 5.

Any overdose or incorrect administration of MOXR0916 or atezolizumab should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.1 MOXR0916 and Placebo

The dose of MOXR0916 to be administered in this study is 300 mg IV Q3W. This dose is fixed and not dependent on body weight. Patients randomized to the control arm will *discontinue placebo infusions following unblinding by the investigator (Section 4.2.3).*

Table 2 Administration of First and Subsequent MOXR0916 Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted. • Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • MOXR0916 should be infused over 60 (±10) minutes. • If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (±5 minutes for all timepoints) and at 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • MOXR0916 should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±10) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded every 15 (±5) minutes during the infusion, at the end of the infusion (±5 minutes), and at 30 (±5) minutes after the infusion.

There will be no dose modification for MOXR0916 in this study. General guidance on treatment interruption or discontinuation is provided in Section 5.1.4. Guidelines on study drug administration in the context of management of specific adverse events, including infusion-related reactions (see Table 13) is provided in Section 5.1.5.

4.3.2.2 Atezolizumab

The dose of atezolizumab to be administered in this study is 1200 mg IV Q3W. This dose is fixed and not dependent on body weight.

Atezolizumab will be administered after the MOXR0916 infusion, as described in Section 4.3.2.1. There is no minimum observation time between infusions in the absence of symptoms or signs related to the first infusion. In the event of a Grade 1 or 2 infusion-related reaction associated with the MOXR0916 infusion, atezolizumab will not be administered until resolution of symptoms or signs to baseline.

Atezolizumab infusions will be administered per the instructions outlined in Table 3.

Table 3 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted. • Vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded between the MOXR0916 and atezolizumab infusions, within 60 minutes prior to the atezolizumab infusion. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (±5 minutes for all timepoints) and at 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded between the MOXR0916 and atezolizumab infusions, within 60 minutes prior to the atezolizumab infusion. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded every 15 (±5) minutes during the infusion, at the end of the infusion (±5 minutes), and at 30 (±5) minutes after the infusion.

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

There will be no dose modification for atezolizumab in this study. General guidance on treatment interruption or discontinuation is provided in Section 5.1.4. Guidelines on study drug administration in the context of management of specific adverse events, including infusion-related reactions (see Table 13) is provided in Section 5.1.5 and in the Atezolizumab Investigator's Brochure.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (MOXR0916/placebo and atezolizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to 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-Trial Access to MOXR0916 and Atezolizumab

The Sponsor (Genentech, a member of the Roche Group) will offer post-trial access to the study drugs (MOXR0916, for patients assigned to the experimental arm only, and atezolizumab, for patients assigned to either arm) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study treatment after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study 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

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

- The combination of MOXR0916 and atezolizumab 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)
- The Sponsor has discontinued development of the study treatment or data suggest that the study treatment is not effective for UC

  Exceptions may be granted at the Sponsor's discretion.
- The Sponsor has reasonable safety concerns regarding the study treatment as treatment for UC
- Provision of study treatment is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

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

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug to the study completion/ discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Inactivated vaccinations
- Megestrol administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Corticosteroids administered for chronic obstructive pulmonary or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

    After Cycle 2, palliative radiotherapy is permitted, provided that the lesion to be irradiated is not the only site of measurable disease. Study treatment may be continued during palliative radiotherapy.

- Local therapy (e.g., surgery, stereotactic radiosurgery, radiotherapy, radiofrequency ablation) as outlined below:

    Patients experiencing a mixed response requiring local therapy for control of three or fewer lesions may still be eligible to continue study treatment. Patients who receive local therapy directed at a target lesion will no longer be evaluable for radiographic response but will remain evaluable for progression. Such cases must be discussed with and approved by the Medical Monitor

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

4.4.2 Cautionary Therapy

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial

immunologic effects of treatment with MOXR0916 and atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with MOXR0916 and atezolizumab therapy (refer to the MOXR0916 and Atezolizumab Investigator's Brochures for details).

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.3) may be used during the study at the discretion of the investigator

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority–approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section 4.4.1 for details).
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with MOXR0916 and atezolizumab, and for 6 months after the last dose of MOXR0916 and atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or five half-lives of the drug (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with MOXR0916 and atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of MOXR0916 and atezolizumab.

4.5 STUDY ASSESSMENTS

Following the Sponsor's decision to curtail enrollment, certain study assessments have

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

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other administrative disruption that precludes the visit, the visit should be scheduled on the nearest following feasible date.

Collection of any non-safety-related data or patient samples may be terminated by the Sponsor at any time if further collection of such data or samples is also not related to the study's primary objective. The decision to discontinue any data collection will be communicated to sites (Institutional Review Boards and Ethics Committees) by means of a memorandum and will not require a protocol amendment.

4.5.1 Informed Consent Forms and Screening Log

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

Prior to signing the main Informed Consent Form for the study, patients may give consent specifically for the collection and testing of archival or fresh tumor tissue for PD-L1 expression by signing a Prescreening Informed Consent Form.

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

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including stage, date of diagnosis, and prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol, and drugs of abuse will be recorded at baseline. A history of pleural or pericardial effusion or of ascites requiring intervention should be entered in the medical history. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity. Race/ethnicity will be recorded because of the potential contribution of this variable to differences in observed pharmacokinetics, pharmacodynamics, toxicity, and/or response to treatment.

4.5.3 Physical Examinations

A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

ECOG Performance Status (see Appendix 6) should be assessed per the schedule of assessments in Appendix 1).

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, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

Vital signs should be measured within 60 minutes prior to the first infusion, between the MOXR0916 and atezolizumab infusions (within 60 minutes prior to the atezolizumab infusion) and, if clinically indicated, during or after the infusions (see Section 4.3.2). In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

Vital signs collected at the screening visit and the treatment discontinuation visit should be recorded in the eCRF. For all other visits, only those vital signs that are obtained prior to the first study drug infusion of the day or that constitute an adverse event (e.g., temperature for event of fever) or a primary manifestation of an adverse event (e.g., blood pressure associated with an infusion related reaction or heart rate associated with an arrhythmia) should be recorded in the eCRF. All vital signs collected per protocol should be documented in the patient's medical record.

Blood oxygen saturation will be measured by pulse oximetry.

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline and *during* the *study, with* the *imaging modality (e.g., CT vs. MRI scan, contrast-enhanced vs. non-contrast) and the frequency to* be *determined primarily by the investigator based* on the *patient's disease characteristics and local institutional standards* (i.e., *approximately every 6*–12 weeks). At the investigator's discretion, tumor assessments may be performed at any time if progressive disease is suspected. Tumor assessments will continue until radiographic disease progression (or loss of clinical benefit as determined by the investigator for patients who continue treatment after disease progression according to RECIST v1.1),

withdrawal of consent, loss to follow-up, death, or study termination by the Sponsor, whichever occurs first.

Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will be monitored with a follow-up scan in 6 (±1) weeks. Tumor assessments should be continued every 6 (±1) weeks thereafter until two consecutive scans demonstrate stability or improvement with respect to the first scan that showed radiographic disease progression, at which point the scan frequency *may be liberalized at the investigator's discretion*.

All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to randomization do not have to be repeated at screening.

Screening assessments *should* include CT scans (with IV contrast *recommended* unless contraindicated or MRI scans of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest and MRI scans of the abdomen, pelvis, and head *are recommended*.

Brain imaging (either MRI or contrast-enhanced CT) is required at screening for any patient with treated brain metastases (see Section 4.1.2) and as clinically indicated based on symptoms or signs suggestive of new or worsening CNS metastases. An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Patients with treated asymptomatic CNS metastases may be eligible, provided they meet all of the criteria detailed in Section 4.1.2.

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

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

CT scans of the neck or extremities should also be performed if clinically indicated and repeated throughout the study if there is evidence of disease at screening. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Response will be assessed by the investigator using RECIST v1.1 (see Appendix 3). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

4.5.6.1 Local Laboratory Tests

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: CBC, including WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). A manual differential can be done if clinically indicated.
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH

  Bicarbonate is not a required analyte for patients in countries where it is not considered a standard chemistry measurement.
- Serum amylase and lipase
- Serum ferritin and C-reactive protein (CRP)
- Coagulation (PT or INR, and aPTT)
- Thyroid function testing: thyroid-stimulating hormone, free thyroxine (T4)
- HIV serology
- HBV serology (HBsAg, antibody against HBsAg [HBsAb], and antibody against hepatitis B core antigen [HBcAb])

  If a patient has a positive serology for HBcAb at screening, an HBV DNA test must also be performed. The test sample should be collected prior to initiation of study treatment, but the result is not required to determine eligibility.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  HCV RNA test is required prior to Cycle 1, Day 1 for consideration of eligibility if patient has positive serology for anti-HCV.
- Pregnancy test

  All women of childbearing potential (see Section 4.1.1) will have a serum pregnancy test at screening. Urine or serum pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

4.5.6.2 Central Laboratory Assessments

Samples for the following laboratory tests will be sent to one or several central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for these central assessments. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

- A tumor tissue sample, either an archival specimen or a pre-treatment biopsy, must be submitted at baseline for determination of PD-L1 expression and for exploratory research on biomarkers

  A representative FFPE tumor specimen in a paraffin block (preferred) or at least 15 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. If only 10−14 slides are available, the patient may still be eligible for the study, after discussion with and approval by the Medical Monitor. After signing of the Informed Consent Form, retrieval and submission of an archival tumor sample can occur ≥ 28 days prior to initiation of study treatment.

  Acceptable samples include those from resections, core-needle biopsies (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsies. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

  Patients whose tumor tissue is not evaluable by the central laboratory for expression of PD-L1 are not eligible. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method in order to be evaluable. Tumor tissue should be of good quality based on total and viable tumor content. If multiple tumor specimens are submitted (e.g., an archival specimen and tissue from relapsed disease), patients may be eligible if at least one specimen is evaluable for PD-L1. The highest PD-L1 score among the submitted samples will be used for the purpose of stratification and, in the event that enrollment is limited to PD-L1 selected patients, to determine eligibility.

Biological samples will be destroyed when the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Data arising from sample analysis will be subject to the confidentiality standards

described in Section 8.4.

4.5.7 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings should be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs should be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

Copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must discontinue study treatment (MOXR0916 and atezolizumab) if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Use of non-protocol anti-cancer therapy
- Pregnancy
- Symptomatic deterioration attributed to disease progression
- Radiographic disease progression per RECIST v1.1, with the exception of patients who meet all of the criteria for treatment beyond radiographic progression outlined in Section 3.1

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

- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance

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

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments and PRO assessments as outlined in the schedule of activities (see Appendix 1).

4.6.2 Patient Discontinuation from Study

After study treatment discontinuation, *all adverse events will be monitored* and *recorded for at least 90 days after the last dose of study treatment or until initiation of another systemic* anti-cancer therapy*, whichever occurs first (see Section* 5.3.1*). Patients will discontinue from study upon completion of safety follow-up, or upon* any of the following *(whichever* occurs *first):*

- Death
- Loss to follow-up
- Study termination by the Sponsor
- Patient withdraws consent for follow-up

If a patient withdraws consent for follow-up, this request must be documented in the source documents and signed by the investigator. The primary reason for withdrawal of consent from the study should be documented on the appropriate eCRF. Patients will not be actively followed for any reason after consent has been withdrawn. In such cases, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. Patients who withdraw from the study will not be replaced.

4.6.3 Study 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.

4.6.4 Site Discontinuation

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

- Excessively slow recruitment

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

MOXR0916 is not approved for any non-experimental use, and clinical development is ongoing. Atezolizumab received accelerated approval in the United States for the treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has worsened during or following platinum-containing chemotherapy, or within 12 months of receiving platinum-containing chemotherapy. The safety plan for patients in this study is based on clinical experience with MOXR0916 and atezolizumab in completed and/or ongoing studies. The anticipated important safety risks for MOXR0916 and atezolizumab are outlined below. [redacted] Please refer to the respective Investigator's Brochures for a complete summary of safety information for MOXR0916 and atezolizumab.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below (see Section 5.1.5).

5.1.1 Risks Associated with Atezolizumab and Potential Risks of MOXR0916

The safety plan for patients in this study is based largely on the clinical experience with atezolizumab in completed and ongoing studies. Based on the available characterization of mechanism of action, and preliminary clinical data from ongoing studies, MOXR0916 may cause adverse events similar to but independently of atezolizumab, may exacerbate the frequency or severity of atezolizumab-related adverse events, or may have non-overlapping toxicities with atezolizumab. Hence all risks associated with atezolizumab are regarded as potential risks for MOXR0916. The anticipated important safety risks for atezolizumab are outlined below. Refer to the Atezolizumab Investigator's Brochure and MOXR0916 Investigator's Brochure for

complete summaries of safety information.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of MOXR0916 and atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. After initiation of study treatment, all adverse events and serious adverse events will be recorded during the trial and for up to 90 days after the last dose of study treatment or until the initiation of another systemic anti-cancer therapy, whichever occurs first. See Section 5.3 for details regarding safety reporting for this study.

Specific anticipated or potential toxicities associated with administration of MOXR0916 and atezolizumab as well as the measures taken intended to avoid or minimize such toxicities in this trial are described in the following sections. General guidance on treatment interruption or discontinuation in response to adverse events is provided in Section 5.1.4. Management guidelines for specific adverse events are described in Section 5.1.5.

5.1.1.1 Immune-Related Hepatitis

Cases of hepatitis, some leading to fatal outcomes, have been observed in clinical trials with atezolizumab. Most of these hepatic events however were non-serious elevations of liver enzymes. [redacted]

The risk of immune-related hepatitis with MOXR0916 in combination with atezolizumab is unknown. [redacted]

Patients with clinically significant liver disease or hepatic enzyme elevations will be excluded from this study (see Section 4.1.2), and hepatic enzymes will be regularly monitored during the study (see Appendix 1).

Guidelines for management of patients who develop hepatic toxicity are provided in Section 5.1.5.1.

5.1.1.2 Immune-Related Pneumonitis

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. The majority of patients with pulmonary events experienced only mild to moderate events. Across atezolizumab clinical trials, pneumonitis events occurred more frequently in the NSCLC patient population versus other tumor populations, most likely due to higher baseline incidence, higher prevalence of other risk factors, and atezolizumab-induced immunologic response to the tumor. [redacted] The risk of immune-related pneumonitis with MOXR0916 in

combination with atezolizumab is unknown. [redacted]

Patients with a history of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest CT scan will be excluded from this trial.

Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have CT scans of the chest performed at every tumor assessment.

Guidelines for management of patients who develop immune-related pneumonitis are provided in Section 5.1.5.2.

5.1.1.3 Immune-Related Colitis

Cases of diarrhea or colitis have been observed in clinical trials with atezolizumab. [redacted] The risk of immune-related colitis with MOXR0916 in combination with atezolizumab is unknown. [redacted]

Guidelines for management of patients who develop diarrhea or colitis are provided in Section 5.1.5.3.

5.1.1.4 Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab and observed following MOXR0916 monotherapy and in combination with atezolizumab. The risk of dermatologic toxicity with MOXR0916 in combination with atezolizumab is unknown. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Guidelines for management of patients who develop diarrhea or colitis are provided in Section 5.1.5.4.

5.1.1.5 Immune-Related Pancreatitis

Symptoms of abdominal pain associated with elevations of amylase and lipase suggestive of pancreatitis have been associated with the administration of atezolizumab. Most events identified were non-serious elevations in lipase or amylase. The risk of immune-related pancreatitis with MOXR0916 or MOXR0916 in combination with

atezolizumab is unknown. [redacted]

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests.

Guidelines for management of patients who develop pancreatic events, including pancreatitis are provided in Section 5.1.5.5.

5.1.1.6 Immune-Related Endocrinopathies

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and *pituitary disorders* have been associated with the administration of atezolizumab. [redacted] The risk of immune-related endocrinopathies with MOXR0916 in combination with atezolizumab is unknown. [redacted]

Guidelines for management of patients who develop endocrine events are provided in Section 5.1.5.6.

5.1.1.7 *Immune-Related Myocarditis*

Immune-related myocarditis has been associated with the administration of atezolizumab. The risk of immune-related myocarditis with MOXR0916 or MOXR0916 in combination with atezolizumab is unknown. [redacted]

5.1.1.8 Immune-Related Meningoencephalitis

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab, and has been reported in a patient receiving atezolizumab. The risk of immune-related meningoencephalitis with MOXR0916 or MOXR0916 in combination with atezolizumab is unknown. [redacted].

Patients with signs and symptoms of meningoencephalitis, in the absence of an

identified alternate etiology, should be treated according to the guidelines provided in Section 5.1.5.8.

5.1.1.9 Immune-Related Neurologic Disorders

Guillain-Barré syndrome, including one fatal event, has been observed in patients receiving atezolizumab. Myasthenic syndrome/myasthenia gravis has also been observed in patients receiving atezolizumab. The risk of immune-related neurologic disorders with MOXR0916 or MOXR0916 in combination with atezolizumab is unknown. [redacted] Patients should be monitored for symptoms of motor and sensory neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies of neuropathies.

Guidelines for management of patients who develop neurologic events are provided in Section 5.1.5.9.

5.1.1.10 Infusion-Related Reactions

Infusion-related reactions are known to occur with the administration of monoclonal antibodies and have been observed in patients receiving atezolizumab. The identified reactions occurred within 24 hours and were generally mild to moderate in severity, and few patients developed serious adverse events. The signs and symptoms of infusion-related reactions following atezolizumab share considerable overlap with several very common atezolizumab risks including influenza-like illness, pyrexia, and rash. Infusion-related reactions have also been observed following MOXR0916. Similar to atezolizumab, most events have been mild to moderate in nature.

[redacted].

Guidelines for management of patients who develop infusion-related reactions are provided in Sections 5.1.5.10 and 4.3.2.

5.1.2 Potential Risks Specific to MOXR0916

In addition to the risks associated with atezolizumab in Section 5.1.2, which are all considered potential risks for MOXR0916, the following potential risks are described for MOXR0916 based on its particular mechanism of action. As an agonist of OX40, MOXR0916 is anticipated to enhance effector T-cell proliferation, survival and function, and to reverse regulatory T cell-mediated immunosuppression. Therefore MOXR0916

may increase the risk of cytokine release syndromes as well as autoimmune inflammation (referred to immune-related adverse events in Section 5.1.1). In addition, due to the intact Fc effector function of MOXR0916, lymphopenia via antibody-dependent cell-mediated cytotoxicity (ADCC) is a theoretical risk.

5.1.2.1 Cytokine Release Syndrome and Macrophage Activation Syndrome

Cytokine release syndrome (CRS), macrophage activation syndrome (MAS), as well as systemic immune activation (SIA, Section 5.1.3.1), may be considered as part of a continuum of disorders associated with an exaggerated immune response, with overlapping signs, symptoms and presentation. The supportive and interventional management for these disorders is largely the same, with additional diagnostic features described for MAS (Tothova and Berliner 2015; Jordan et al. 2011) and SIA.

Mild flu-like symptoms such as fever, headache, and myalgias may occur following infusion (hours to days). In contrast, severe, exaggerated cytokine release observed with CD28 superagonists (Suntharalingam et al. 2006) is not anticipated in response to MOXR0916 given that OX40 expression is transient and restricted to antigen-experienced T cells. [redacted]

MAS has been reported with blinatumomab as well as chimeric antigen receptor adoptive T-cell therapy (Teachey et al. 2013; Lee et al. 2014). While MAS has not been described with immune checkpoint inhibitors or stimulatory T-cell agonists (including atezolizumab and MOXR0916), a theoretical risk remains. MAS should be included in the differential diagnosis for patients who develop a sepsis-like syndrome or severe CRS, and workup should include serum ferritin, typically dramatically elevated in MAS, as well as complete blood count, liver function tests, serum triglycerides, and coagulation profile. A bone marrow evaluation should also be considered (Henter et al. 1991; Henter et al. 2007; Tothova and Berliner 2015). Cytokine-specific treatment with agents such as tocilizumab should be considered in the event of severe or life-threatening cytokine release syndrome and/or suspected MAS (see Section 5.1.5.11).

5.1.2.2 Enhanced Immune Response during Acute Infection

OX40L has been shown to regulate inflammation in the innate immune response to infection in an animal model of polymicrobial sepsis (Karulf et al. 2010); improved survival, decreased cytokine production, and a decrease in remote organ damage were observed in OX40L(-/-) mice. These observations suggest that concurrent administration of an OX40 agonist has the potential to exacerbate inflammation in response to an emergent infection.

[redacted]

or in Study GO29674 of MOXR0916 in combination with atezolizumab.

Patients with evidence of active or recent infections will be excluded from the study. In addition, individuals who have received a live-attenuated viral vaccine within 4 weeks of Day 1 or anticipate the need for such a vaccine for the duration of the study will be excluded. Patients will also be closely monitored for any infection that occurs during the course of the study. In the case of a newly onset clinically significant infection during the study, study treatment will be temporarily suspended until resolution (see Section 5.1.4).

5.1.2.3 Lymphopenia

Given the IgG1 backbone of MOXR0916 with intact Fc effector function, ADCC-mediated reduction in lymphocyte count is a potential risk. In nonclinical studies with cynomolgus monkeys, repeat dose toxicity studies did not demonstrate a decrease in overall lymphocyte counts. Transient lymphopenia was observed following the use of another monoclonal antibody directed against OX40 (Curti et al. 2013); however, this was not a DLT in the Phase I trial.

[redacted]

Patients with a lymphocyte count less than 500 cells/μL will be excluded from this trial (see Section 4.1.2); complete blood counts will be monitored regularly (see Appendix 1).

5.1.3 Potential for Overlapping Toxicities with MOXR0916 and Atezolizumab

No nonclinical toxicology studies have been conducted with the combination of MOXR0916 and atezolizumab. Based on nonclinical and/or clinical studies with each molecule as a single agent, as well as molecules with similar mechanisms of action, there is a potential for overlapping toxicity in patients treated with the combination of MOXR0916 and atezolizumab. Since the expected pharmacological activity of these two molecules is to increase adaptive T-cell immune responses via complementary mechanisms, the combination may be associated with heightened immune-mediated toxicity relative to either agent alone. Such toxicity could manifest as a higher incidence or greater severity of autoimmune inflammation events (including each of the events detailed in Section 5.1.1), cytokine release syndromes (including macrophage activation syndrome and SIA (see Sections 5.1.2.2 and 5.1.3.1), and sequelae of enhanced response to acute infection (see Section 5.1.2.2).

The largest clinical experience to date with the combination of complementary modulators of adaptive immunity is derived from trials of ipilimumab combined with nivolumab (Wolchok et al. 2013; Antonia et al. 2014; Hammers et al. 2014, Antonia et al. 2016). In a Phase I trial of this combination in patients with advanced melanoma, an

increased frequency of immune-related toxicities, including Grade 3/4 events, was observed for the recommended Phase II concurrent regimen of nivolumab 1 mg/kg and ipilimumab 3 mg/kg Q3W, as compared with either single agent alone (Wolchok et al. 2013; Sznol et al. 2014). Nevertheless, most immune-related events in this trial were qualitatively similar to those observed with ipilimumab or nivolumab monotherapy and were largely manageable and reversible.

Based on these data, and the combination safety profile demonstrated to date in Study GO29674, it is anticipated that immune-related adverse events following treatment with MOXR0916 and atezolizumab will likewise be monitorable and manageable in the setting of this combination study, which has incorporated the extensive experience with immune checkpoint inhibitors to date into the design and safety management plan (see Section 5.1.5) in order to reduce the potential risks to participating patients.

5.1.3.1 Systemic Immune Activation

SIA is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, SIA is considered a potential risk when atezolizumab is given in combination with other immunomodulating agents, including MOXR0916.

SIA should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of study treatment.

Recommendations regarding early identification and treatment of SIA are provided in Section 5.1.5.11.

5.1.4 Dose Modification: General Guidance

There will be no dose modifications for MOXR0916 or atezolizumab in this study. Patients may temporarily suspend study treatment as appropriate for management of toxicity, as described in Section 5.1.5. Based on the available characterization of mechanism of action, MOXR0916 may cause adverse events similar to but independently of atezolizumab, may exacerbate the frequency or severity of atezolizumab-related adverse events, or may have non-overlapping toxicities with atezolizumab. Since these scenarios cannot be distinguished one from another in the clinical setting, immune-related toxicities should generally be attributed to both agents, and dose interruptions or treatment discontinuation in response to immune-related adverse events should be applied to both MOXR0916 and atezolizumab.

Characterization of the safety profiles of MOXR0916 and atezolizumab is ongoing, and it is plausible that specific immune-mediated toxicities will emerge that can be attributed with confidence to one agent rather than the combination. In such cases, selective interruption or discontinuation of either MOXR0916 or atezolizumab and the associated benefit/risk for individual patients should be discussed with the Medical Monitor.

Similarly, individual patients may be rechallenged with study drugs in a selective or staggered fashion following recovery from treatment-related toxicity after discussion of benefit and risk with the Medical Monitor.

In general, if a planned administration of MOXR0916 and atezolizumab is delayed for $\geq 12\ weeks$ for management of toxicity, then the patient should discontinue study treatment and be followed for safety and efficacy as specified in study assessments. However, if, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming MOXR0916 and atezolizumab after a hold $\geq 12\ weeks\ after\ onset\ of\ the\ adverse\ event$, study treatment may be restarted with the approval of the Medical Monitor. For example, if patients must be tapered off steroids used to treat adverse events, study treatment may be held for $\geq 12\ weeks\ after\ event\ onset$. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Dose interruptions for reason(s) other than toxicity, 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.

5.1.5 Management of Patients Who Experience Specific Adverse Events

Toxicities associated or possibly associated with MOXR0916 and/or atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-related 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 MOXR0916 and atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

Guidelines for management of specific adverse events are outlined in the subsections below. These guidelines are intended to inform rather than supplant clinical discretion in managing individual cases. The investigator should consider the benefit-risk balance a given patient might be experiencing prior to further administration of MOXR0916 and atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of MOXR0916 and atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-related event. Such patients can be rechallenged with MOXR0916 and/or atezolizumab only after approval by both the investigator (or an appropriate delegate) and the Medical Monitor has been documented.

5.1.5.1 Hepatic Events

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and reviewed before administration of the next dose of study treatment.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. Management guidelines for hepatic events are provided in Table 4.

Table 4 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue MOXR0916 and atezolizumab. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	All events: • Monitor LFTs more frequently until return to baseline values. Events of > 5 days' duration: • Withhold MOXR0916 and atezolizumab *for up to 12 weeks after event onset.* [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • *If* event resolves to Grade 1 or better*, resume MOXR0916 and atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding study treatment, permanently* discontinue MOXR0916 and atezolizumab and contact Medical Monitor. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue MOXR0916 and atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function tests.

[a] MOXR0916 and atezolizumab may be withheld for a *longer* period of time *(i.e.,* > 12 weeks *after event onset)* to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] *If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before MOXR0916 and atezolizumab can be resumed.*

[c] Resumption of study treatment may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with MOXR0916 and atezolizumab only after approval by both the investigator (or an appropriate delegate) and the Medical Monitor has been documented.

5.1.5.2 Pulmonary Events

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 5.

Table 5 Management Guidelines for Pulmonary Events, including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue MOXR0916 and atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold MOXR0916 and atezolizumab *for up to 12 weeks after event onset.* [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • *If* event resolves to Grade 1 or better*, resume MOXR0916 and atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding study treatment, permanently* discontinue *MOXR0916 and* atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue MOXR0916 and atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage

[a] MOXR0916 and atezolizumab may be withheld for a *longer* period of time *(i.e.,* >12 weeks *after event onset)* to allow for corticosteroids *(if initiated)* to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] *If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before MOXR0916 and atezolizumab can be resumed.*

[c] Resumption of study treatment may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with MOXR0916 and atezolizumab only after approval by both the investigator (or an appropriate delegate) and the Medical Monitor has been documented.

5.1.5.3 Gastrointestinal Events

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis. Management guidelines for gastrointestinal events are provided in Table 6.

Table 6 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue *MOXR0916 and atezolizumab*. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• *Withhold MOXR0916 and atezolizumab for up to 12 weeks after event onset.* [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • *If* event resolves to Grade 1 or better*, resume MOXR0916 and atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding MOXR0916 and atezolizumab, permanently* discontinue study treatment and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• *Withhold MOXR0916 and atezolizumab for up to 12 weeks after event onset.* [a] • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • *If* event resolves to Grade 1 or better*, resume MOXR0916 and atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding study treatment, permanently* discontinue *MOXR0916 and atezolizumab* and contact Medical Monitor if event does not resolve to Grade 1 or better within 12 weeks. [c]

Table 6 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue *MOXR0916 and atezolizumab* and contact Medical Monitor. [c] • Refer patient to gastrointestinal specialist for evaluation and confirmation biopsy. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] *MOXR0916 and atezolizumab* may be withheld for a *longer* period of time *(i.e.,* >12 weeks *after event onset)* to allow for corticosteroids *(if initiated)* to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] *If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before MOXR0916 and atezolizumab can be resumed.*

[c] Resumption of *MOXR0916 and atezolizumab* may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with MOXR0916 and atezolizumab only after approval by both the investigator (or an appropriate delegate) and the Medical Monitor has been documented.

5.1.5.4 Dermatologic Events

A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be performed unless contraindicated, and if possible, photos of the rash should also be obtained and submitted to the Sponsor. Management guidelines for gastrointestinal events are provided in Table 7.

Table 7 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue MOXR0916 and atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue MOXR0916 and atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve
Dermatologic event, Grade 3	• Withhold MOXR0916 and atezolizumab *for up to 12 weeks after event onset.* [a] • Refer patient to dermatologist. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • *If* event resolves to Grade 1 or better, *resume MOXR0916 and atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding study treatment, permanently* discontinue MOXR0916 and atezolizumab and contact Medical Monitor [c]
Dermatologic event, Grade 4	• Permanently discontinue MOXR0916 and atezolizumab and contact Medical Monitor. [c]

[a] *MOXR0916 and* atezolizumab may be withheld for a *longer* period of time *(i.e.,* > 12 weeks *after event onset)* to allow for corticosteroids *(if initiated)* to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before MOXR0916 and atezolizumab can be resumed.*

[c] Resumption of study treatment may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with MOXR0916 and atezolizumab only after approval by both the investigator (or an appropriate delegate) and the Medical Monitor has been documented.

5.1.5.5 Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	• Continue MOXR0916 and atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold MOXR0916 and atezolizumab *for up to 12 weeks after event onset.* [a] • Refer patient to gastrointestinal specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • *If* event resolves to Grade 1 or better*, resume MOXR0916 and atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding study treatment, permanently* discontinue MOXR0916 and atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue MOXR0916 and atezolizumab and contact Medical Monitor. [c]
Immune-related pancreatitis, Grade 3	• Withhold MOXR0916 and atezolizumab *for up to 12 weeks after event onset.* [a] • Refer patient to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • *If* event resolves to Grade 1 or better*, resume MOXR0916 and atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding study treatment, permanently* discontinue MOXR0916 and atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-related pancreatitis, Grade 4	• Permanently discontinue MOXR0916 and atezolizumab and contact Medical Monitor. [c] • Refer patient to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] *MOXR0916 and atezolizumab* may be withheld for a *longer* period of time *(i.e.,* > 12 weeks*)* to allow for corticosteroids *(if initiated)* to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] *If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before MOXR0916 and atezolizumab can be resumed.*

[c] Resumption of study treatment may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with MOXR0916 and atezolizumab, only after approval by both the investigator (or an appropriate delegate) and the Medical Monitor has been documented.

5.1.5.6 Endocrine Events

Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. *Pituitary hormone levels and function tests (e.g.,* TSH, *growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone,* prolactin, *adrenocorticotropic hormone [ACTH] levels and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may* help to differentiate primary *pituitary insufficiency from primary* adrenal insufficiency. Management guidelines for endocrine events are provided in Table 9.

Table 9 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue MOXR0916 and atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold MOXR0916 and atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	TSH ≥0.1 mU/L and <0.5 mU/L: • Continue MOXR0916 and atezolizumab. • Monitor TSH every 4 weeks. TSH <0.1 mU/L: • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold MOXR0916 and atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume MOXR0916 and atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue MOXR0916 and atezolizumab and contact Medical Monitor for life-threatening immune-related hyperthyroidism.[c]
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold MOXR0916 and atezolizumab *for up to 12 weeks after event onset*.[a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • *If* event resolves to Grade 1 or better and patient is stable on replacement therapy (if required), *resume MOXR0916 and atezolizumab.*[b] • *If* event does not resolve to Grade 1 or better or patient is not stable on replacement therapy *while withholding study treatment, permanently discontinue MOXR0916 and atezolizumab and contact Medical Monitor.*[c]
Hyperglycemia, Grade 1 or 2	• Continue MOXR0916 and atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.

Table 9 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hyperglycemia, Grade 3 or 4	• Withhold MOXR0916 and atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume MOXR0916 and atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis pan-hypopituitarism), Grade 2-3	• *Withhold MOXR0916 and atezolizumab for up to 12 weeks after event onset.* [a] • *Refer patient to endocrinologist.* • *Perform brain MRI (pituitary protocol).* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.*[a] • *Initiate hormone replacement therapy if clinically indicated.* • *If event resolves to Grade 1 or better, resume MOXR0916 and atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue MOXR0916 and atezolizumab and contact Medical Monitor.* [c] • *For recurrent hypophysitis, treat as a Grade 4 event.*
Hypophysitis (pan-hypopituitarism), Grade 4	• *Permanently discontinue MOXR0916 and atezolizumab and contact Medical Monitor.*[c] • *Refer patient to endocrinologist.* • *Perform brain MRI (pituitary protocol).* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.*[a] • *Initiate hormone replacement therapy if clinically indicated.*

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone;

[a] *MOXR0916 and Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before MOXR0916 and atezolizumab can be resumed.*

[c] *Resumption of study treatment may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with MOXR0916 and atezolizumab only after approval by both the investigator (or an appropriate delegate) and the Medical Monitor has been documented.*

5.1.5.7 *Immune-Related Myocarditis*

Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-related myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g. in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of pre-existing cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 10.

Table 10 Management Guidelines for Immune-Related Myocarditis

Event	*Management*
Immune-related myocarditis, Grade 1	• *Refer patient to cardiologist* • *Initiate treatment as per institutional guidelines.*
Immune-related myocarditis, Grade 2	• *Withhold MOXR0916 atezolizumab for up to 12 weeks after event onset* [a] *and contact Medical Monitor.* • *Refer patient to cardiologist* • *Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate.* • *Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.*[a] • *If event resolves to Grade 1 or better, resume MOXR0916 and atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue MOXR0916 and atezolizumab and contact Medical Monitor.* [c]
Immune-related myocarditis, Grade 3-4	• *Permanently discontinue MOXR0916 and atezolizumab and contact Medical Monitor.* [c] • *Refer patient to cardiologist* • *Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate.* • *Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.* [a,b] • *If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.*

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device; IV = intravenous.

[a] *MOXR0916 and atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before MOXR0916 and atezolizumab can be resumed.*

[c] *Resumption of study treatment may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with MOXR0916 and atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

5.1.5.8 Immune-Related Meningoencephalitis

Immune-related meningoencephalitis should be suspected in any patient presenting with

signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Immune-Related Meningoencephalitis

Event	Management
Immune-related meningoencephalitis, all grades	• Permanently discontinue MOXR0916 and atezolizumab and contact Medical Monitor. [a] • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

IV = intravenous.

[a] Resumption of study treatment may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with MOXR0916 and atezolizumab only after approval by both the investigator (or an appropriate delegate) and the Medical Monitor has been documented.

5.1.5.9 Neurologic Disorders

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 12.

Table 12 Management Guidelines for Neurologic Disorders

Event	Management
Immune-related neuropathy, Grade 1	• Continue MOXR0916 and atezolizumab. • Investigate etiology.
Immune-related neuropathy, Grade 2	• Withhold MOXR0916 and atezolizumab *for up to 12 weeks after event onset*. • Investigate etiology. • Initiate treatment as per institutional guidelines. • *If* event resolves to Grade 1 or better, *resume MOXR0916 and atezolizumab.* [b] • *If event does not resolve to Grade 1 or better while withholding study treatment, permanently* discontinue MOXR0916 and atezolizumab and contact Medical Monitor. [c]
Immune-related neuropathy, Grade 3 or 4	• Permanently discontinue MOXR0916 and atezolizumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue MOXR0916 and atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or intravenous prednisone or equivalent.

[a] MOXR0916 and atezolizumab may be withheld for a *longer* period of time *(i.e.,* >12 weeks *after event onset)* to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] *If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before MOXR0916 and atezolizumab can be resumed.*

[c] Resumption of study treatment may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with MOXR0916 and with atezolizumab only after approval by both the investigator (or an appropriate delegate) and the Medical Monitor has been documented.

5.1.5.10 Infusion-Related Reactions

Guidelines for medical management of infusion-related reactions during Cycle 1 are provided in Table 13. For subsequent cycles, infusion-related reactions should be managed according to institutional guidelines. *Metamizole (dipyrone) is prohibited in treating atezolizumab associated infusion-related reactions, due to its potential for causing agranulocytosis.*

Note: In principle, patients who cannot tolerate infusion of one agent could continue

study treatment with the other agent alone, if tolerated. In practice, it might not always be possible to attribute an infusion-related event selectively to one agent. An infusion-related event that begins during the first infusion of the day (MOXR0916) can reliably be attributed to MOXR0916, but an adverse event with onset after the second infusion has begun could represent a reaction to atezolizumab or a delayed-onset reaction to MOXR0916. Therefore, subsequent cycles of study treatment in a patient who experiences a Grade 3 or Grade 4 infusion-related event will be handled as follows:

- Patients who experience a Grade 3 event that begins during the MOXR0916 infusion, but prior to the atezolizumab infusion, and is hence attributed solely to MOXR0916, can receive subsequent cycles of atezolizumab as tolerated. Rechallenge with MOXR0916 following premedication in subsequent cycles, following approval of the Medical Monitor, is allowed provided that the next dose of MOXR0916 is infused over a minimum of 90 minutes.
- Patients who experience a Grade 3 event that begins after the atezolizumab infusion has begun, and hence following the MOXR0916 infusion, will permanently discontinue atezolizumab. As attribution to MOXR0916 cannot be excluded, administration of subsequent cycles of MOXR0916 requires the precautions described above.
- Patients who experience a Grade 4 event that is attributed solely to MOXR0916 will permanently discontinue MOXR0916. Patients who experience a Grade 4 event that is temporally related to atezolizumab, such that attribution to MOXR0916 cannot be excluded will permanently discontinue both atezolizumab and MOXR0916.

Table 13 Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	• Interrupt MOXR0916 or atezolizumab infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, *consider administration of* oral premedication with *antihistamines,* anti*pyretics, and/or analgesics* and monitor closely for IRRs.
IRR, Grade 3 or 4	• Stop infusion. No further administration of either study drug will occur at this visit. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue MOXR0916 and/or atezolizumab and contact Medical Monitor. [a]

IRR = infusion-related reaction; IV = intravenous.

[a] Resumption of study treatment may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with MOXR0916 and/or atezolizumab, as applicable, only after approval by both the investigator (or an appropriate delegate) and the Medical Monitor has been documented.

5.1.5.11 Cytokine Release Syndrome, Macrophage Activation Syndrome, and SIA

Cytokine release syndrome, macrophage activation syndrome, and SIA may be considered as part of a continuum, with overlapping symptoms and presentation. The supportive and interventional management for these disorders is largely the same, with additional diagnostic features described for MAS (Jordan et al. 2011; Tothova and Berliner 2015) and SIA provided in Table 14.

Recommendations regarding early identification and management of SIA are provided below. In the event of suspected SIA, study treatment should be withheld and the Medical Monitor should be contacted immediately for additional guidance.

Early disease recognition is critical, and SIA should be suspected if, in the absence of an

alternative etiology, the patient meets two or more of the following criteria:

- Hypotension that is refractory to aggressive IV fluid challenge

  Vasopressor support may be required.
- Respiratory distress that requires aggressive supportive care

  Supplemental oxygen and intubation may be required.
- Fever $>38.5°C$
- Acute renal or hepatic failure
- Bleeding from coagulopathy
- Any of the following unexplained laboratory abnormalities (change from baseline): cytopenias (in two or more lineages), significant transaminitis, and coagulopathy

For patients with suspected SIA, an 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)

Laboratory tests with normal results should be repeated frequently in patients for whom a high clinical suspicion of SIA exists.

If cytopenias are present (Grade ≥ 2 in two or more lineages) or ferritin is $\geq$ 3000 ng/mL, the following evaluations should also be performed:

- Bone marrow biopsy and aspirate (assess for evidence of hemophagocytosis)
- Soluble interleukin 2 (IL-2) receptor (sCD25)
- Natural killer cell activity
- Cytomegalovirus, Epstein-Barr virus, and herpes-simplex virus evaluation (for reactivated or active disease)
- Diagnostic criteria and recommended management for SIA are provided in Table 14. The diagnostic criteria apply only when alternative etiologies have been excluded.

Table 14 Diagnostic Criteria and Recommended Management for Systemic Immune Activation

Systemic Immune Activation Diagnostic Criteria (applicable only when alternative etiologies have been excluded)	
Major Criteria	**Minor Criteria**
• Fever ≥38.5°C on more than one occasion • Ferritin ≥3000 ng/mL • Cytopenias (Grade ≥2 in two or more lineages) • Age-adjusted soluble IL-2 receptor elevated by ≥2 standard deviations • Severe dysfunction in two or more organs • Decreased fibrinogen	• Splenomegaly • Hemophagocytosis in bone marrow, spleen, or lymph nodes • Elevated GGT or LFTs (AST, ALT, or total bilirubin) • Elevated triglycerides • Elevated LDH • Decreased natural killer cell activity

Diagnosis and Management of Systemic Immune Activation		
Number of Criteria	**Diagnosis**	**Action to Be Taken**
≥4 major criteria	Consistent with SIA	• Permanently discontinue study treatment. • Consider treatment with an immunosuppressive agent (i.e., tocilizumab, infliximab, cyclosporine A, or etoposide) and IV corticosteroids (i.e., methylprednisolone 1 g once daily or equivalent). • Contact the Medical Monitor for additional recommendations. • Consider HLH-94 protocol if there is no clinical improvement (Henter et al. 1997).
3 major criteria OR 2 major plus ≥3 minor criteria	Probable SIA	• Depending on clinical severity, follow guidelines for "Consistent with SIA" or "Possible SIA" diagnosis. • The Medical Monitor may be contacted for recommendations.
2 major plus ≤2 minor criteria OR 1 major plus ≥4 minor criteria	Possible SIA	• Withhold study treatment. • Consider treatment with IV corticosteroids. • The Medical Monitor may be contacted for additional recommendations. • Follow guidelines for "Consistent with SIA" diagnosis if there is no clinical improvement or if clinical worsening occurs. • If clinical improvement occurs, study treatment may be resumed following a benefit-risk assessment by the Medical Monitor.

GGT=γ-glutamyl transpeptidase; IL-2=interleukin-2; IV=intravenous; LFT=liver function test; SIA=systemic immune activation.

Notes: Criteria are adapted from a Delphi Survey of 26 experts who provided helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients (Hejblum et al. 2014).

Case reports and recommendations have been published for cytokine-release syndrome (Teachey et al. 2013; Lee et al. 2014; Maude et al. 2014), and, on the basis of etiologic similarities, these practices have been incorporated into the above treatment recommendations.

These recommendations do not replace clinical judgment and are intended as suggested guidance.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study 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 (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

General Drug Development Adverse Events

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

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

Adverse Events of Interest Specific to MOXR0916 in Combination with Atezolizumab

- Conditions (regardless of grade) suggestive of an autoimmune disorder, including but not limited to hepatitis, pneumonitis, colitis, endocrinopathies, pancreatitis, thyroiditis, rheumatoid arthritis, Type I diabetes, vasculitis, neuritis, systemic lupus erythematosus, Sjögren's syndrome, and multiple sclerosis.

- Grade ≥ 3 acute infection (bacterial, viral, zoonotic, or fungal)
- Grade ≥ 3 events suggestive of hypersensitivity, cytokine release, systemic inflammatory response, or infusion reaction syndromes, including but not limited to influenza-like illness, fever, chills, rash, urticaria, dyspnea, wheezing, angioedema, tachycardia, and hypotension occurring within 24 hours of the end of the infusion.
- Grade ≥ 3 events suggestive of cytokine release syndrome (occurring ≥24 hours after the end of the infusion), including but not limited to influenza-like illness, nausea, headache, fevers, chills, tachycardia, hypotension, and shortness of breath.
- Grade ≥ 3 lymphopenia that also represents ≥ 50% decrease from baseline (regardless of whether the event otherwise meets criteria for reporting of an abnormal laboratory value as an adverse event, as described in Section 5.3.5.5).
- Grade ≥ 3 rash, vitiligo, or pruritus
- Grade ≥ 3 diarrhea
- Grade ≥ 3 AST/ALT/total bilirubin elevation—asymptomatic
- Grade ≥ 2 AST/ALT/total bilirubin elevation—with constitutional symptoms
- Grade ≥ 2 hypoxia or dyspnea not attributable to underlying malignancy or other pulmonary disease
- Grade ≥ 2 pleural effusion
- Grade ≥ 2 pericardial effusion
- Any adverse event, regardless of grade, requiring systemic corticosteroids for management

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 Section 5.4–5.6.

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

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study treatment**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported

(see Section 5.4.2 for instructions for reporting serious adverse events).

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

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 15 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 15 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 16):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as 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 16 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of 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	An adverse event will be considered related, unless it fulfills the criteria 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 first dose of study drug).

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 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology 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 $\times$ ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ 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 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of malignancy should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur within 90 days of the last dose of study treatment, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). The IMC (Section 3.1.2) will monitor the frequency of deaths from all causes.

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Urothelial Carcinoma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events, with the exception of medically significant events that lead to hospitalization (and therefore represent serious adverse events) or study conduct change such as treatment interruption. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1 criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol e.g., for study drug administration or insertion of access device for study drug administration
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event

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

instead:

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

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

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study 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 5.4.2).

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

Genentech Medical Monitor contact information:

Medical Monitors: [redacted], M.D., Ph.D.

Telephone Nos.: Office: [redacted]

Mobile: [redacted]

Email: [redacted]

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 [redacted] Pharmacovigilance and Drug Safety Services immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study 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 study drug. 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 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 using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 months after the last

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

5.4.3.2 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 study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. 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. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. 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.

5.4.3.3 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). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

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.

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 90 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- MOXR0916 Investigator's Brochure
- Atezolizumab Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The Sponsor has determined that the original scientific aims of this study are no longer evaluable as a result of the Sponsor's decision to prematurely halt enrollment due to slow patient accrual. However, the original statistical considerations and analysis plan are retained below for reference.

This study is designed to evaluate the safety and activity of MOXR0916 plus atezolizumab or placebo plus atezolizumab in previously untreated patients with locally advanced or metastatic UC who have not received prior systemic therapy in the locally advanced/metastatic setting and who are ineligible to receive cisplatin-based therapy.

As described in Section 3.1.1, this study will enroll up to approximately 225 patients with evaluable tissue at approximately 75 sites globally. [redacted]

6.1 DETERMINATION OF SAMPLE SIZE

The primary objective of this study is to test the hypothesis of greater treatment effect of MOXR0916 plus atezolizumab on duration of PFS and OS relative to the placebo plus atezolizumab. For the co-primary endpoints of PFS and OS in the primary patient population, at 70% event maturity (112 PFS or OS events), the trial will have 81% power to detect a PFS hazard ratio of 0.50 at a two-sided significance level of 0.005 (corresponding to an improvement from 3 to 6 months in median PFS), and 80% power to detect an OS hazard ratio of 0.58 at a two-sided significance level of 0.045 (corresponding to an improvement from 13.3 to 22.9 months in median OS). Total type I error will be controlled at a 0.05 significance level.

Notably, the trial is able to detect only very large benefits in OS. The trial will not, however, have adequate power to detect all potentially clinically meaningful differences in OS. For example, with 112 OS events, there is only 45% power to detect a hazard ratio of 0.70 (corresponding to an improvement from 13.3 to 19 months in median OS) at a two-sided significance level of 0.045. Thus, a statistically negative outcome in the co-primary OS analysis does not necessarily rule out a clinically meaningful outcome.

Operating characteristics (power and expected total number of events) for true underlying hazard ratio values of 0.50, 0.60, and 0.75 are provided in Table 17.

Table 17 Operating Characteristics for Proposed Study Design for Several Possible True Underlying Hazard Ratio Values

	True Underlying Hazard Ratio		
	0.50	0.60	0.75
Expected number of events	102	107	113
Power of log-rank test [a]	93%	74%	32%
95% confidence interval for true hazard ratio [b]	(0.34, 0.74)	(0.41, 0.88)	(0.52, 1.08)

Note: Operating characteristics are based on the following assumptions: event times are exponentially distributed, median overall survival in the control arm is 13.3 months, and patients are enrolled over 13 months and followed for an additional 32 months

[a] Two-sided $\alpha = 0.045$.

[b] Confidence intervals are based on the assumption that the point estimate is equal to the true underlying value of the hazard ratio in each column.

Additionally, with 60 PFS events in the PD-L1 IC2/3 population (corresponding to 75% event maturity), there is 77% power to detect a HR of 0.50 at a two-sided significance level of 0.05. The upper bound of the two-sided 95% CI for the HR will be 0.83.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study treatment administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study treatment discontinuation will be also tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be listed by treatment arm and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including but not limited to age, sex, baseline ECOG, and presence of visceral metastases) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 EFFICACY ANALYSES

The co-primary and secondary efficacy analyses will be conducted among all randomized patients in appropriate study populations (primary population or PD-L1 IC2/3 population) with patients grouped according to their assigned treatment (i.e., ITT) analysis. Specifically, formal hypothesis testing of the co-primary efficacy endpoints of

PFS and OS will be conducted in the ITT primary patient population at significance levels of 0.005 and 0.045, respectively.

Other secondary endpoints, including PFS and OS in the PD-L1 IC2/3 subpopulation, as well as ORR, DOR, and PROs (including pain, fatigue, other symptoms, and interference scores from the MDASI) in both the primary patient population and in the PD-L1 IC2/3 population will also be analyzed but are not included in the formal hypothesis testing framework. Results will be presented with 95% confidence intervals unless otherwise specified.

6.4.1 Co-Primary Efficacy Endpoints

6.4.1.1 Analysis Plan for Progression-Free Survival

PFS is defined as the time from randomization to the date of first documented disease progression or death, whichever occurs first. Disease progression for PFS analysis will be determined on the basis of investigator assessment with the use of RECIST v1.1.

The primary PFS analysis will occur after approximately 112 events (corresponding to 70% event information) have been observed in the primary population. This analysis is expected to occur approximately 18 months after enrollment of the first patient.

Data for a patient without disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment (or at the date of randomization plus 1 day if no tumor assessment was performed after the baseline visit). Data from a patient who is lost to follow-up will be included in the analysis and censored on the last date of tumor assessment that the patient was known to be progression-free.

The two-sided stratified log-rank test will be used to compare PFS between the two treatment arms. Kaplan-Meier methodology will be used to estimate the PFS curve and median PFS for each treatment arm. Stratified Cox proportional-hazards models will be used to estimate the HR and its 95% CI. The results from the unstratified log-rank test will also be provided.

Prior to this primary PFS efficacy analysis, no interim analysis will be conducted for any of the efficacy endpoints, and patient study treatment assignment will remain blinded to members of the study team who are not part of the IMC.

6.4.1.2 Analysis Plan for Overall Survival

OS is defined as the time from randomization to death from any cause. Data for patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Data from patients without post-baseline information will be censored at the date of randomization plus 1 day.

The two-sided stratified log-rank test will be used to compare OS between the two treatment arms. Kaplan-Meier methodology will be used to estimate the OS curve and

median OS for each treatment arm. Stratified Cox proportional-hazards models will be used to estimate the HR and its 95% CI. The results from the unstratified test will also be provided.

Two interim analyses and one final analysis of OS are planned in the primary patient population. The final OS analysis will occur after approximately 112 events (corresponding to 70% event information) have been observed in the primary population. This analysis is expected to occur approximately 45 months after enrollment of the first patient.

The first OS interim analysis will be conducted at the time of unblinding for the primary PFS analysis in the primary patient population. Approximately 48 events, (corresponding to 43% information relative to final analysis) are expected at the time of the first OS interim analysis. The second interim analysis will be conducted after approximately 80 events (corresponding to 71% information relative to final analysis), have been observed in the primary population. The second OS interim analysis is expected to occur approximately 27 months after enrollment of the first patient.

The actual number of observed OS events and the amount of information at the interim analyses may be different from the estimates presented above. The stopping boundaries have been computed using the Lan-DeMets approximation to O'Brien-Fleming boundaries. The stopping boundaries for superior (inferior) efficacy will be HR ≤ 0.39 (HR ≥ 2.59) and HR ≤ 0.57 (HR ≥ 1.74) at the interim analyses and HR ≤ 0.68 (HR ≥ 1.47) at the final analysis. The overall type I error rate is controlled at the level of 4.5%, with cumulative α of 0.001 and 0.014 spent at the first and second interim analyses.

[redacted]

6.4.2.2 Analysis Plan for Objective Response

Objective response is defined as the percentage of patients who had experienced objective response (complete or partial response) as determined by using RECIST v1.1 as assessed by the investigators. Objective response will be evaluated by treatment arm. Patients will be grouped according to the treatment arm assigned at randomization, and patients without post-baseline overall response assessments will be counted as

non-responders.

6.4.2.3 Analysis Plan for Duration of Response

DOR is defined as the time from the first occurrence of a documented objective response to the time of the first documented disease progression or death from any cause (whichever occurs earlier). Objective response (described above) and disease progression for the DOR analysis will be determined on the basis of investigator assessment with the use of RECIST v1.1.

The analysis of DOR will include only patients who achieved an objective response to study treatment. DOR will be estimated using the Kaplan-Meier methodology. Because the determination of DOR is based on a non-randomized subset of patients, no formal hypothesis testing will be performed.

6.4.2.4 Analysis Plan for Patient-Reported Symptoms and Impact on Functioning

The MDASI-supported endpoints will be analyzed in the primary population, regardless of PD-L1 status, and in the PD-L1 IC2/3 population. Baseline is defined as the last available assessment prior to the first dose of study treatment.

MDASI completion compliance will be documented and calculated as the number of forms received divided by the number expected at every assessment.

Each MDASI symptom score is based on a one-item scale and ranges from 0 to 10 (indicating a severe symptom). Symptom severity will be categorized as follows: asymptomatic/mild (0–3), moderate (4–6), and severe (7–10).

The 6-item Symptom Interference score will be derived according to the MDASI user manual: a prorated score ranging from 0 to 10 will be computed if more than 50% of the constituent items (items 14 to 19) are completed; the score will be considered missing if less than 50% of the items are completed (Cleeland et al. 2000). Patients with a score of 5 or higher on the Symptoms Interference score are considered functionally impaired.

Secondary endpoints include time to pain progression, time to fatigue progression, and time to pain palliation. Pain or fatigue progression events will be defined as the first increase of ≥2 points from baseline. The pain palliation event will be defined as the first decrease of >2 points from baseline in the absence of opioid initiation or increase. The same time-to-event methods as described above for OS and PFS in Section 6.4 will be applied to these endpoints. Data for patients with missing baseline assessment, or without a post-baseline assessment will be censored at the date of randomization plus 1 day.

For the secondary endpoint of proportion of patients reporting symptom interference with daily living at the time of progression, the Symptom Interference score obtained on or immediately prior to the date of radiographic progression according to RECIST v1.1 will

be utilized.

6.4.3 Exploratory Efficacy Endpoints

PFS, ORR, and DOR may be evaluated using definitions of response per *immune*-modified RECIST criteria by treatment arm in both the primary and PD-L1 IC2/3 patient populations.

Progression events for symptoms other than pain or fatigue will be defined as the first increase of ≥ 2 points from baseline. The same time-to-event methods as described above for OS and PFS in Section 6.4 will be applied to these endpoints.

MDASI scores and change from baseline may be descriptively analyzed using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Mean changes in symptom scores and Symptom Interference scores from baseline will be used to evaluate the patients' longitudinal experience of disease and treatment.

Additional exploratory analyses may be performed to evaluate the relationship between symptom severity and symptom interference with daily living and clinical progression as determined by the investigator.

The EQ-5D-5L will be included to derive utility to inform pharmacoeconomic models and therefore will not be part of the CSR.

6.5 SAFETY ANALYSES

Safety analyses will be conducted in the entire, pooled ITT population of all randomized patients, regardless of PD-L1 status, who received at least one dose of MOXR0916 or atezolizumab.

Safety analyses will be performed by treatment arm and will be based on actual treatment received. Specifically, a patient will be included in the MOXR0916 plus atezolizumab arm of the safety analyses if the patient received any amount of MOXR0916, regardless of the initial treatment assignment at randomization.

During enrollment, interim safety data will be reviewed approximately every six months by an IMC as described in Section 3.1.2). Thereafter, analysis of safety data will be conducted by the Sponsor at the time of the primary PFS analysis in the primary population and at subsequent analyses of OS.

Safety endpoints will include incidence, nature, and severity of adverse events (using NCI CTCAE, Version 4), including serious adverse events and adverse events of special interests, changes in vital signs, physical findings, and clinical laboratory results following the administration of MOXR0916 plus atezolizumab. Drug exposure will be summarized, including duration and dosage. Verbatim description of adverse events will

be mapped to the Medical Dictionary for Regulatory Activities thesaurus terms and graded according the NCI CTCAE, Version 4. All adverse events that occur during or after the first study treatment, until 90 days after the last dose of study treatment or initiation of another systemic anti-cancer therapy, whichever occurs first, will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events and adverse events leading to study treatment discontinuation or interruption will be summarized accordingly. Multiple occurrence of the same event will be counted once at the maximum severity. Laboratory data with values outside of the normal ranges will be identified. Additionally, selected laboratory data, including ATA results, will be summarized by treatment arm and grade. Vital signs will also be summarized by treatment arm and visit. Deaths and causes of deaths will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Individual and mean serum MOXR0916 concentration versus time data will be tabulated and plotted. The pharmacokinetics of MOXR0916 will be summarized by estimating area under the curve, C_{max}, C_{min}, clearance, and V_{ss} (if data allow). Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Individual and mean serum atezolizumab concentration versus time data will be tabulated, plotted, and compared to historical data.

Additional PK analyses will be conducted as appropriate.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with any ATA assessments with patients grouped according to treatment received.

The numbers and proportions of ATA-positive patients and ATA-negative patients during both the treatment and follow-up periods will be summarized by treatment group. Patients are considered to be ATA positive if they are ATA negative or with missing data at baseline but develop an ATA response following study treatment administration (treatment-induced ATA response), or if they are ATA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., $\geq$0.60 titer units) than the titer of the baseline sample (treatment-enhanced ATA response). Patients are considered to be ATA negative if they are ATA negative or with missing data at baseline and all post-baseline samples are negative, or if they are ATA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ATA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

6.8 BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in tumor tissue and blood in an effort

to better understand the association of these markers with study-drug response, including efficacy and/or adverse events. Specific evaluations may include, but not be limited to, PD-L1 expression by IHC, OX40 expression by IHC, presence of CD8 and tumor infiltrating lymphocytes by IHC, expression of immune and tumor biology associated genes, and next-generation sequencing for identification of somatic mutations and characterization of tumor mutational load and other aberrations associated with UBC tumor biology. Biomarker analyses may be reported in a separate report.

Exploratory biomarker analyses may be performed in either the primary population, the PD-L1 IC2/3 population, or for select biomarkers deemed not to be related to PD-L1 status, in the entire, pooled ITT population.

6.9 INTERIM ANALYSES

6.9.1 Planned Interim Analyses

There will be no interim efficacy analyses prior to the primary PFS analysis in the primary population. Interim efficacy analyses for OS will be conducted as described in Section 6.4.1.2.

An IMC will convene approximately every 6 months during enrollment to review available safety data and to make recommendations regarding study conduct to ensure the safety of patients enrolled on the study. In the absence of significant safety concerns or other extenuating circumstances, accrual will continue in the study while the reviews are being conducted. Pending review of accumulating safety data, the IMC may choose to meet more frequently, if necessary. On the basis of these interim safety results, however, the IMC may recommend to continue, modify, or terminate the study (see Section 3.1.2). However, as the IMC will review only safety data, it cannot undertake decisions to halt the trial based on early efficacy or futility.

The members, roles, responsibilities and communication processes of the IMC will be outlined in a separate charter.

6.9.2 Optional Interim Analyses

There will be no interim efficacy analyses prior to the primary PFS analysis in the primary population. Following the primary PFS analysis, however, the Sponsor may choose to conduct up to two additional interim efficacy analyses for OS (i.e., beyond what is specified in Section 6.9.1). The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

departments involved in a clinical 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 study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 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 U.S. 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 (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

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

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., the date when the number of OS events specified for the final analysis has been observed).

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. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' 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 by Genentech and will be managed by Genentech and a Contract Research Organization (CRO). The CRO will provide clinical operations management, data management, and medical monitoring support.

Treatment assignment will be conducted using an IxRS. Data will be recorded via an EDC system with the use of eCRFs (see Section 7.2). A central laboratory will be used for a subset of laboratory assessments as specified in Section 4.5.6.

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.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical 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 Activities

Assessment Window (Days)	Screening	Cycle 1			Cycle ≥2	Treatment Discontinuation	Follow-Up
	Day −28 to Day −1	Day 1	Day 8 (±1)	Day 15 (±1)	Day 1 (±3)	≤30 Days after Last Dose [a]	
Informed consent [b]	x						
Medical history and demographic information [c]	x						
HIV, HBV, HCV serology [d]	x						
Concomitant medications [e]	x	x	x	x	x	x	
Adverse events [f]	x	x	x	x	x	x	x
Tumor assessment [g]	x	*The imaging modality and frequency of tumor assessments will be determined by the investigator.*					
Complete physical examination [h]	x					x	
Limited physical examination [i]		x[j]			x[j]		
ECOG Performance Status	x	x[j]			x[j]	x	
Vital signs [k]	x	x			x	x	
Pulse oximetry, resting	x				x	x	
12-lead ECG [l]	x					x	
Weight	x	x[j]			x[j]	x	
Height	x						
Hematology [m]	x	x[j]			x[j]	x	
Serum or plasma chemistry [n]	x	x[j]			x[j]	x	

Appendix 1
Schedule of Activities (cont.)

Assessment Window (Days)	Screening	Cycle 1			Cycle ≥2	Treatment Discontinuation	Follow-Up
	Day −28 to Day −1	Day 1	Day 8 (±1)	Day 15 (±1)	Day 1 (±3)	≤30 Days after Last Dose [a]	
Pregnancy test [o]	x				x [p]	x	
Coagulation panel (aPTT, PT/INR)	x					x	
Urinalysis [q]	x	x			x [p]	x	
TSH, free T4	x				x [p]	x	
Serum amylase and lipase	x				x [j]	x	
Serum ferritin and CRP	x						
Baseline tumor tissue sample [r]	x						
Study treatment infusion [s]		x			x		

CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = antibody against hepatitis B core antigen; HBsAb = antibody against hepatitis B surface antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IV = intravenous; PD-L1 = programmed death-ligand 1; RECIST = Response Evaluation Criteria in Solid Tumors; TSH = thyroid-stimulating hormone.

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

[a] Patients will be asked to return to the clinic within 30 days after the last dose of study treatment for a discontinuation visit. Tumor assessment scans performed within 6 weeks prior to the treatment discontinuation visit do not need to be repeated. The visit at which a response assessment shows progressive disease resulting in MOXR0916 and atezolizumab discontinuation may be used as the treatment discontinuation visit, in which case all assessments associated with the treatment discontinuation visit should be performed at that time.

[b] Written informed consent is required for performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur prior to 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 study entry (except where otherwise specified) may be used for screening assessments rather than repeating such tests. Results for the following laboratory tests must be obtained within 14 days prior to Cycle 1, Day 1: hematology, serum/plasma chemistry, coagulation panel, serum pregnancy test.

Appendix 1
Schedule of Activities (cont.)

[c] Medical history includes clinically significant diseases, surgeries, cancer history (including stage, date of diagnosis, and prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol, and drugs of abuse will be recorded at baseline. A history of pleural or pericardial effusion or of ascites requiring intervention should be entered in the medical history.

[d] All patients will be tested for HIV locally prior to enrollment into the study, and HIV-positive patients will be excluded from the study. HBsAg, HBsAb, and HBcAb should be collected during screening and tested locally. In patients who have positive serology for HBcAb, an HBV DNA test sample should be collected prior to initiation of study treatment, but the result is not required to determine eligibility.

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

[f] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment or initiation of another anti-cancer therapy, whichever occurs first. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study treatment. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or study-related procedures until a final outcome can be reported.

[g] *The imaging modality (e.g., CT vs. MRI scan, contrast-enhanced vs. non-contrast) and the frequency of tumor assessments will be determined primarily by the investigator based on the patient's disease characteristics and local institutional standards (i.e., approximately every 6–12 weeks).* At the investigator's discretion, tumor assessments may be performed at any time if progressive disease is suspected. Tumor assessments will continue until radiographic disease progression (or loss of clinical benefit as determined by the investigator for patients who continue treatment after disease progression according to RECIST v1.1), withdrawal of consent, initiation of new anti-cancer therapy, loss to follow-up, death, or study termination by the Sponsor, whichever occurs first. Patients who continue treatment beyond radiographic disease progression per RECIST v1.1 will be monitored with a follow-up scan in 6 (±1) weeks or earlier if clinically indicated. Tumor assessments should be continued every 6 (±1) weeks thereafter until two consecutive scans demonstrate stability or improvement with respect to the first scan that showed radiographic disease progression, at which point the scan frequency *may be liberalized at the investigator's discretion.*

[h] Complete physical exam includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

[i] Perform a limited, symptom-directed physical examination at specified timepoints or as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[j] ECOG performance status, weight, limited physical examination, local hematology and serum/plasma chemistry panels (including

Appendix 1
Schedule of Activities (cont.)

amylase/lipase), may be obtained ≤ 96 hours before Day 1 of each cycle.

[k] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first infusion of MOXR0916, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, at 15, 30, 45, and 60 minutes (±5 minutes for all timepoints) during and at 30 (±10) minutes after the infusion. For the first infusion of atezolizumab, vital signs should be measured between the MOXR0916 and atezolizumab infusions (within 60 minutes prior to the atezolizumab infusion), and if clinically indicated, at 15, 30, 45, and 60 minutes (±5 minutes for all timepoints) during, and at 30 (±10) minutes after the infusion. For subsequent MOXR0916 infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, every 15 (±5) minutes during the infusion, at the end of the infusion (±5 minutes), and at 30 (±10) minutes after the infusion. For subsequent atezolizumab infusions, vital signs should be measured between the MOXR0916 and atezolizumab infusions (within 60 minutes prior to the atezolizumab infusion), and, if clinically indicated or if symptoms occurred during the previous infusion, every 15 (±5) minutes during the infusion, at the end of the infusion (±5 minutes), and at 30 (±10) minutes after the infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

[l] 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.

[m] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, platelet count, and WBC count with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). A manual differential can be done if clinically indicated. During screening, hematology results must be obtained within 14 days prior to Cycle 1, Day 1.

[n] Serum or plasma chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin. Bicarbonate is not a required analyte for patients in countries where it is not considered a standard chemistry measurement.

[o] Serum pregnancy test (for women of childbearing potential, as defined in Section 4.1.1) must be performed and documented as negative within 14 days prior to Cycle 1, Day 1. Urine or serum pregnancy tests (for women of childbearing potential only) will be performed at the specified subsequent visits. If a urine pregnancy test is positive, dosing will be delayed until the patient's status is determined by a serum pregnancy test.

[p] On Day 1 of Cycle 2 and every two cycles thereafter (i.e., Cycle 4, Day 1; Cycle 6, Day 1; Cycle 8, Day 1; etc.). Tests may be performed ≤ 96 hours before Day 1.

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

[r] If archival tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria. Refer to Section 4.5.6.2 for tissue

Appendix 1
Schedule of Activities (cont.)

sample requirements.

[s] MOXR0916 will be administered prior to atezolizumab. The initial dose of MOXR0916 will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Similarly, the initial dose of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Dosing will occur only if the clinical assessment, local laboratory test results, and ECG if applicable, are acceptable. If a tumor assessment was performed during the previous cycle, results must be reviewed by the investigator before dosing.

Appendix 2
Modified Bajorin Risk Score

Risk factor	No visceral metastases (0 points)	Bone and/or lung metastases (1 point)	Liver metastases (2 points regardless of ECOG)
ECOG 0 or 1 (0 points)	0 + 0 = 0	0 + 1 = 1	2
ECOG 2 (1 point)	1 + 0 = 1	1 + 1 = 2	2

ECOG = Eastern Cooperative Oncology Group.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF 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 $\leq$ 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 $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with short axis $\geq$ 10 mm 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

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

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:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and 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 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) since 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 not considered measurable unless subsequent progression in the lesion has been demonstrated.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Appendix *3*
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the 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, since 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 AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 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, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

Appendix *3*
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION 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 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 considered non-target lesions.

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 since 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. Lymph node 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.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), 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").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring 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 node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) 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 CT scan that the radiologist may not feel comfortable assigning an exact measurement 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 "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since 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 "too small to measure" should also be

ticked).

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

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. 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 maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the eCRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

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

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

Appendix *3*
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While 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 schedule of activities.

- 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 lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, 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 on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

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 PR or CR. 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.

Appendix 3
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

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, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: 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 all 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.

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 measurements are made on only a subset of target lesions at a timepoint, 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 lesions 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.

Appendix *3*
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (cont.)

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in 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 lesions as shown in Table 1.

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.

REFERENCES

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.

Appendix 4
New York Heart Association Functional Classification

Class	Description
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased.

Excerpted from Oxford Textbook of Medicine. Vol 2, p. 2228. Oxford Press 1997.

Appendix 5
Anaphylaxis Precautions

EQUIPMENT NEEDED

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

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. 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 6
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead