Clinical Trial Protocol

Protocol Number:	SOGUG-2020-IEC(VEJ)-1
Title:	Phase II, multicenter, non-randomized, single-arm, open-label trial of atezolizumab in combination of split-doses of gemcitabine plus cisplatin in patients with locally advanced or metastatic urothelial carcinoma
Short title:	Study of atezolizumab combined with split-dose gemcitabine plus cisplatin in urothelial carcinoma
Acronym:	AUREA
Nº EudraCT:	2020-001326-65
Sponsor:	Spanish Oncology Genitourinary Group (SOGUG) [redacted]
Coordinating Investigator:	**Guillermo de Velasco, M.D., PhD.** [redacted]

VERSION 3.0 - 22AUG2023

Confidentiality Statement

The information contained in this document is the property of the sponsor and therefore is provided confidentially for review by you, your investigative team, the Investigational Ethics Committee, and the competent authorities. This information must not be revealed to any other party without previous authorization in writing by the sponsor, except as needed to obtain the informed consent of the subjects who may be given the medicinal product.

SPONSOR'S PROTOCOL SIGNATURE PAGE

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonization Good Clinical Practice, and all applicable Health Authority requirements and national laws.

[redacted]

SOGUG Chairman	**Signature**	**Signature date (DD-mm-YYYY)**

Dr. Guillermo de Velasco

Coordinating Investigator	**Signature**	**Signature date (DD-mm-YYYY)**

PRINCIPAL INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

I have read this protocol and agree to conduct this clinical trial in accordance with all the provisions of the Protocol, any approved protocol amendments, International Conference on Harmonization Good Clinical Practice, Helsinki Declaration and all applicable Health Authority requirements and national laws

Site: _____

Name: _____

Date:_____

Principal Investigator Signature:_____

1. SUMMARY

1.1. Type of application

Clinical trial with approved medications with a potential better regimen.

1.2. Study Title

Phase II, multicenter, non-randomized, single-arm, open-label trial of atezolizumab in combination of split-doses of gemcitabine plus cisplatin in patients with locally advanced or metastatic urothelial carcinoma

1.3. Protocol Number and Version

SOGUG-2020-IEC(VEJ)-1 - VERSION 3.0 22AUG2023

1.4. Nº EudraCT

2020-001326-65

1.5. Sponsor Data

Spanish Oncology Genitourinary Group (SOGUG)

[redacted]

1.6. Coordinating Investigator

Guillermo de Velasco, M.D., PhD.

[redacted]

1.7. Principal Investigators

The list of sites and the corresponding Principal Investigators is provided in the attached document.

1.8. Study Sites

It is expected the participation of 12 Sites in Spain.

1.9. Monitoring Organization

MFAR Clinical Research

[redacted]

1.10. Disease under study

Locally advanced and metastatic urothelial carcinoma (mUC)

1.11. Study Phase

Phase II clinical trial; Investigator Initiated Study (IIS)

1.12. Study Treatments

All study treatments are intended for administration as described below (regarding maximum treatment duration as per protocol), until PD, unacceptable toxicity, investigator's decision or

patient's consent withdrawal (whichever occurs first).

- **Atezolizumab** at a fixed dose of 1200 mg/m^2 by intravenous (IV) infusion on D1 of each cycle up to disease progression, unacceptable toxicity or absence of clinical benefit. AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation. In case that the site cannot provide the drug for regulatory reasons (for example, the indication is not financed) and always with prior approval by the study sponsor (SOGUG) and by Roche, and if it is thus indicated in the contract between the Sponsor and the Site, the patient could continue in treatment with Atezollizumab participating in a Post-Trial Access (PTA) Program, previously approved by Roche. The maximum duration of the PTA will be 1 year.

- **Gemcitabine** 1000 mg/m^2 IV on D1 and 1000 mg/m^2 IV on D8 of each 21-day cycle *plus* **Cisplatin** 70 mg/m^2 by IV on split-dose schedule of 35 mg/m^2 on day 1 (D1) and 35 mg/m^2 on day 8 (D8) <u>for up to 6 cycles.</u>

1.13. Objectives

Primary Objective:

To evaluate the preliminary efficacy of atezolizumab plus split-dose gemcitabine and cisplatin (GC) for the first-line setting, in patients with histologically confirmed advanced (locally advanced and metastatic) urothelial cancer in terms of overall response rate (ORR) assessed by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Secondary Objectives

Efficacy:

- To evaluate the *duration of response (DoR)* associated with the study treatment, understood as the time from first confirmed response (CR or PR) to the date of the documented progressive disease as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.
- To determine the *overall survival (OS)* of patients with locally-advanced or mUC treated with the intended treatment regimen, understood as the time from first dosing date to the date of death. A subject who has not died will be censored at last known date alive.
- To evaluate the *time to response (TtR)* associated with the study treatment, understood as the time from the first dose of the study treatment and confirmed response (CR or PR) based on RECIST 1.1 criteria.
- To evaluate the *clinical benefit rate (CBR)*, defined as the percentage of patients who have achieved complete response, partial response and stable disease. Stable disease should be maintained for at least 6 months to be considered as CBR event.

- To determine the *progression-free survival (PFS)* of patients with locally-advanced or mUC treated with the intended treatment regimen, defined as the time from first dosing date until disease progression or death from any cause. Patients who have not progressed and start a new line of treatment will be censored.

Safety:

- To evaluate *safety* of the intended treatment regimen based on the frequency and severity of adverse events assessed by NCI CTCAE v5.0.

Exploratory objectives

- To explore potential correlation of efficacy with relevant potential prognostic factors/stratification factors
- To evaluate the relationship between the expression of PD-L1 and microbiome with ORR and PFS during experimental treatment.

1.14. Endpoints

Primary endpoint:

- *Overall Response Rate (ORR)*

Secondary endpoints

- *Duration of response* (DoR)
- *Overall Survival* (OS)
- *Time to response* (TtR)
- *Clinical benefit* (CB)
- *Progression-Free Survival* (PFS)

Safety endpoints

- *Adverse events* (AE)
- *Treatment-related AEs* (TRAEs)

Exploratory endpoints

- Biomarkers expression

1.15. Sample Size

A minimum of 66 patients will be included in the trial.

1.16. Eligibility and withdrawal criteria

Inclusion criteria

1. Male or female subjects ≥ 18 years old.
2. Written informed consent approved by the Independent Ethics Committee (IEC), prior to the performance of any trial activities.

3. Patients with histologically documented, locally advanced (T4B, any N; or any T, N2-3) or metastatic urothelial carcinoma (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).*

4. Patients should not be eligible (unfit) for full dose of cisplatin, in the investigator's judgement, based on:

   a. Age older than 70 years.

   b. ECOG Performance status (PS) 2 or Karnofsky PS of 60 - 70% (only 15 patients will be included with ECOG 2).

   c. Measured creatinine clearance (ClCr) > 30 and < 60 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for the determination of creatinine clearance:

      Males:

      $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

      Females:

      $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

   d. Any other reason the physician considers but should specify in the CRF and discussed with the PI.

5. At least one measurable lesion through radiographic tumor evaluation (CT scan or magnetic resonance imaging/MRI) as defined by RECIST version 1.1, that has not been previously irradiated within 4 weeks prior to the study enrolment.

6. Patients with an archival or *de novo* tumor biopsy (representative formalin-fixed paraffin-embedded/FFPE paraffin block obtained as close as possible to the patient inclusion) with an associated pathology report, for testing of PD-L1 expression, prior to study enrollment. Samples in unstained slides could be acceptable (at least 15 slides).

7. Patients with adequate normal organ and marrow function as defined below:

   a. Haemoglobin ≥ 9.0 g/dL.
   b. Absolute neutrophil count (ANC) ≥ 1500 per mm^3.
   c. Platelet count ≥ 100,000 per mm^3.
   d. Serum bilirubin ≤ 1.5 X institutional upper limit of normal (ULN) unless liver metastases are present, in which case it must be ≤ 2X ULN. This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology); however, they will be allowed only in consultation with their physician.

e. Serum transaminases (ALT, AST and GGT) ≤ 2.5X institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 3X ULN.

8. No major active bleeding.

9. Female subjects of childbearing potential (not surgically sterile or at least 2 years postmenopausal) must provide a negative urine pregnancy test at screening, and use a medically accepted double barrier method of contraception (i.e. condom with spermicide + IUD or cervical caps). In addition, they must agree to continue the use of this double barrier method for the duration of the study and for 6 months after participation in the study.

10. Males should agree to abstain from sexual intercourse with a female partner or agree to use a double barrier method of contraception (i.e. condom with spermicide, in addition to having their female partner use some contraceptive measures such as oral contraceptive drugs, intrauterine device (IUD) hormonal contraception, or cervical caps), for the duration of the study and for 6 months after participation in the study

11. Willingness and ability of patients to comply with the protocol for the duration of the study including undergoing treatment as well as availability for scheduled visits and examinations including follow up.

Exclusion criteria

1. Prior treatment with any immune checkpoint inhibitor therapy (e.g., CTLA4, PD-1, or PD-L1 targeting agent).*

   **Note*: Prior adjuvant or neoadjuvant treatment with targeted therapy/checkpoint inhibitors is allowed, as long as the last dose was administered at least 12 months prior to the patient inclusion in this trial.

2. Presence of active second malignancy and/or prior malignancy in the last 2 years is allowed except for the following:
   a. adequately treated basal cell or squamous cell skin cancer,
   b. adequately treated Stage I or II cancer from which the patient is currently in complete remission per investigators' clinical judgment.

3. Patient receiving radiation therapy within 4 weeks before inclusion.

4. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

5. Active or prior documented inflammatory bowel disease (e.g.., Crohn's disease and ulcerative colitis).

6. History of allogeneic organ transplant.

7. Subjects having a diagnosis of immunodeficiency or are receiving systemic steroid therapy or any other form of immunosuppressive therapy within 28 days prior to the first dose of trial treatment.

8. Current or prior use of immunosuppressive medication within 7 days prior to enrolment, except the following:
    a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);
        i. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;
        ii. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
9. The subject has uncontrolled, significant intercurrent or recent illness (within 6 months prior to inclusion) including, but not limited to, the following conditions:

    a. Cardiovascular disorders:
        i. Class 3 or 4 congestive heart failure as defined by the New York Heart Association, unstable angina pectoris, and serious cardiac arrhythmias.
        ii. Uncontrolled hypertension defined as sustained blood press > 150 mm hg systolic or > 100 mm hg diastolic despite optimal antihypertensive treatment.
        iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction, other ischemic event, or thromboembolic event (e.g., deep venous thrombosis [DVT] and pulmonary embolism) within 6 months before inclusion. Subjects with a more recent diagnosis of DVT are allowed if stable, asymptomatic, and treated with LMWH for at least 6 weeks before study treatment.

    b. Gastrointestinal disorders (e.g., malabsorption syndrome or gastric outlet obstruction) including those associated with a high risk of perforation or fistula formulation:
        i. Tumours invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.
        ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before inclusion. Note: complete healing of an intra-abdominal abscess must be confirmed prior to start of the treatment.

    c. Clinically significant hematemesis or hemoptysis of > 0.5 teaspoon (> 2.5 ml) of red blood or history of other significant bleeding within 3 months before treatment.

    d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation.

    e. Lesions invading major pulmonary blood vessels.

    f. Other clinically significant disorders such as:
        i. Active infection requiring systemic treatment, infection with human immunodeficiency virus or acquired immunodeficiency syndrome-related illness, or chronic hepatitis B or C infection.
        ii. Serious non-healing wound/ulcer/bone fracture.
        iii. Malabsorption syndrome.
        iv. Moderate to severe hepatic impairment (child-pugh B or C).
        v. Requirement for hemodialysis or peritoneal dialysis.
        vi. Uncontrolled diabetes mellitus.

10. Major surgery (e.g., GI surgery and removal or biopsy of brain metastasis) within 8 weeks before inclusion. Complete wound healing from major surgery must have occurred 4 weeks before study treatment and from minor surgery (e.g., simple excision, tooth extraction) at least 10 days before study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

11. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

12. Any test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or chronic infection.

13. Women who are pregnant or are breastfeeding.

14. Male patients must be surgically sterile or must agree to use effective contraception during the period of therapy.

15. Any of the following within 6 months prior to study entry: myocardial infarction, uncontrolled angina, uncontrolled hypertension, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack.

16. Previously identified allergy or hypersensitivity to components of the study treatment formulations.

1.17. Planned trial period

- Enrolment/recruitment period: 12 months
- First patient first visit (FPFV): 8ENE2021
- Last patient last visit (LPLV): January 2024 (expected)
- Treatment period: Up to 24 months of LPFV
- Follow-up period: 24 months
- Planned end of study date: First quarter 2024 (expected)

GLOSSARY OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ADR	**Adverse drug reaction**
AE	**Adverse event**
aUC	**Advanced urothelial cancer**
BMI	**Body Mass Index**
BP	**Blood Pressure**
CIs	**Confidence intervals**
CK	**Creatine kinase (CK), also known as creatine phosphokinase (CPK) or phosphocreatine kinase**
CB	**Clinical benefit**
CR	**Complete Response**
CRA	**Clinical Research Associate**
CTCAE	**Common Terminology Criteria for Adverse Events**
CT Scan	**Computed Tomography Scan**
DMP	**Data Management Plan**
CYP	**Cytochromes P450 enzymes**
DoR	**Duration of response**
DVP	**Data Validation Plan**
ECHO	**Echocardiogram**
ECG	**Electrocardiogram**
ECOG	**Eastern Cooperative Oncology Group**
eCRF	**Electronic Case Report Form**
EDC	**Electronic Data Capture**
ECG	**Electrocardiogram**
EMA	**European Medicines Agency**
ESMO	**European Society of Medical Oncology**
FBE	**Full blood examination**
FDA	**US Food and Drug Administration**

FFPE	**Formalin-fixed paraffin-embedded**
FPFV	**First patient first visit**
FU	**Follow-up**
GC	**Gemcitabine plus cisplatin**
GCP	**Good Clinical Practice**
G-CSF	**Granulocyte colony-stimulating factor**
GH	**Growth hormone**
Hb	**Haemoglobin**
IB	**Investigator Brochure**
ICF	**Informed Consent Form**
ICH	**International Conference on Harmonization**
ICI	**Immune Checkpoint Inhibitors**
IEC	**Independent Ethics Committee**
IgG1	**Immunoglobulin G1**
IIS	**Investigator Initiated Study**
IMP	**Investigational Medicinal Product**
ISF	**Investigator Site File**
ITT	**Intention To Treat**
IUD	**Intrauterine device**
LPLV	**Last visit Last patient**
MedDRA	**Medical Dictionary for Regulatory Activities**
MRI	**Magnetic Resonance Imaging**
mUC	**Metastatic urothelial cancer**
MUGA	**Multigated Acquisition Scan**
MVAC	**Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin**
NCI	**National Cancer Institute (USA)**
ORR	**Overall response rate**
OS	**Overall Survival**
PD	**Progression disease**
PE	**Physical Examination**

PFS	**Progression Free Survival**
PI	**Principal Investigator**
PP	**Per Protocol**
PR	**Partial Response**
PS	**Performance Status**
QD	**Quaque die, every day “once daily”**
QxW	**Every X weeks**
RECIST	**Response Evaluation Criteria In Solid Tumours**
REEC	**Registro Español de Estudios Clínicos (Spanish Registry of Clinical Studies)**
Rx	**Radiography**
SAE	**Serious adverse event**
SAP	**Statistical Analysis Plan**
SAR	**Serious adverse reaction**
SC	**Subcutaneous**
SD	**Stable disease**
SDV	**Source Data Verification**
SmPC	**Summary of Product Characteristics**
SP	**Safety Population**
SUSAR	**Suspected unexpected serious adverse reaction**
PD-1	**Programmed death-1**
PD-L1	**Programmed death ligand-1**
TR	**Translational Research**
UC	**Urothelial cancer**
ULN	**Upper Limit of Normality**
VS	**Vital Signs**
WBC	**White Blood Count**
wGC	**weekly Gemcitabine plus cisplatin**
WHO	**World Health Organization**

2. GENERAL INFORMATION

2.1. Study Identification

Short title: Study of atezolizumab and split-dose cisplatin/gemcitabine and in urothelial carcinoma

Protocol number: SOGUG-2020-IEC (VEJ-1)

EudraCT No.: 2020-001326-65

2.2. Monitoring Organization

MFAR Clinical Research
[redacted]

2.3. Sponsor information

Spanish Oncology Genitourinary Group (SOGUG)
[redacted]

2.4. Coordinating investigator

Guillermo de Velasco M.D., PhD.
[redacted]

2.5. Investigators and study centres

It is expected the participation of 12 Sites in Spain. The list of Sites and the corresponding Principal Investigators is provided in a separated document.

3. INVESTIGATIONAL MEDICINAL PRODUCT (IMP) DESCRIPTION

3.1. Study medication

Atezolizumab:

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01XC

Presentation: 60 mg/mL glass vials of 20-mL, nominal atezolizumab amount per vial, 1200 mg. Commercial medication labeled for clinical trial.

Pharmaceutical form: Concentrate for solution for infusion. Clear, colourless to slightly yellowish liquid.

Supply: Roche Pharma will supply atezolizumab to the Sponsor that will supply this product to the sites pharmacy.

Gemcitabine

Pharmacotherapeutic group: Antineoplastic agents - Alkylating agents - Antimetabolites - Pyrimidine analogues, ATC code: L01BC05

Presentation:; Glass vial: *200 mg/5.3 mL *or* 200 mg/2 mL; 1000 mg/10 mL or 1000 mg/26.3mL; 1500 mg/15 mL and *2000 mg/52.6 mL *or* 2000 mg/20 mL. Commercial medication not-labeled for clinical trial.

Pharmaceutical form: *Concentrate for solution for infusion according to different commercial presentations authorized in Spain.

Supply: By participating sites under standard treatment criteria

Cisplatin

Pharmacotherapeutic group: Antineoplastic agents - Other antineoplastic agents, ATC code: L01XA01

Presentation: 1 mg/mL glass vials of 10-mL, 50-mL and 100-mL. Commercial medication not-labeled for clinical trial.

Pharmaceutical form: Concentrate for solution for infusion.

Supply: By participating sites under standard treatment criteria.

4. RATIONALE AND OBJECTIVES

4.1. Rationale

4.1.1. Current state of the art

Cisplatin-based chemotherapy (70 mg/m^2) has been the standard of care for first-line treatment for surgically unresectable and metastatic patients fit enough to tolerate cisplatin for more than 30 years (*Saxman SB, et al. 1997; Von der Maase, et al. 2000; Bellmunt J, et al. 2016*). However, a standard dose schedule is not feasible for a significant number of patients (about 50%). Age-related physiological changes and comorbidities are common in the uro-oncology field and, as expected, affect treatment choices and outcomes. Renal function impairment, cardiovascular disease, neuropathy, hearing loss are commonly reported in patients with bladder cancer (*Bellmunt J, et al. 2016*; *Katz H, et al. 2017*); but its toxicity (*van Leenders GJLH, 2019*).

According to the most recent update on cumulative evidence and as summarized in the most recent ESMO Bladder Cancer Treatment Recommendations published on 16 December 2019, a number of cisplatin-containing regimens are acceptable although gemcitabine and cisplatin [I, A] is the most widely accepted (*Von der Maase, et al. 2000*). Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) [I, B], MVAC with granulocyte colony-stimulating factor (G-CSF) [I, B], and gemcitabine, cisplatin and paclitaxel [I, C] are alternatives which have established themselves as options over time (*Loehrer PJ, et al. 1992; Sternberg CN, et al 2006; Bellmunt J, et al. 2012; Grande E, et al. 2019*). Although these specific regimens may lack proven advantage or non-inferiority compared with gemcitabine and cisplatin, they can be considered as options in selected patients.

4.1.2. Split-Dose Cisplatin

For those patients with mUC cisplatin-ineligible or who have progressed on a platinum-based regimen treatment options are limited (*Koshkin VS, et al. 2018*) and are usually palliated with carboplatin-based regimen, single-agent taxane or gemcitabine, or split-dose cisplatin-based regimens may be employed. In fact, some studies have presented data on up to 50% of patients eligible for cisplatin might be treated with carboplatin-based chemotherapy based on physician criteria (ie. IMvigor 130; *Grande E, et al. 2019*).

The difficult-to-treat concept of this disease entails the undoubtedly high age of most of around 80% of patients with UC (*Gore JL, et al. 2010*).

Administration of cisplatin 35 mg/m2 on day 1 + 8 or 1 + 2 (i.e., split schedule) is a commonly used alternative. Several studies have reported that split dose GC has comparable response rates in metastatic disease to other platinum containing regimens (*Morales-Barrera R, et al. 2012*), but has a favourable toxicity profile and considerably less time burden on day care facilities (*Sellers LE, et al. 2016*). These led us to consider that split dose GC should be a feasible alternative to the longer more toxic regimens, particularly in metastatic disease.

4.1.3. PD-L1 and the role of atezolizumab in mUC

Expression of programmed death ligand-1 (PD-L1) is prevalent among many human tumors (*Dong et al. 2002*), and its overexpression is associated with poor prognosis for patients with certain cancers (*Thompson et al. 2006; Hamanishi et al. 2007; Okazaki T and Honjo T, 2007; Hino et al. 2010, Mu et al. 2011*). Therefore, interruption of the PD-L1/PD 1 pathway represents an attractive strategy to reinvigorate tumor-specific T cell immunity.

Since May 2016, five different agents targeting the PD-1/PD-L1 pathway (atezolizumab, pembrolizumab, nivolumab, avelumab, durvalumab) have received FDA approval for the treatment of aUC in the platinum-refractory setting, while pembrolizumab and atezolizumab are FDA-approved for cisplatin-ineligible patients in the first-line setting (*Koshkin VS 2018*). For platinum or chemotherapy-ineligible patients with mUC, immune checkpoint inhibitors (ICI) such as inhibitors of programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) are approved regardless of PD-L1 expression, including pembrolizumab and atezolizumab (*Einstein and Sonpavde, 2019*).

Atezolizumab is a humanized immunoglobulin (IgG1) monoclonal antibody that is produced in Chinese hamster ovary (CHO) cells. Atezolizumab targets programmed death-ligand 1 (PD-L1) on tumor-infiltrating immune cells (ICs) or tumor cells (TCs) and prevents interaction with the programmed death-1 (PD-1) receptor and B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells and other immune cells. The PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T cell response through increased T cell priming, expansion, and/or effector function. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc effector function. By eliminating Fc-effector function and antibody-dependent cell-mediated cytotoxicity, antibody-mediated clearance of activated effector T cells is also eliminated.

Atezolizumab has demonstrated efficacy and a tolerable safety profile in a range of cancers, including locally advanced or mUC (*Herbst RS, et al. 2014; Powles T, et al. 2014, Fehrenbacher L et al. 2016; McDermott DF, et al. 2016; Rosenberg JE, et al. 2016*). Cumulative data on efficacy at the time of this study design (March 2020) suggest that atezolizumab as a single-agent for first-line in patients with mUC entails clinical benefit in terms of objective responses, durable responses, and OS.

Clinical data from the first-line cisplatin-ineligible IMvigor210 cohort—the first report of an anti–PD-L1/PD-1 checkpoint inhibitor in this setting— atezolizumab conferred significant clinical benefit (*Rosenberg JE, et al. 2016*), leading to accelerated regulatory approval, and several biomarkers associated with response were identified. Furthermore, encouraging durable response rates, survival and tolerability (*Balar AV, et al. 2017*) have been also reported.

Interim results (2018) from the ongoing IMvigor 130 trial (atezolizumab *vs* atezolizumab plus platinum-based chemotherapy in locally advanced/mUC not previously treated) has shown a reduction on survival for those patients treated with atezolizumab alone when compared to those who received platinum-based chemotherapy (carbo- or cis- at physician discretion), not previously treated and with tumors showing a low-PD-L1 expression (<5% of immune cells with positive staining) (*EMA Tecentriq Assessment Report*).

4.2. Hypothesis

The results of trials combining checkpoint inhibitors or platinum-based chemotherapy plus PD-1/PD-L1 inhibitors are eagerly awaited. The combination of split cisplatin with atezolizumab is a feasible treatment that may provide better outcomes than carboplatin/based combinations.

In the IMvigor130, 52% of patients considered cisplatin eligible at the entry of the study were treated with carboplatin. Subanalysis presented at ESMO 2019 (*Grande E, et al. 2019*) has also shown a longer median OS are achieved with cisplatin-based chemotherapy combined with atezolizumab (21.7 months) when compared to the carboplatin-based chemotherapy plus atezolizumab (14.2 months), with similar findings when it comes to PFS 8.8 months with cisplatin/gemcitabine/atezolizumab vs 7.1 months carboplatin/gemcitabine/atezolizumab.

A reasonable strategy may be the use of split cisplatin with atezolizumab to increase the number of patients receiving cisplatin.

4.3. Rationale for dose selection

As per Atezolizumab Investigator's Brochure (IB) at the time of this study design (*version 15, July 2019*), the standard fixed dose of 1200, equivalent to 15mg/kg in a typical patient. No dose-limiting toxicities were observed at the 20 mg/kg dose level and the incidence and intensity of AEs reported have not been shown to be dependent on dose. A maximum tolerated dose has not been established. Atezolizumab is supplied in vials containing the fixed 1200 mg dose of drug substance, which minimizes the chance of overdose. Because the dose per patient is not based on weight or body surface area, and no dose calculation is required, the risk of overdose due to medication errors is minimal. The data available to date suggest that the potential for harm from overdose is very low.

Weekly gemcitabine with GC every 3-4 weeks is considered conventional first-line chemotherapy for aUC. Weekly split-dose cisplatin with wGC might be less toxic and have similar activity. Considering the probable lower nephrotoxicity of fractionated cisplatin, prospective evaluation of wGC might be warranted across cisplatin-eligible and -ineligible patients to develop a single chemotherapy template for the development of combinations with biological agents in a broad population of patients (*Maughan BL, et al. 2013*).

In conclusion, the proposed scientific rationale and the preliminary benefit-risk profile of the study treatments observed in previous trials support the further investigation of the combination in the patient population and dosification regimen chosen for this study.

4.4. Study Objectives

4.4.1. Primary Objectives

To evaluate the preliminary efficacy of atezolizumab plus split-dose gemcitabine and cisplatin

(GC) for the first-line setting, in patients with histologically confirmed advanced (locally advanced and metastatic) urothelial cancer in terms of overall response rate (ORR) assessed by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

4.4.2. Secondary Objectives

Efficacy:

- To evaluate the *duration of response (DoR)* associated with the study treatment, understood as the time from first confirmed response (CR or PR) to the date of the documented progressive disease as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.
- To determine the *overall survival (OS)* of patients with locally-advanced or mUC treated with the intended treatment regimen, understood as the time from first dosing date to the date of death. A subject who has not died will be censored at the last known date alive.
- To evaluate the *time to response (TtR)* associated with the study treatment, understood as the time from the first dose of the study treatment and confirmed response (CR or PR) based on RECIST 1.1 criteria.
- To evaluate the *clinical benefit rate (CBR)*, defined as the percentage of patients who have achieved complete response, partial response and stable disease. Stable disease should be maintained for at least 6 months to be considered as a CBR event.
- To determine the *progression-free survival (PFS)* of patients with locally-advanced or mUC treated with the intended treatment regimen, defined as the time from first dosing date until disease progression or death from any cause. Patients who have not progressed and start a new line of treatment will be censored.

Safety:

- To evaluate *safety* of the intended treatment regimen based on the frequency and severity of adverse events assessed by NCI CTCAE v5.0.

4.4.3. Exploratory objectives

- To explore potential correlation of efficacy with relevant potential prognostic factors/stratification factors
- To evaluate the relationship between the expression of PD-L1and microbiome with ORR and PFS during experimental treatment.

5. STUDY DESIGN

5.1. Study design

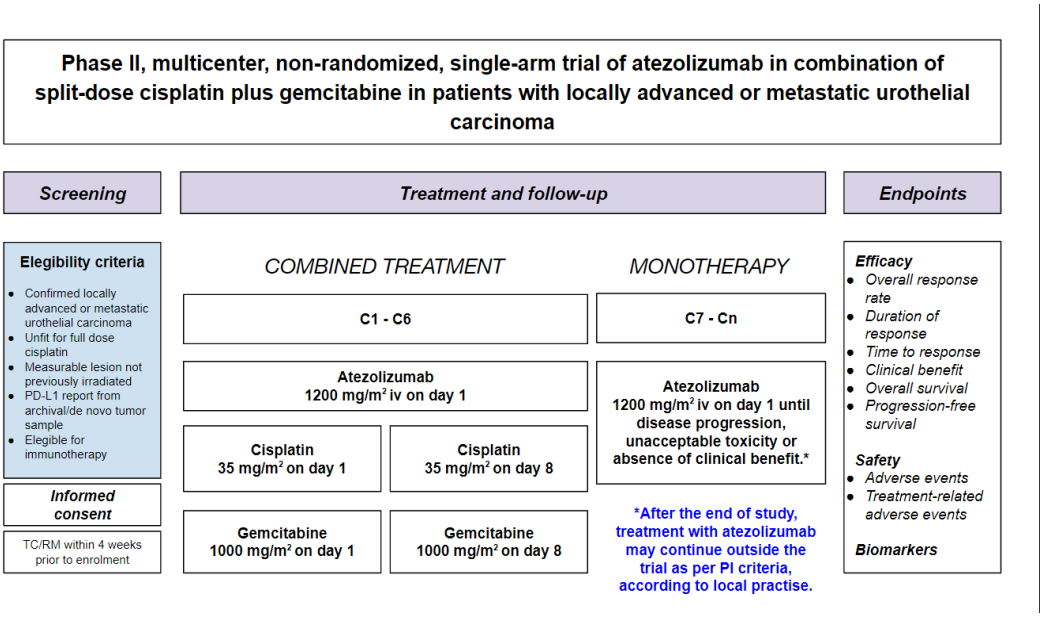
The AUREA study is a multicenter, open labelled, single arm, Phase II clinical trial of of atezolizumab in combination of split-dose cisplatin plus gemcitabine in patients with locally advanced or metastatic urothelial carcinoma (additional details on the eligibility criteria of the study are found in section 6 of this protocol).

The design includes screening phase, combined treatment initial phase, monotherapy treatment phase, follow-up phase and translational research with biopsies, blood samples and faecal samples.

The dose scheme includes the initial dose of atezolizumab (1200 mg) intravenously administered every 21 days (one cycle) up to disease progression, unacceptable toxicity or absence of clinical benefit. Dose adjustment or dose reductions of atezolizumab are not expected. Additional information on the treatment, modifications, and dose delays is available in section 7 of this protocol. AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation. In case that the site cannot provide the drug for regulatory reasons (for example, the indication is not financed) and always with prior approval by the study sponsor (SOGUG) and by Roche, and if it is thus indicated in the contract between the Sponsor and the Site, the patient could continue in treatment with Atezollizumab participating in a Post-Trial Access (PTA) Program, previously approved by Roche. The maximum duration of the PTA will be 1 year.

Study treatment will begin as soon as possible after signing the informed consent (as per ***section 5.2*** of this protocol) and inclusion will be completed as per ***section 5.3*** of this protocol.

Figure 1. Study design



5.2. Patient selection

Once all regulatory and sponsor requirements are completed confirming that the study is fully active in the corresponding site, informed consents can be offered to potential patients, and patient selection can start in this site.

5.3. Screening period and screening failure

Informed consent will be obtained prior to the start of the specified screening window. Procedures conducted as part of the subject's routine clinical management (e.g.., blood count determinations and imaging studies) prior to signing of ICF may be used for screening or for defining baseline data, provided these procedures are conducted as specified in the protocol.

Other procedures (such as the faecal sample collection) must be developed once the patient has provided the signed consent for participation.

Once ICFs are signed, a trial screening number will be assigned to each patient after registering at Electronic Data Capture (EDC) platform. Each site will receive access to the EDC platform to register each screened case because as per GCP guidelines, it is mandatory to register every patient who signs a consent form.

Furthermore, within the Investigator Site File (ISF), a Patient Identification List will be included in order to identify patients according to local normal practice. This document will allow for immediate and unequivocal identification of patients participating in this clinical trial.

This document will always be stored under Investigator staff custody at the site. The screening number will identify patients throughout the screening period while procedures needed to confirm the subjects' suitability for the trial protocol, such as clinical laboratory tests, imaging, and others are performed.

Screening determinations should be performed as per indications specified in ***Table 4*** include ICF signature, eligibility assessments, tumour characteristics, ECG, clinical evaluation (AE,

PE, ECOG, VS, BMI, and symptom control), laboratory determinations (FBE, Biochemistry, electrolytes, liver panel TF), Pancreatic enzymes, serology, urinalysis, pregnancy test, concomitant medication, biological samples (tumour sample, biomarkers), CT Scan / MRI. Availability of archival tumor blocks should be verified. Additional information about screening procedures can be found in ***Section 8.4*** of this protocol.

5.4. Patient registration/enrollment

After confirming that a patient fulfils all eligibility criteria of the study (***Section 6***, *study population*), site staff will initiate the electronic case report form (eCRF) registration procedure. Once registration has been completed, the site staff will receive the "Inclusion confirmation communication", and study treatment can be initiated as per ***Section 7*** *(treatment description*).

5.5. Treatment description, doses and schedules

During treatment, patients should be visited at baseline for administration of the study treatment (Day 1 of each cycle) as follows: Atezolizumab 1200 mg, gemcitabine 1000 mg/m^2 and cisplatin 35 mg/m^2. A second visit on day 8 (D8) should be compiled in order to administer the second dose of gemcitabine 1000 mg/m^2 and cisplatin 35 mg/m^2 cisplatin.

Atezolizumab will be administered first as a IV infusion according to what is detailed in section 7.4 of this protocol, followed by the cisplatin infusion and then the gemcitabine infusion. The GC infusion will start at least 30 minutes after completion of the atezolizumab infusion. At the investigator's discretion, atezolizumab may be administered over a longer infusion time (60 minutes) if the participant developed a prior infusion reaction.

This regimen will be repeated every three weeks (q3w) for up to 6 cycles. Once cycle 6 is done, Atezolizumab 1200 mg/m^2 will be administered as monotherapy every 3 weeks until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent or absence of clinical benefit. AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation. In case that the site cannot provide the drug for regulatory reasons (for example, the indication is not financed) and always with prior approval by the study sponsor (SOGUG) and by Roche, and if it is thus indicated in the contract between the Sponsor and the Site, the patient could continue in treatment with Atezollizumab participating in a Post-Trial Access (PTA) Program, previously approved by Roche. The maximum duration of the PTA will be 1 year.

All chemotherapy agents' preparation, premedication, administration, monitoring, and management of complications are to follow local prescription guidelines and regulations. The dose of chemotherapy may be capped per local standards.
All participants will be monitored continuously for adverse events (AEs) while on study treatment. Treatment modifications (eg, dose delay, reduction, retreatment, or discontinuation)

will be based on specific laboratory and adverse event criteria, as described in ***Section 5.2*** and ***Section 5.3***.

Table 1. AUREA's trial treatment schedule

Drug	Drug	Frequency	Administration	Treatment period	Use
Atezolizumab	**1200 mg**	**Q3W**	**IV infusion**	**Day 1 of each cycle**	**Experimental**
Gemcitabine	**1000 mg/m^2/day**	**Q3W**	**IV infusion**	**Day 1 and Day 8 of each cycle up to 6 cycles**	**Experimental**
Cisplatin	**35 mg/m^2/day**	**Q3W**	**IV infusion**	**Day 1 and Day 8 of each cycle up to 6 cycles**	**Experimental**

5.6. Duration of study, recruitment, treatment and follow-up

- Enrolment/recruitment period: 12 months
- First patient first visit (FPFV): 8ENE2021
- Last patient last visit (LPLV): January 2024 (expected)
- Treatment period: Up to 24 months from LPFV
- Follow-up period: 24 months
- Planned end of study date: First quarter 2024 (expected)

5.7. Determinations during the study

Determination during the study will be performed as per ***Table 4*** and ***Section 8.3*** of this protocol.

5.7.1. Screening phase

The baseline assessments and procedures should be performed within 28 days before inclusion, and when applicable, as close as possible to the start of study treatment.

5.7.2. Treatment phase

Before each treatment administration chemotherapy/atezolizumab administration laboratory, medical consulting and other determinations will be performed according to ***Table 4*** and ***Section 8.5*** to ensure that treatment can be safely administered.

A CT Scan or MRI will be performed at baseline, on week 9, week 18 and then every 12 weeks (q12w) ± 1w until objective disease progression as per PI's criteria or death (whichever comes first). Blood samples for biomarkers studies should be collected before administration of cycle 4 and at the time of PD (end of treatment if applicable).

For patients with progression reported as per RECIST criteria at week 9, continuity of treatment with atezolizumab should be evaluated by the PI of each site as per clinical benefit criteria.

5.7.3. Safety visit (after the end of treatment by any reason)

Safety follow-up visits will be scheduled up to 30 days after the last dose of study treatment (end of treatment).

5.7.4. Follow up until progression

After the end of the combined treatment with atezolizumab and split dose of gemcitabine and cisplatin, if the patient has finished treatment without progression and does not start a new treatment line, will be visited every 12 weeks. At the time of progression blood samples should be collected for biomarkers studies.

5.7.5. Follow up after progression

Overall, after progression, patients will continue the long-term follow up every 6 months until death or end of study. Sponsor will ask the survival status of all patients at the final clinical trial database closing, in order to maximise the median follow up of patients for overall survival data.

In cases where atezolizumab treatment has been maintained because of clinical benefit, follow up will comply with the "Follow up until progression" conditions, with visits every 12 weeks along with radiological evaluation/assessment of the disease.

5.8. End of study (EoS)

The end of study is defined as the Last Patient Last Visit (LPLV) and will be considered at 24 months after last patient first visit (LPFV), Sponsor will ask survival status of all patients at the final clinical trial database closing, in order to maximise the median follow up of patients for overall survival data.

5.9. Outcome assessments

5.9.1. Response evaluation according RECIST 1.1

All patients will have their best response according to RECIST criteria 1.1 from the start of study treatment until the end of treatment classified as outlined below:

- Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later.

- Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Tumour markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.
- Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.
- Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment, for example where the tumour burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

5.9.2. Safety assessments

Safety parameters are AE, SAE, AESI, pregnancy, medication error, overdose. Additional safety information could be derived from ECG, lab test, pregnancy test, or vital sign exam. The assessment of adverse events will include the type of event (including symptoms, physical exam findings and laboratory abnormalities), the incidence, severity, timing, seriousness, and relatedness regarding the treatment under study. Adverse events will be recorded and reported in the corresponding section of the case report form. The grade of adverse events will be coded according to the National Cancer Institute's Common Toxicity criteria (NCI-CTCAE v5.0 scoring system). The worst toxicity score will be recorded. In case of SAE and AESI the investigator should immediately fill in the dedicated SAE form and send it by as detailed in ***Section 9.2***

6. STUDY POPULATION

6.1. Inclusion criteria

1. Male or female subjects ≥ 18 years old.

2. Written informed consent approved by the Independent Ethics Committee (IEC), prior to the performance of any trial activities.

3. Patients with histologically documented, locally advanced (T4B, any N; or any T, N2-3) or metastatic urothelial carcinoma (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).*

4. Patients should not be eligible (unfit) for full dose of cisplatin, in the investigator's judgement, based on:

   a. Age older than 70 years

   a. ECOG Performance status (PS) 2 or Karnofsky PS of 60 - 70% (only 15 patients will be included with ECOG 2)

   b. Measured creatinine clearance (ClCr) > 30 and < 60 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for the determination of creatinine clearance:

      Males:

      $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

      Females:

      $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

   c. Any other reason the physician considers but should specify in the CRF and discussed with the PI.

5. At least one measurable lesion through radiographic tumor evaluation (CT scan or magnetic resonance imaging) as defined by RECIST version 1.1, that has not been previously irradiated within 4 weeks prior to the study enrolment.

6. Patients with an archival or *de novo* tumor biopsy (representative formalin-fixed paraffin-embedded/FFPE paraffin block obtained as close as possible to the patient inclusion) with an associated pathology report, for testing of PD-L1 expression prior to study enrollment. Samples in unstained slides could be acceptable (at least 15 slides).

7. Patients with adequate normal organ and marrow function as defined below:

   a. Haemoglobin (Hb) ≥ 9.0 g/dL.
   b. Absolute neutrophil count (ANC) ≥ 1500 per mm^3.
   c. Platelet count ≥ 100,000 per mm^3.

d. Serum bilirubin ≤ 1.5 X institutional upper limit of normal (ULN) unless liver metastases are present, in which case it must be ≤ 2X ULN. This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology); however, they will be allowed only in consultation with their physician.
e. Serum transaminases (ALT, AST and GGT) ≤ 2.5X institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 3X ULN.

8. No major active bleeding.

9. Female subjects of childbearing potential (not surgically sterile or at least 2 years postmenopausal) must provide a negative urine pregnancy test at screening, and use a medically accepted double barrier method of contraception (i.e. condom with spermicide + IUD or cervical caps). In addition, they must agree to continue the use of this double barrier method for the duration of the study and for 6 months after participation in the study.

10. Males should agree to abstain from sexual intercourse with a female partner or agree to use a double barrier method of contraception (i.e. condom with spermicide, in addition to having their female partner use some contraceptive measures such as oral contraceptive drugs, intrauterine device (IUD) hormonal contraception, or cervical caps), for the duration of the study and for 6 months after participation in the study

11. Willingness and ability of patients to comply with the protocol for the duration of the study including undergoing treatment as well as availability for scheduled visits and examinations including follow up.

6.2. Exclusion criteria

1. Prior treatment with any immune checkpoint inhibitor therapy (e.g., CTLA4, PD-1, or PD-L1 targeting agent).*

   **Note*: Prior adjuvant or neoadjuvant treatment with targeted therapy/checkpoint inhibitors is allowed, as long as the last dose was administered at least 12 months prior to the patient inclusion in this trial.

2. Presence of active second malignancy and/or prior malignancy in the last 2 years is allowed except for the following:
   a. adequately treated basal cell or squamous cell skin cancer,
   b. adequately treated Stage I or II cancer from which the patient is currently in complete remission per investigators' clinical judgment.

3. Patient receiving radiation therapy within 4 weeks before inclusion.

4. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

5. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis).

6. History of allogeneic organ transplant.

7. Subjects having a diagnosis of immunodeficiency or are receiving systemic steroid therapy or any other form of immunosuppressive therapy within 28 days prior to the first dose of trial treatment.

8. Current or prior use of immunosuppressive medication within 7 days prior to enrolment, except the following:
    a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);
        i. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;
        ii. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
9. The subject has uncontrolled, significant intercurrent or recent illness (within 6 months prior to inclusion) including, but not limited to, the following conditions:

    a. Cardiovascular disorders:
        i. Class 3 or 4 congestive heart failure as defined by the New York Heart Association, unstable angina pectoris, and serious cardiac arrhythmias.
        ii. Uncontrolled hypertension defined as sustained blood press > 150 mm hg systolic or > 100 mm hg diastolic despite optimal antihypertensive treatment.
        iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction, other ischemic event, or thromboembolic event (e.g., deep venous thrombosis [DVT] and pulmonary embolism) within 6 months before inclusion. Subjects with a more recent diagnosis of DVT are allowed if stable, asymptomatic, and treated with LMWH for at least 6 weeks before study treatment.

    b. Gastrointestinal disorders (e.g., malabsorption syndrome or gastric outlet obstruction) including those associated with a high risk of perforation or fistula formulation:
        i. Tumours invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.
        ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before inclusion. Note: complete healing of an intra-abdominal abscess must be confirmed prior to start of the treatment.

c. Clinically significant hematemesis or hemoptysis of > 0.5 teaspoon (> 2.5 ml) of red blood or history of other significant bleeding within 3 months before treatment.

d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation.

e. Lesions invading major pulmonary blood vessels.

f. Other clinically significant disorders such as:
   i. Active infection requiring systemic treatment, infection with human immunodeficiency virus or acquired immunodeficiency syndrome-related illness, or chronic hepatitis B or C infection.
   ii. Serious non-healing wound/ulcer/bone fracture.
   iii. Malabsorption syndrome.
   iv. Moderate to severe hepatic impairment (child-pugh B or C).
   v. Requirement for hemodialysis or peritoneal dialysis.
   vi. Uncontrolled diabetes mellitus.

10. Major surgery (e.g., GI surgery and removal or biopsy of brain metastasis) within 8 weeks before inclusion. Complete wound healing from major surgery must have occurred 4 weeks before study treatment and from minor surgery (e.g., simple excision, tooth extraction) at least 10 days before study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

11. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

12. Any test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or chronic infection.

13. Women who are pregnant or are breastfeeding.

14. Male patients must be surgically sterile or must agree to use effective contraception during the period of therapy.

15. Any of the following within 6 months prior to study entry: myocardial infarction, uncontrolled angina, uncontrolled hypertension, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack.

16. Previously identified allergy or hypersensitivity to components of the study treatment formulations.

6.3. Criteria for withdrawal from the treatment and study

6.3.1. Permanent Interruption of study treatments

Any reason for discontinuing investigational products must be clearly recorded on the electronic case report forms (eCRF).

Patients will receive the product under investigation as per schedule described in section 5.5 of this protocol or until any of the following occurs:

- *Objective disease progression*. However, patients with disease progression at week 9 who are continuing to derive clinical benefit from the study treatment will be eligible to continue with single-agent atezolizumab, provided that the treating physician has determined that the benefit/risk for doing so is favorable;
- *Global deterioration of health status requiring discontinuation*;
- Unacceptable toxicity. If the unacceptable toxicity is attributed to one of the two study treatments, the investigator (in discussion with the sponsor) may continue treatment with the other study treatment;
- Investigator's decision;
- Pregnancy;
- Protocol violation, only when non-compliance might significantly impact in patients safety and/or trial results validity, as per case by case Sponsor assessment/criteria;
- Lost to follow-up;
- Patient refused further treatment (follow-up permitted by patient);
- Study terminated by sponsor;
- Death.

For all participants, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration' in the source data and in the eCRF.

A temporary interruption in study medication due to an AE is not considered to be permanent discontinuation from investigational product.

Tumor assessments for participants, who discontinue study treatment without radiographic progression, should continue as per protocol until radiographic progression is determined.

Chemotherapy dose reduction is allowed in study. Any participant with two prior dose reductions to one agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent. A participant who is discontinued from the chemotherapy treatment will remain on the study and receive atezolizumab.

If a participant meets criteria for discontinuation and the investigator is unable to determine whether the event is related to atezolizumab or chemotherapy, the participant should discontinue all treatments.

The assessment for discontinuation of atezolizumab should be made separately from the assessment made for discontinuation of chemotherapy. If criteria for discontinuation for atezolizumab are met before the first 6 atezolizumab + split-doses of gemcitabine and cisplatin chemotherapy cycles have been completed, the split-dose GC chemotherapy may continue until 6 cycles have been completed.

6.3.2. Withdrawal from the study

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw at any time.

The investigator may also, at his/her discretion, withdraw the subject from participating in this study at any time, or the sponsor may discontinue the study.

Reasons for early withdrawal from the study should be documented in the eCRF as:

- Study closed/terminated by sponsor;
- Lost to follow-up;
- Investigator's decision;
- Subject withdrew consent (refused further follow-up);
- Major protocol non-compliance. Protocol violation, only when non-compliance might significantly impact in patients safety and/or trial results validity, as per case by case Sponsor assessment/criteria;
- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstances, every effort should be made to document patient outcomes, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Date of withdrawal from the study, with reason for withdrawal, will be recorded on the eCRF. In the case of death, a death certificate should be obtained if possible, with the cause of death evaluated and documented.

Note: Patients withdrawn the trial for any reason, cannot enter again.

7. TREATMENT DESCRIPTION

For the purpose of this study, the investigational products as defined by (ICH E6 1.33) are atezolizumab, cisplatin and gemcitabine.

7.1. Study medication

7.1.1. Atezolizumab

Atezolizumab will be supplied as 60 mg/mL glass vials of 20-mL, nominal atezolizumab amount per vial, 1200 mg.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines.

The information on the study treatment will be in accordance with approved submission documents.

AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation. In case that the site cannot provide the drug for regulatory reasons (for example, the indication is not financed) and always with prior approval by the study sponsor (SOGUG) and by Roche, and if it is thus indicated in the contract between the Sponsor and the Site, the patient could continue in treatment with Atezollizumab participating in a Post-Trial Access (PTA) Program, previously approved by Roche. The maximum duration of the PTA will be 1 year.

7.1.2. Gemcitabine and Cisplatin

Gemcitabine and cisplatin will be supplied as per site clinical standards.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines, under commercial presentation and each site availability.

The information on the study treatment will be in accordance with approved submission documents.

7.2. Treatment accountability and compliance

According to local legislation, the investigator will record in the medical history that the patient is taking the medication as prescribed for each new cycle in the study.

7.2.1. Atezolizumab accountability and compliance

Atezolizumab will be dosed at the investigational site, compliance will be assessed by reviewing the consistency of information in the IWRS, the eCRF, patient records, nurse sheets, and in the pharmacy source documentation.

7.2.2. Gemcitabine and Cisplatin accountability and compliance

Compliance of the split-dose GC chemotherapy will be assessed by reviewing the consistency of information in the eCRF, patient records, nurse sheets, and in the pharmacy source documentation.

7.3. Preparation and Dispensing

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

Investigational products should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

7.3.1. Atezolizumab preparation and dispensing

Atezolizumab will be dosed at the investigational site. Atezolizumab must not be used for any purpose other than the trial. The administration of trial investigational products to patients who have not been enrolled into the trial is not covered by the trial insurance.

7.3.2. Gemcitabine plus cisplatin preparation and dispensing

The GC treatment will be administered in quantities appropriate for the study visit schedule and according to local practice. A qualified staff member will record all the study treatment using the local practise. Procedures described in each institution's pharmacy or hospital standard operating procedure manual should be followed when handling hazardous drugs.

7.4. Investigational Medical Products Administration

7.4.1. Atezolizumab administration

Atezolizumab will be administered after all procedures/assessments have been completed as described in the Schedule of Activities (***Table 4***), as a 1-hour IV infusion once every 3 weeks until disease progression, unacceptable toxicity or absence of clinical benefitt. AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation. In case that the site cannot provide the drug for regulatory reasons (for example, the indication is not financed) and always with prior approval by the study sponsor (SOGUG) and by Roche, and if it is thus indicated in the contract between the Sponsor and the Site, the patient could continue in treatment with Atezollizumab participating in a Post-Trial Access (PTA) Program, previously approved by Roche. The maximum duration of the PTA will be 1 year.

The infusions must not be administered as an intravenous push or bolus. The initial dose of atezolizumab must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Atezolizumab will be administered in IV infusion bags containing 0.9% sodium chloride (NaCl) and infusion lines equipped with 0.2 or 0.22 m in-line filters. The IV bag may be constructed of polyvinyl chloride, polyolefin, polyethylene, or polypropylene. The IV infusion line may be constructed of polyvinyl chloride, polyethylene, polybutadiene, or polyurethane and the 0.2 or 0.22 m in-line filter may be constructed of polyethersulfone or polysulfone. The use of administration supplies composed of materials other than those listed should be avoided if possible. Atezolizumab can be diluted to concentrations between 3.2 mg/mL and 16.8 mg/mL in IV bags containing 0.9% NaCl. Atezolizumab must be prepared/diluted under appropriate aseptic conditions as it does not contain antimicrobial preservatives.

The prepared solution for infusion should be used immediately to limit microbial growth in case of potential accidental contamination. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user. For flat or fixed dosing (1200 mg for this clinical trial) in IV infusion bags, the dose solution may be stored at 2°C–8°C (36°F – 46°F) for 24 hours or at ambient temperature ≤ 25°C (77°F) for 8 hours. This time includes storage and time for administration for infusion.. Do not shake or freeze infusion bags containing the dose solution.

Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the Dosage and Administration Instruction contained in the Summary of Product Characteristics, and when applicable, the corresponding Pharmacy Guidelines.

Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. See more information in ***Appendix 1***.

7.4.1.1. Intrapatient Atezolizumab Dose Reduction

The dose amount required to prepare the atezolizumab infusion solution will be based on the corresponding flat dose of 1200 mg established in this protocol. Overall, Atezolizumab dose reduction for toxicity management is not permitted. Toxicity management (dose delay or discontinuation) in case of immune-mediated events is described in ***Appendix 1***.

7.4.2. Gemcitabine and cisplatin administration

The infusions must not be administered as an intravenous push or bolus. The estimated total infusion time for this treatment takes up to two hours for Day 1 and Day 8 of each 21-days cycle. Typically, IV hydration is given both before and after cisplatin and can add up to two hours on administration days. Infusion times may vary depending on physician preference or patient tolerability.

7.4.2.1. Gemcitabine administration

Gemcitabine will be administered after all procedures/assessments have been completed as described in the Schedule of Activities (***Table 4***), as a 30-minutes IV infusion on days 1 and 8 once every 3 weeks for a maximum of 6 cycles.

Gemcitabine is tolerated well during infusion and may be administered ambulant. If extravasation occurs, generally the infusion must be stopped immediately and started again in another blood vessel. The patient should be monitored carefully after the administration. Treatment omitted will not be reinstated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 ($x10^6$/l) and the platelet count reaches 100,000 ($x10^6$/l).

7.4.2.2. Cisplatin administration

Cisplatin should be administered by intravenous infusion over a period of 2 hours (up to 8 hours) on days 1 and 8 once every 3 weeks for a maximum of 6 cycles. Adequate hydration must be maintained from 2 to 12 hours prior to administration until minimum 6 hours after the administration of cisplatin. Hydration is necessary to cause sufficient diuresis during and after treatment with cisplatin. It is realised by intravenous infusion of one of the following solutions specified on the SmPC.

7.4.2.3. Intrapatient Gemcitabine and Cisplatin Dose Reduction

According to the current version of Gemcitabine Summary of Product Characteristics (*Gemcitabine SmPC*) at the time of this study design (March 2020), dose modifications are considered in case of ***haematological toxicity*** as described below. For the matter of this study, information on dose modification recommendations for gemcitabine given in monotherapy or in combination with cisplatin for bladder cancer are described.

Dose modifications due to haematological toxicity: Initiation of a cycle
For all indications, the patient must be monitored before each dose for platelet and granulocyte counts. Patients should have an absolute granulocyte count of at least 1,500 (x 10^6 /l) and platelet account of 100,000 (x 10^6 /l) prior to the initiation of a cycle.

Dose modifications due to haematological toxicity: Within a cycle
Dose modifications of gemcitabine within a cycle should be performed according to ***Table 2***:

Table 2. Dose modification of gemcitabine within a cycle for bladder cancer, NSCLC and pancreatic cancer, given in monotherapy or in combination with cisplatin

Absolute granulocyte count (x 10^6/l)	Platelet count (x 10^6/l)	Percentage of standard dose of Gemcitabine (%)
> 1,000 and	**> 100,000**	**100**
500 - 1,000 or	**50,000-100,000**	**75**
<500 or	**< 50,000**	**Omit dose***

*Treatment omitted will not be reinstated within a cycle before the absolute granulocyte count reaches at least 500 (x106 /l) and the platelet count reaches 50,000 (x10^6 /l).

Dose modifications due to haematological toxicity: Subsequent cycles for all indications
The gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following hematologic toxicities (***Table 3***):

Table 3. Dose modification of gemcitabine in subsequent cycles for all indications

	Count (x 10^6/l)	**Time**	**Percentage of standard dose of Gemcitabine (%)**
Absolute granulocyte	**< 500**	**> 5 days**	**75**
	< 100	**> 3 days**	**75**
Platelet count	**< 25,000**	**Not applicable**	**75**
Febrile neutropenia	**-**	**-**	**75**
Cycle delay > 1 week to toxicity	**-**	**-**	**75**

Patients will be monitored closely for toxicity; Gemcitabine may be adjusted by dosing interruption with or without dose reduction as indicated in ***Table 2*** and ***Table 3.***

Management of patients requiring more than 2 dose reductions of any of the IMPs (one dose level decrease at a time) should be discussed with the Coordinating Investigator.

Patients who have undergone dose reduction may also undergo dose re-escalation back to the previous dose level at the discretion of the Investigator in the absence of Grade ≥2 non-hematologic treatment-related toxicity for at least 28 days.

Cisplatin reduction will be followed as indicated for Gemcitabine reduction following the current version of Cisplatin Summary of Product Characteristics (Cisplatin SmPC).

No chemotherapy reduction as allowed in Cycle 1 Day 1.

7.5. Special Precautions for Investigational Medical Products

7.5.1. Special Precautions for Atezolizumab

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Pneumonitis secondary to PD1/PDL1 inhibitor drugs is a rare but potentially serious side effect, patients should be monitored for signs and symptoms of pneumonitis during physical examination (PE), and causes other than immune-mediated pneumonitis should be ruled out in the case of findings during PE.

For more updated information follow the IB (Investigator's Brochure)

7.5.1.1. Hepatic impairment

No dedicated studies of atezolizumab have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of atezolizumab between patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin 1.0 to 1.5 ULN and any AST, n=71) and normal hepatic function (bilirubin and AST ≤ ULN, n=401). No data are available in patients with either moderate (bilirubin > 1.5 to 3.0 x ULN and any AST) or severe (bilirubin > 3.0 ULN and any AST) hepatic impairment. Hepatic impairment was defined by the National Cancer Institute criteria of hepatic dysfunction. More information available in the current version of Atezolizumab Investigator's Brochure.

7.5.1.2. Renal impairment

No dedicated studies of atezolizumab have been conducted in patients with renal impairment. More information available in the current version of Atezolizumab Investigator's Brochure.

7.5.1.3. Reproductive and Developmental Toxicity

Reproductive and developmental toxicity studies with atezolizumab have not been conducted. The PD-L1/ programmed death 1 (PD-1) signaling pathway is well established as essential in maternal/fetal tolerance and embryo-fetal survival during gestation (*Guleria et al. 2005; Habicht et al. 2007; D'Addio et al. 2011*). Administration of atezolizumab is expected to have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality.

7.5.1.4. Immune-mediated adverse reactions

Most immune-mediated adverse reactions that occur during treatment with atezolizumab are reversible with the interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-mediated adverse reactions affecting more than one body system have been observed; these may occur after the last dose of atezolizumab.

For suspected immune-mediated adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical studies in patients whose immune-mediated adverse reactions could not be controlled with systemic corticosteroid use, the administration of other systemic immunosuppressants may be considered.

Atezolizumab must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones. Specific guidelines for the management of atezolizumab-specific adverse events is available in ***Appendix 1***.

1) Pulmonary events

Pneumonitis secondary to PD1/PDL1 inhibitor drugs is a rare but potentially serious side effect, patients should be monitored for signs and symptoms of pneumonitis during physical examination (PE), and causes other than immune-mediated pneumonitis should be ruled out in

the case of findings during PE.

Cases of pulmonary events, including dyspnea, cough, fatigue and pulmonary infiltrates, have been observed in clinical trials with atezolizumab. Patients should be monitored for pulmonary signs and symptoms.

Treatment with atezolizumab should be withheld for Grade 2 pulmonary event , and corticosteroids equivalent 1 to 2 mg/kg/day oral prednisone should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 pulmonary events.

2) Hepatic events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in ***Appendix 1***.

3) Gastrointestinal events

Immune-mediated colitis has been associated with the administration of atezolizumab. All events of diarrhea or colitis should be thoroughly evaluated for other common etiologies. For events of significant duration or or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis. More information provided in ***Appendix 1***.

4) Endocrine events

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected.

Thyroid-stimulating hormone (TSH) and free triiodothyronine (T3) and thyroxine (T4) levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, GH, 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. More information provided in ***Appendix 1***.

5) Ocular events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). More

information provided in ***Appendix 1***.

6) Immune-Mediated Myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab and should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type Natriuretic Peptide]) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope.

Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of 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 ***Appendix 1***.

7) Infusion-Related Reactions and Cytokine-Release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated infusion-related reactions, due to IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end -organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (*Rotz et al. 2017*; *Adashek and Feldman 2019*), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs during Cycle 1 and CRS are provided in ***Appendix 1***.

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

8) 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 ***Appendix 1***.

9) Dermatologic events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in ***Appendix 1***.

10) Neurologic Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in ***Appendix 1***.

11) Immune-Mediated Meningoencephalitis

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness.

Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process. All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in ***Appendix 1***

12) Renal events

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in ***Appendix 1***.

13) Immune-Mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase/CK increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

14) Severe Cutaneous Adverse Reactions (SCAR)

SCARs are a heterogeneous group of immunologically mediated drug eruptions. Although rare, these events are potentially fatal, and mainly constituted by erythema multiforme, acute generalised exanthematous pustulosis, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS). As per epidemiology data, the incidence of SJS and TEN ranges from 0.8 to 5.3 and 1.2 to 6 per million person-years respectively.

A cumulative analysis of the company safety database across the TECENTRIQ (atezolizumab) program identified at total of 99 cases of SCARs, of which 36 were confirmed by histopathology or specialist diagnosis, in patients who have received TECENTRIQ (atezolizumab). Approximately 23,654 clinical trial patients and 106,316 patients in post-marketing settings have been exposed to TECENTRIQ (atezolizumab) as of 17 May 2020. The incidence rates of SCAR, regardless of severity, from pooled atezolizumab monotherapy (N=3178) and combination therapy (N=4371) company sponsored clinical studies were 0.7% and 0.6% respectively. One fatal case of TEN was reported in a 77 year old female patient who received atezolizumab monotherapy.

Patients with signs and symptoms of SCAR should be treated according to the guidelines in ***Appendix 1***.

15) Pericardial disorders

Immune-Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis.

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted.

Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in the next Table.

Event	Management
Immune-mediated myocarditis, Grade 2, 3 or -4	Permanently discontinue atezolizumab and contact Medical Monitor. Refer patient to cardiologist. Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD, or pericardiocentesis as appropriate.
Immune-mediated pericardial disorders, Grades 2-4	Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. If 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.

16) Facial paresis

Immune-mediated facial paresis is considered a rare event (0.1%) in patients receiving atezolizumab monotherapy. Patients should be monitored for symptoms of motor and sensory neuropathy. No fatal events have been reported in the monotherapy population (n 3178) or observed across the atezolizumab clinical development program.

17) Myelitis

Immune-mediated myelitis is considered a rare event (0.1%) in patients receiving atezolizumab monotherapy. No fatal events have been reported in the monotherapy population (n 3178) or observed across the atezolizumab clinical development program.

7.5.2. Special Precautions for Gemcitabine

Prolongation of the infusion time and increased dosing frequency have been shown to increase toxicity. Further information on particular risk for toxicity (including haematological toxicity, hepatic insufficiency, concomitant radiotherapy, live vaccinations, cardiovascular risk, pulmonary effects, renal, fertility or sodium control are displayed in the Gemcitabine SmPC.

7.5.3. Special Precautions for Cisplatin

This agent should only be administered under the direction of oncologists in specialist units under conditions permitting adequate monitoring and surveillance. Supportive equipment should be available to control anaphylactic reactions.

Cisplatin reacts with metallic aluminium to form a black precipitate of platinum. All aluminium containing IV sets, needles, catheters and syringes should be avoided. The solution for infusion should not be mixed with other drugs or additives.

Appropriate monitoring and management of the treatment and its complications are only possible if adequate diagnosis and exact treatment conditions are available.

Further information on particular risks including nephrotoxicity, neuropathies, ototoxicity, allergic reactions, hepatic function and haematological formula, carcinogenic potential, injection site reactions are displayed in the Cisplatin SmPC.

7.6. Investigational Product Storage

The investigational products should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational products are only dispensed to study participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Storage conditions stated in the SRSD (ie, IB) will be superseded by the storage conditions stated on the label. Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery.

The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct patients on the proper storage requirements for take-home investigational products.

7.6.1. Atezolizumab storage

Atezolizumab must be refrigerated at 2°C - 8°C (36°F - 46°F) upon receipt until use. Atezolizumab and the diluent vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab Drug Product or the diluent; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial. Vial contents should not be frozen or shaken and should be protected from light by keeping the vial in the outer carton. This information is also available in the pharmacy manual.

7.6.2. Gemcitabine and cisplatin storage

Gemcitabine and cisplatin must be stored and controlled as specified in the product label.

7.7. Investigational Product Accountability

The delegated investigation site staff must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All bottles of study drug must be returned to the investigator by the patient at the end of each cycle and at the end of the trial, the sponsor will provide instructions as to the disposition of any unused investigational product if the investigative site is unable to destroy at site per local procedures.

7.8. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product Atezolizumab (e.g., at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor, and all destruction must be adequately documented.

7.9. Concomitant Treatments

Medications or vaccinations specifically prohibited in the Exclusion Criteria are also not allowed during the active treatment period, except for the administration of inactivated influenza vaccine.

If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from study therapy or medication/vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication/vaccination schedule requires the mutual agreement of the investigator, the sponsor, and the patient.

Concomitant treatment considered necessary for the patient's wellbeing may be given at the discretion of the treating physician. All concomitant treatments, blood products, as well as non-drug interventions received by patients from screening until the end of study visit will be recorded on the CRF.

Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (e.g., antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (e.g., transfusions).

Concurrent anticancer therapy with agents other than atezolizumab and GC are not allowed. Medications intended solely for supportive care (i.e., antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

7.9.1. Inhibitors and Inducers of CYP Enzymes

Because antibodies are cleared principally by catabolism (i.e., cleavage to small peptides and amino acids), atezolizumab is not expected to show pharmacokinetic interactions with other drugs, and is therefore not expected to interact with other drugs through protein binding, effects on cytochrome P450 activity, renal excretion or competition for common drug transporter proteins. No formal pharmacokinetic drug interaction studies have thus been undertaken with atezolizumab.

7.9.2. Concomitant Surgery

No specific information on the effect of Atezolizumab on wound healing are reported in the current version of IB nor SmPC.

7.9.3. Concomitant Radiotherapy

Toxicity of concurrent administration of gemcitabine (simultaneous or ≤ 7 days apart) depends on many different factors, including the dose of gemcitabine, the frequency of gemcitabine administration, radiation dose, radiotherapy planning technique, tissue to radiate and the theoretical irradiation volume. For the matter of this study, radiotherapy within 4 weeks prior to inclusion is considered an exclusion criteria.

For non-concurrent gemcitabine administration (administered> 7 days apart), data analysis

does not indicate an increased toxicity when gemcitabine is administered at least 7 days before or after radiotherapy, except for late skin toxicity. The data that can be started administration of gemcitabine when the acute effects of radiation therapy have resolved or at least one week after radiation therapy. Radiation injury has been detected in irradiated tissues (e.g. esophagitis, colitis, and pneumonitis) in association with both concurrent and non-concurrent use of gemcitabine. Further information can be obtained in the current version of Gemcitabine SmPC.

7.9.4. Other Prohibited Concomitant Medications and Therapies

Clarifications about Steroid Use: Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes (*Schleimer RP, et al. 1984; Khan MM, 2008*).

Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressants such as steroids will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA4 compounds indicate that short-term use of steroids may be employed without compromising clinical outcomes (*Weber JS, et al. 2012*).

Therefore, the use of steroids during this trial is restricted as follows:

- *Therapeutic use:* for the treatment of infusion-related reactions and short-term treatment of irAEs, steroids are permitted according to the modalities indicated in ***Appendix 1***.
- *Physiologic use:* steroid replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.
- *Prophylactic use*, e.g., for the prevention of acute infusion-related reactions, is prohibited, ***except*** prior to CT or MRI.

7.10. Rescue Medications and Supportive Care

7.10.1. Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- *Diarrhea:* All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- *Nausea/Vomiting*: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

- *Anti-infectives:* Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice. Prophylactic administration should be considered for the cases outlined in ***Appendix 1***.

- *Anti-inflammatory or narcotic analgesics* may be offered as needed. Acetaminophen/paracetamol to a maximum total daily dose of 2 g is permitted. Daily intake over 2 g is prohibited.

- Patients who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, coumadin or other coumarin derivatives or other anticoagulants (including direct Xa inhibitors) may be allowed; however, appropriate monitoring of prothrombin time/international normalized ratio (PT/INR) should be performed.

8. STUDY PROCEDURES AND EVALUATIONS

8.1. Definition of efficacy variables

- *Overall Response Rate (ORR):* Assessed by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. This will be considered as the percentage/proportion of patients with confirmed complete response (CR) or partial response (PR) as their overall best response throughout the study period.

- *Duration of response* (DoR): Time from first confirmed response (CR or PR) to the date of the documented PD as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.

- *Time to response* (TtR): Time from first dosing date to the date of the documented ORR as determined using RECIST 1.1 criteria.

- *Progression-Free Survival* (PFS): Time from first dosing date to the date of confirmed PD. A subject who has not died will be censored at the last known date alive. PFS rate will be assessed through the proportion of patients free of PD at the end of follow-up.

- *Clinical benefit (CB)*: Percentage/proportion of patients with complete response (CR) or partial response (PR) or maintained stable disease (SD) as their overall best response throughout the study period, assessed by imaging follow-up (CT scan/MRI), on week 9, week 18 and then, every 12 weeks.

- *Overall Survival* (OS): Time from first dosing date to the date of death and the proportion/percentage of patients alive at the end of follow-up. A subject who has not died will be censored at the last known date alive. Survival will be assessed by recording patient status at each visit according to ***Table 4***. Long term follow up to be performed every 6 months.

8.2. Safety and tolerability

Safety assessments: Safety parameters are AE, SAE, AESI, pregnancy, medication error, overdose. Additional safety information could be derived from ECG, lab test, pregnancy test, or vital sign exam.

The assessment of adverse events will include the type of event (including symptoms, physical exam findings and laboratory abnormalities), the incidence, severity, timing, seriousness, and relatedness regarding the treatment under study. Adverse events will be recorded and reported in the corresponding section of the case report form. The grade of adverse events will be coded according to the National Cancer Institute's Common Toxicity criteria (NCI-CTCAE v5.0 scoring system). The worst toxicity score will be recorded. In case of SAE and AESI the investigator should immediately fill in the dedicated SAE form and send it by as detailed in ***Section 9.2.***

- *Adverse events (AE) assessment:* type, frequency, outcome of adverse events.
- *Treatment-related AEs:* An event is assessed as related to study treatment when there is a reasonable possibility that study treatment caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between study treatment and the event. This event is called a suspected adverse reaction. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.
- *Serious adverse events (SAEs)* assessment: type, frequency, grade, outcome, relation with study treatment, all considering the total number and proportion based on the intention-to-treat and per protocol populations.

8.3. Study determinations

Table 4 details the study determinations to be performed and the corresponding timeline.

Table 4. Study determinations

Visit	SCR	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7 up to Cycle N	Safety Visit	PFS FU	EOS FU
Timeline	≤ 28 D prior to inclusion	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	D8	D1	within 30d after EOT	Q12W	Q6 months
Visit window		+/- 3d												Q3W +/-3d	+/-3d	+/- 7d	
Clinical Assessments																	
Informed consent	x																
Medical History (Medical and oncology specific)	x																
Physical Exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
ECOG	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		

Contraception check	x	x		x		x		x		x		x		x	x		
Vital signs (BP, PR)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Laboratory and biological sample studies																	
Archival tumor block	x																
Blood collection (biomarkers)	x							x						x (D1C7)		x at DP	
Faecal sample (biomarkers)	x							x								x at DP	
Coagulation	x	x		x		x		x		x		x	x	x	x		
Hematology*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Blood chemistry*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Thyroid function	x	x		x		x		x		x		x		x	x		
HBV/HCV test	x																
Pregnancy test (serum/urine)	x	x		x		x		x		x		x		x	x		
Urinalysis	x	x		x		x		x		x		x		x	x		
Cardiac monitoring																	
ECG	x	**If clinically indicated**													x		
FEVI	x	**If clinically indicated**													x		
Disease assessment																	
Tumor evaluation	x		**On week 9 , week 18 (prior starting atezolizumab monotherapy and every 12 weeks +/-7 days thereafter until the of objective disease progression or death (whichever comes first)**														
Survival assessment																	x
IMP follow-up																	
Treatment dosing compliance		x	x	x	x	x	x	x	x	x	x	x	x	x			
Chemotherapy administration		x	x	x	x	x	x	x	x	x	x	x	x				
Atezolizumab administration		x		x		x		x		x		x		x			
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
New systemic cancer treatment																x	x
Safety assessment																	
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		

D: Day/s; Q3W: Every 3 weeks; Q12W: Every 12 weeks; EOT: End of treatment; PFS: Progression-free survival; EOS: End of study.

Informed consent: Informed consent of study procedures may be obtained prior to the screening. If laboratory or imaging procedures were performed for different reasons prior to signing consent, these can be used for screening purposes with the consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of inclusion.

Medical History: Should include information on prior systemic adjuvant or neoadjuvant therapy regimens, surgery and radiation therapy. Comorbidities: cardiovascular disease, previous cancer and diabetes, pulmonary disease,

dementia, etc.

Physical exam: Includes an examination of major body systems and weight (height at screening only). Additional PE may be performed as clinically indicated. During the physical examination, a stethoscope will be used to carefully auscultate the lungs, additional respiratory functional tests should be performed as per local practise when suspecting pneumonitis (more information is provided in annex 1 of this protocol).

ECOG PS: ECOG may be recorded by telephone if the patient is not coming to site for other reasons.

Contraception check: Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his/her designee will instruct the patient to call immediately if one or both contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

Vital signs: To include blood pressure (BP) and pulse rate (PR). Body weight is to be recorded at each visit along with vital signs.

Laboratory Studies:** Complete blood count that includes total white blood cell count with leukocyte formula, Hb, and platelet count. The analytical studies may be performed up to 72 hours before the scheduled visits in order to have the results at the time of the patient's visit. ***During the first 6 cycles of treatment with split doses of gemcitabine plus cisplatin, complete blood count and biochemistry (liver, renal and electrolytes) on D1 and D8are mandatory for patient safety assurance and treatment continuation. Biochemistry tests include albumin, alkaline phosphatase, lactate dehydrogenase (LDH), calcium, magnesium, phosphorus, sodium, potassium, creatinine, creatine kinase, direct bilirubin, indirect bilirubin, total bilirubin, total protein, urea, uric acid, amylase, lipase, and glucose tests. Liver test panel functions include alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT) tests. Tests for pancreatic enzymes include lipase, protease (optional), amylase, and trypsinogen (optional) tests. If screening clinical chemistry and haematology assessments are performed within 3 days prior to day 1 (first infusion day), they do not need to be repeated at day 1.

Faecal samples: Specimens will be collected at baseline (before start of treatment), Cycle 4 Day 1 and after progression; the sample must be processed and retained in the local laboratory until Sponsor indications for shipment.

Thyroid Function: TSH and free T4.

HBV/HCV test: Serology including HIV, hepatitis B (HBsAg and anti-HBc), and hepatitis C virus (HCV).

Pregnancy test (serum/urine): For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of the study drug, and every 4 weeks thereafter. Pregnancy tests may occur on day 1, but the results must be available and reviewed by the treating physician or investigator prior to commencing an infusion.

Urinalysis: Protein, glucose, blood, Urine dipstick/other semiquantitative method, for urine protein: if ≥ 2+, collect 24-hour.

ECG: 12-lead ECG. Any clinically significant abnormalities detected require triplicate ECG results.

FEVI: MUGA Scan or ECHO, the technique used at screening will be consistently used throughout the study, in the following assessments.

Tumor assessments: CT scan or MRI is to be performed at baseline, on week 9, on week 18 and q12w ± 1w until the confirmation of objective disease progression or death (whichever comes first). The same imaging technique used to characterize each identified and reported lesion at screening will be employed in the following tumor assessments. This schedule must be followed regardless of any delays in dosing, in case of suspected pseudo-progression; treatment should be continued until progression of disease is confirmed from the imaging results. RECIST assessments will be performed on images from CT scans (preferred) or MRI, each preferably with IV contrast of the neck, chest, abdomen (including liver and adrenal glands), and pelvis. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of inclusion and, ideally, should be performed as close as possible to and prior to the start of treatment. CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response. Assessment of response will be performed using RECIST 1.1. If radiologic imaging shows disease progression, the confirmatory scans should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessment at the next scheduled visit.

Treatment dosing compliance: Study drug compliance will be assessed by the Investigator and/or study personnel at each patient's visit, and it will be captured in the patient's records as part of source documentation at each patient's visit. Corresponding drug administration information will be reported also in the eCRF.

Chemotherapy dispensing/administration: Results for LTFs, electrolytes, and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or investigator prior to dosing. Specific details on haematological and renal function parameters for treatment interruption and resuming are detailed in the gemcitabine and cisplatin administration section.
Atezolizumab dispensing/administration: Every 3 weeks until PD or unacceptable toxicity. Continuation of atezolizumab treatment could be considered for patients who have been reported with PD on the week 9 radiological evaluation but, according to the PI's criteria, might be considered as with clinical benefit.
Adverse events: Adverse events should be documented and recorded at each visit using NCI-CTCAE v5.0. AEs (serious and non-serious) should be recorded in the eCRF and patient records, from the time the patient has taken at least 1 dose of study treatment through and including 90 calendar days after the last dose of IMP. If a patent begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. For SAEs, the active reporting period to Sponsor or it designated, begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in this study, through and including 90 calendar days after the last administration of the investigational products.
Concomitant medications: Concomitant medication will be recorded from 28 days prior to start of study treatment and up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (i.e., antiemetics treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (e.g. transfusions).
Biomarker study: Archival Tumor block at baseline and processed blood samples at baseline, day 1 of cycle 7 (D1), and at EOT/progression. Blood samples should be obtained in all patients at the time of EOT (even by toxicity without progressing) and samples are to be stored at site at -80 ºC and are to be sent at the end of study (1 dry ice shipment per site).
New systemic cancer treatment: Information on subsequent treatments should include the list of post-treatment therapies, drugs administered, and the date of initiation and discontinuation of each drug, and the corresponding disease progression date (if applicable). All the data will be recorded in the medical record and in the eCRF.
Survival assessment (EOS): After progression, the patient will be followed for survival until death, loss of follow-up, total patient consent withdrawal (refusing to any trial procedure), or end of study. Patient long term follow-up to determine status (alive, death, loss of follow up, etc.) may be performed by phone, if the patient is not coming to the clinic due to other reasons. The investigator must document in writing the results of the phone call in the patient records and in the eCRF.

8.4. Determinations in the selection phase (screening and baseline determinations)

Within 28 days prior to inclusion:

- Informed consent
- Medical History (Medical and oncology specific)
- Archival tumor block
- HBV/HCV test
- ECG
- FEVI
- Tumor assessment
- Thyroid function
- Urinalysis

Within 3 days prior to inclusion (not needed to be repeated if it is performed within 3 days to treatment initiation)

- Physical Exam
- ECOG
- Contraception check
- Vital signs (BP, PR)
- Coagulation

- Hematology
- Blood chemistry
- Pregnancy test (serum/urine)
- Blood collection (biomarkers)
- Faecal sample collection (biomarkers)
- Adverse events
- Concomitant medications

8.5. Determinations and procedures during the treatment period (up to cycle 6)

8.5.1. Day 1 (considering 3 week cycles)

- Physical Exam
- ECOG
- Contraception check
- Vital signs (BP, PR)
- Coagulation
- Hematology
- Blood chemistry
- Thyroid function
- Pregnancy test (serum/urine)
- Urinalysis
- Adverse events
- Concomitant medications
- Treatment dosing compliance
- Atezolizumab administration
- Split doses of gemcitabine and cisplatin administration

8.5.2. Day 8 (considering 3 week cycles)

- Physical Exam
- ECOG
- Vital signs
- Hematology
- Blood chemistry
- Adverse events
- Treatment dosing compliance
- Concomitant medication
- Split doses of gemcitabine and cisplatin administration

8.5.3. Other determinations during treatment

- **Tumor assessment:** On week 9, week 18 (prior starting atezolizumab monotherapy and every 12 weeks +/-7 days thereafter until the confirmation of objective disease progression or death (whichever comes first).
- **Safety determinations:** Hematology and Blood chemistry (including renal function assessment with urea and creatinine) should be evaluated weekly during the first 6 cycles of treatment as per recommendations for gemcitabine treatment.
- **When clinically indicated:** ECG, and FEVI.

8.5.4. Determinations and procedures on day 1 of cycle 7 (D1-C7) and subsequent cycles (D1-Cn)

- Physical Exam
- ECOG
- Contraception check
- Vital signs (BP, PR)
- Coagulation
- Hematology
- Blood chemistry
- Thyroid function
- Pregnancy test (serum/urine)
- Urinalysis
- Treatment compliance dosing
- Atezolizumab administration
- Concomitant medication
- Adverse event

When clinically indicated: *urinalysis, ECG, and FEVI.*

Additionally at D1-C7:

- Blood collection (biomarkers) only D1 C7.
- Tumor assessment: CT Scan or MRI prior to D1C7 (on week 18 from treatment starting).

When applicable

- ***Tumor assessment:*** *CT Scan or MRI is to be performed on week 9, week 18 and every 12 weeks until the confirmation of objective disease progression or death (whichever comes first).*
- ***When clinically indicated:*** *ECG, and FEVI.*

8.6. Determinations at safety visit

- Physical Exam
- ECOG
- Contraception check
- Vital signs (BP, PR)
- Coagulation
- Hematology
- Blood chemistry
- Thyroid function
- Pregnancy test (serum/urine)
- Urinalysis
- ECG
- FEVI
- Adverse events
- Concomitant medications

8.7. Follow-up determinations

8.7.1. Follow up after end of treatment (prior PD)

Every 12 weeks:

- **Tumor assessment:** CT Scan or MRI is to be performed on week 9, week 18 and every 12 weeks until the confirmation of objective disease progression or death (whichever comes first).
- New systemic cancer treatment.
- **By the time of disease progression,** Blood collection (biomarkers)

8.7.2. Follow up after end of treatment (after PD)

Every 6 months:

- New systemic cancer treatment
- Survival assessment

9. SAFETY EVALUATION

ICH GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

Any event involving adverse drug reactions (ADR), illnesses with onset during the study or exacerbations of pre-existing illnesses should be recorded.

In addition, clinically significant changes in physical examination findings and abnormal objective test findings (e.g., x-ray, ECG) should also be recorded as AE. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- test result is associated with clinically significant symptoms, and/or
- test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
- test result leads to any of the outcomes included in the definition of a SAE, and/or test result is considered to be an AE by the investigator.

9.1. Definitions

The definitions from ICH GCP apply in this trial protocol.

9.1.1. Adverse event (AE)

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject which does not necessarily have a causal relationship with the study treatment.

Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;

- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

9.1.2. Atezolizumab Adverse Event of Special Interest

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 9.2 for reporting instructions).

Adverse events of special interest for this study are as follows:

- 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.
- Suspected transmission of an infectious agent by the study treatment, as defined below
- Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

9.1.3. Laboratory Abnormalities

All laboratory data required by this protocol and any other clinical investigations will be reviewed. Any abnormal value that leads to a change in subject management (eg, dose reduction or delay or requirement for additional medication or monitoring) or that is considered to be of clinical significance by the Investigator will be reported as an AE or SAE as appropriate, unless this value is consistent with the subject's present disease state or is consistent with values obtained prior to entry into the study.

9.1.4. Medication errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, the wrong patient at the wrong time, or at the wrong dosage strength.

Such medication errors occurring to a study participant are to be captured on the eCRF, and reported through the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.
Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AEs are captured on an AE CRF page.
The guidance on reporting of medication errors also applies to the reporting of overdose.

9.1.4.1. Atezolizumab overdose

The standard fixed dose of Atezolizumab is 1200 mg is equivalent to 15 mg/kg in a typical patient. No dose-limiting toxicities were observed at the 20 mg/kg dose level and the incidence and intensity of AEs reported have not been shown to be dependent on dose. A maximum tolerated dose has not been established.
Atezolizumab is supplied in vials containing the fixed 1200 mg dose of drug substance, which minimizes the chance of overdose. Because the dose per patient is not based on weight or body surface area, and no dose calculation is required, the risk of overdose due to medication errors is minimal.
The data available to date suggest that the potential for harm from overdose is very low.

9.1.4.2. Gemcitabine overdose

There is no known antidote for overdose of gemcitabine. Doses as high as 5700 mg/m2 have been administered by intravenous infusion over 30-minutes every 2 weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

9.1.4.3. Cisplatin overdose

An acute overdose of cisplatin may result in renal failure, liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, untreatable nausea and vomiting and/or neuritis. An overdose may be fatal.

There is no specific antidote in the event of an over dosage of cisplatin. Even if haemodialysis is initiated 4 hours after the overdose it has little effect on the elimination of cisplatin from the body following a strong and rapid fixation of cisplatin to proteins.

Treatment in the event of an overdose consists of general support measures.

9.1.5. Adverse reaction (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered.

9.1.6. Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that at any dose:

1. Results in death (is fatal),
2. Is life-threatening,
3. Requires or prolongs inpatient hospitalization,
4. Results in persistent or significant disability or incapacity,
5. Is a congenital anomaly or birth defect, or
6. Is medically significant.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE.

Medical and scientific judgement should be exercised in deciding whether urgent reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the above definition.

Any suspected transmission of an infectious agent through the medication is also considered a SAE.

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; 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 9.2 for reporting instructions).

9.1.7. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in the previous sections, and will be handled as SAEs in the safety database.

9.1.8. Life Threatening Event

It is any event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

9.1.9. Hospitalization / Prolongation of Hospitalization

Any event requiring hospitalization (or prolongation of hospitalization) that occurs or worsens during a patient's participation in a clinical study must be reported as a serious adverse event. Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the investigator or treating physician.

Hospitalizations that do not meet the criteria for serious adverse event reporting are:

1. Reasons described in protocol (e.g., drug administration, protocol-required investigations). Hospitalizations or prolonged hospitalization for a complication of therapy administration or procedures will be reported as a Serious Adverse Event.
2. Hospitalization or prolonged hospitalization for technical, practical or social reasons, in the absence of an adverse event.
3. Pre-planned hospitalizations (i.e., planned before study entry). Any surgery or procedure planned before study entry must be documented on the case report form.

9.1.10. Unexpected adverse event (not listed)

An unexpected AA, whose nature or severity does not correspond to the product information. The reference documents to establish the expectedness will be:

- Atezolizumab, last version of Investigator Brochure available for the Sponsor
- Gemcitabine, last version of the SmPC.
- Cisplatin, last version of the SmPC.

9.1.11. Adverse Event Associated With the Use of the Drug (Adverse Reaction)

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the

investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

For combination treatments, causality assessment will be performed for each of the individual drugs included in the combination.

An adverse event is considered associated with the use of the drug (Adverse Reaction) if the attribution is possible, probable, or very likely by the definitions listed below.

9.1.12. Attribution Definitions

Not Related
An adverse event that is not related to the use of the drug.

Doubtful
An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible
An adverse event that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable
An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by de-challenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

9.1.3. Intensity (Severity) Criteria

The intensity of AEs will be classified using the Common Terminology Criteria for AEs of the National Cancer Institute, version 5.0 (NCI-CTCAE) and will be recorded in detail as instructed in the eCRF. If an AE occurs that is not listed in the NCI-CTCAE V5.0 classification system, the 5-point scale detailed below will be used instead:

- Mild: General malaise, without interruption of normal daily activity.
- Moderate: Sufficient general malaise to reduce or affect normal daily activity.
- Severe: Incapacity for work or the development of normal daily activity.
- Life threatening or disabling: Represents an immediate threat to life.
- Death: AE-related.

Grade

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 (v5.0), 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 9.2 for reporting instructions), per the definition of serious adverse event in Section 9.1.

9.1.14. Exposure during Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, within 5 months after the last dose of atezolizumab , or within 6 months after the last dose of atezolizumab, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).

Any pregnancy that occurs in a female partner of a male study participant should also be reported to the sponsor within 24 hours of becoming aware. Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if his partner becomes pregnant during the chemotherapy treatment period or within 6 months after the last dose of chemotherapy. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

In both cases, the investigator must immediately notify the Sponsor Pharmacovigilance Office by sending the Pregnancy form (see ISF).

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, study discontinuation must be reported

following the before procedure described during at least 1 year after child-bearing.

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) or abortion should be reported as a SAE.

9.1.15. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.
An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

9.1.16. Expedited reporting

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report all serious adverse events that are unlisted (unexpected) and be associated with the use of the study drug. The sponsor must report these events to investigators and competent authorities in accordance with current regulations.

9.2. Collection and reporting of Adverse Events information

The sponsor will collect AEs up to 30 days after administration of the last dose of study drug.

All adverse events must be recorded using medical terminology in the source document and the eCRF. Investigators must assess the severity (grade) of the event following NCI-CTCAE V 5.0 Criteria and assign a relationship to study therapy and pursue and obtain information adequate both to determine the outcome and to assess whether it meets the criteria for classification as a SAE requiring immediate notification. The investigator must provide any information as requested by the sponsor in addition to that on the eCRF.

Any serious adverse event which occurs from patient informed consent signature, during the clinical study or within 90 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported. Beyond this period of time, only those SAEs suspected to be related to the study drug will be reported.

All SAEs suspected to be related to study treatment should be followed after the treatment/study withdrawal until the event or its symptoms have resolved or stabilized at a grade acceptable to the Investigator, Chief investigator and/or Sponsor.

Site staff should notify the sponsor, all the pregnancies of female subjects and female partners

of male subjects that occurred during the clinical trial within 24 hours from becoming aware. Site staff should also communicate the outcome of the pregnancy within 24 hours since the awareness.

The cause of death of a deceased patient in a clinical trial, whether the case of an expected event or associated with the investigational agent, is considered an SAE and therefore must be communicated using the SAE form. The autopsy report should be sent to Sponsor identified only with the patient inclusion number.

[redacted]

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to [redacted] within 24 hours.

All SAEs suspected to be related to study drug must be followed up after the time of therapy discontinuation until the event or its consequences resolve or stabilize at an acceptable level for the investigator, the Trial Chief Investigator and/or Sponsor.

Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

10. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the Sponsor.

This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

10.1. Sample size calculation

Fleming's phase II procedure (*Fleming TR, 1982*) will be used. The null hypothesis that the smallest response probability is 0.3 will be tested against a one-sided alternative. In the first stage, 46 patients will be accrued. An intermediate analysis will be performed once these first 46 patients reach 6 months after study treatment initiation. If there are 16 or fewer responses in these 46 patients, the study will be stopped. This intermediate analysis is established as a cut-off point to stop the study if the benefit for the patient in terms of objective response does not justify its continuation with sufficient clarity. If there is no preliminary evidence in the first 46 patients, which allows enough statistical power to reject the null hypothesis, the recruitment will stop as it is considered that the efficacy of the treatment is not sufficient to justify the inclusion of more patients. Otherwise, 20 additional patients will be accrued for a total of 66. The null hypothesis will be rejected if 25 or more responses are observed in 66 patients. This design yields a type I error rate of 0.05 and power of 0.9 when the true response rate is 0.5.

Variables	Descriptions
α	Probability of type I error: 0.05
β	Probability of type II error: 0.1
p_0	Response Probability of Poor Drug (P0) ---> 0.30
P1	Response Probability of Good Drug (P1) ---> 0.50
Nmax	Maximum number of patients to be recruited: 66
Numstage	Number of stages in Phase II clinical trial: 2
n_i	Number of patients to be recruited in stage i= 46
R1	Upper Limit For 1st Stage Rejection of Drug (r1)= 16
R	Upper Limit for 2nd Stage Rejection of Drug (r)= 25

10.2. Study endpoints

10.2.1. Primary endpoint

Overall Response Rate (ORR): Percentage/proportion of patients with confirmed complete response (CR) or partial response (PR) as their overall best response throughout the study period.

10.2.2. Secondary endpoints

Efficacy endpoints:

- ***Duration of response* (DoR):** Time from first confirmed response (CR or PR) to the date of the documented PD as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.
- ***Time to response* (TtR):** Time from first dosing date to the date of the documented ORR as determined using RECIST 1.1 criteria.
- ***Clinical benefit*:** Percentage/proportion of patients with confirmed complete response (CR) or partial response (PR), or stable disease (SD) as their overall best response throughout the study period.
- ***Overall Survival* (OS)**
    - Time from first dosing date to the date of death. A subject who has not died will be censored at the last known date alive.
    - Proportion of patients alive at the end of the atezolizumab plus split dose of gemcitabine and cisplatin combination stage.
    - Proportion of patients alive at the end of follow-up.
- ***Progression-Free Survival* (PFS)**
    - Time from first dosing date to the date of confirmed PD. A subject who has not died will be censored at the last known date alive.
    - Proportion of patients free of PD at 6 months since start of treatment.
    - Proportion of patients free of PD at the end of follow-up.

Safety endpoints

- ***Adverse events* (AE)** assessment: Type, frequency, severity and outcome of adverse events .
- ***Treatment-related AEs:*** Type, frequency, severity and outcome.

Exploratory endpoints

- Biomarkers and/or genes expression and participant outcomes.

10.3. Efficacy assessment

10.3.1. Efficacy variables

Overall Response Rate (ORR) at 6 months from first dose: includes patients with confirmed persistent partial (PR) and complete response (CR) as best response according to RECIST v 1.1, at 6 months from adaptive the study treatment initiation.

Overall Response Rate (ORR) from first dose: includes patients with confirmed persistent partial (PR) and complete response (CR) as best response according to RECIST 1.1, at the end of their participation in the study.

Time to response: Time to response (TTR) is defined as the time from the start of study treatment to the first objective tumor response (tumor shrinkage of ≥30%) observed for patients who achieved a CR or PR.

Duration of response (DOR): DOR is calculated as the time from the date of first documented CR or PR, as per RECIST 1.1, to the first documented progression or death due to underlying cancer.

Overall Survival (OS): Median Overall Survival (mOS) is calculated as the time from the date of inclusion to date of death due to any cause.

Progression-free Survival (PFS): Median Progression free survival (mPFS) is defined as the time from the date of inclusion to the date of the first documented disease progression or death due to any cause, whichever occurs first. PFS will be determined based on tumour assessment (RECIST version 1.1 criteria). The local Investigator's assessments will be used for analyses. Patients who are alive and have not progressed at the last follow-up will be censored at the date of the last available image determination (CT scan or MRI). Patients with no additional image test other than that at baseline will be censored to the day after inclusion. Patients initiating new anticancer therapy (without progression to the study treatment) will be censored to the date of new anticancer therapy initiation.

Clinical Benefit (CB) Rate: Clinical Benefit Rate (CBR) is defined as the percentage of patients who achieved complete response, partial response and stable disease. Stable disease should be maintained for at least 6 months to be considered as a CBR event.

10.4. Safety assessment

The safety population (SP) consists of all enrolled subjects who received at least one dose of study treatment. Patients will be monitored for safety during all the stages of the study. All safety and tolerability assessments will be done at pre-dosing time, unless otherwise specified.

Safety parameters are AE, SAE, AESI, pregnancy, medication error, and overdose. Additional safety information could be derived from ECG, lab test, pregnancy test, or vital sign exam.

The assessment of adverse events will include the type of event (including symptoms, physical exam findings and laboratory abnormalities), the incidence, severity, timing, seriousness, and relatedness regarding the treatment under study. Adverse events will be recorded and reported in the corresponding section of the case report form. The grade of adverse events will be coded according to the National Cancer Institute’s Common Toxicity criteria (NCI-CTCAE v5.0 scoring system). The worst toxicity score will be recorded.

10.5. Definition of study populations

Data will be analysed in the following populations:

1. *Intent-To-Treat (ITT):* All patients that have been enrolled in the trial.
2. *Evaluable population per protocol (PP):* All patients fulfilling all eligibility criteria without any protocol deviation that makes the patient invalid for the primary endpoint evaluation.
3. *Safety population (SP):* All patients receiving at least one dose of the study treatments.

10.6. Data quality control

A Data Management Plan (DMP) will be elaborated for this trial in order to outline the data management procedures and the related responsibilities of trial staff. The DMP will clearly specify the data quality control tasks to be performed and the corresponding responsibility, timelines, etc., according to international guidelines in the subject and GCPs.

Following data entry of the investigator staff into the data capture system (eCRF), the data

entered will be reconciled against the original case report form, review form/clinic notes/laboratory reports by CRA during monitoring visits, according to the monitoring plan. Any identified issues should be clarified with the Investigator staff. Any necessary corrections should be made in the corresponding field of the eCRF.

The monitoring plan will establish that source data verification (SDV) is expected for a subset of variables, according to study status, starting on the approval of this DMP and the SDV strategy agreed.

Remote QC activities will be outlined in the Monitoring Plan for relevant variables as eligibility, primary endpoints, safety endpoints and relevant secondary endpoints.

Performance of these checks is expected on all the patients included (this estimate may vary according to the quality of the data reported by the research team).

Any finding will be reflected in the monitoring report and will be conveniently managed with sites (including Principal Investigator) and informed to the Coordinating Investigator, as the representative of the Sponsor in this study, and when applicable, notified to competent authorities according to local regulations.

10.7. Statistical analysis

For each categorical variable, the results will be summarised by frequencies and percentages/proportions along with 95 % confidence intervals (95% CIs) when applicable.

For each continuous variable, the results will be summarised by descriptive statistics such as median, range, and range or by means, standard deviations, and (95% CIs). For time to event endpoints, Kaplan-Meier estimates at selected time points and corresponding curves will be presented. Time to event is derived relative to the first study treatment administration and will be expressed in weeks and/or months.

Vital signs, ECG parameters, clinical laboratory data (haematology, serum biochemistry, and urinalysis) will be presented in tabular form. Laboratory values will be expressed as absolute values and in grades (ordinal categorical variables), when feasible. In case of laboratory findings reported as adverse events, values will be presented and/or classified according to NCI CTCAE v 5.0.

All adverse events, including treatment-emergent AE (AEs starting after the administration of study treatment and up to study completion) will be summarised by system organ class and preferred term. Grading will be presented by type and in tables showing the frequency and percentage of the within-patient worst grades. In addition, grade ≥ 3 AEs will be summarised separately. Further analyses could be performed.

Analysis will be based on observed data, and missing data for drop-outs are not replaced by methods like LOCF (last option carried forward).

Full analysis details will be outlined in the statistical analysis plan (SAP).

11. LEGAL AND ETHICS CONSIDERATION

11.1. Ethical conduct of the study

The study will be conducted in accordance with the principles of the Helsinki Declaration Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 updated to its latest version Fortaleza, Brazil, October 2013. With the Good Clinical Practice (GCP) standards issued by the Working Party on Medicinal Product Efficacy of the European Economic Community (1990) (CPMP / ICH / 135/95).

And the laws and regulations in force in Spain:

- The Oviedo Convention of April 4, 1997 on human rights and biomedicine, ratified in the BOE in October 1999.
- The rules for the adequate protection of personal data, in accordance with Law 3/2018 Protection of Personal Data and guarantee of digital rights.
- The rights and obligations regarding information and clinical documentation, as provided in Law 41/2002, of November 14, basic regulation of patient autonomy.
- Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for Investigation with medicinal products and the Spanish Clinical Studies Registry.
- Law 14/2007, of July 3, on Biomedical Research.

11.2. Independent Ethical Committee (IEC) Review

Prior to the commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents to the Central IEC for its approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File.

The IEC will be asked to document the date of the meeting at which the favourable opinion or approval was given, with the members and voting members present. Written evidence of favourable opinion or approval that clearly identifies the trial, the clinical trial protocol and the version, the Subject Information and Informed Consent Form, should be provided.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC, before implementation of substantial changes. Relevant safety information will be submitted to the IEC during the course of the trial, in accordance with national regulations and requirements.

Initial IEC positive vote, and all materials approved by the IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

11.3. Authorities

The study protocol and/or related documents will be submitted to regulatory authorities before commencement of the clinical trial, as national authorities in the country where the trial is taking place.

11.4. Informed consent

The patient should sign an informed consent that will include the information for the clinical

trial and associated translational research.

The clinician will have to explain the nature, objectives and possible consequences of the clinical trial in a manner that is understandable by the patient. The patient must give his/her consent before being admitted into the study and before biological samples are taken.

The study subject will provide his/her consent, signing by duplicate the appropriate model. For this purpose, each model must carry the signature of investigator and patient. The investigator will retain one copy of the original of each patient signed consent form.

The investigator will not start any investigation related with the study until the written consent has been obtained.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by the Ethics Committee.

11.5. Confidentiality

In order to guarantee the confidentiality of the clinical trial data according to the provisions of The rules for the adequate protection of personal data, in accordance with Law 3/2018 Protection of Personal Data and guarantee of digital rights, only the personnel designated by the Sponsor will have access to the patient data for monitoring/auditing purposes, Investigators and his/her staff, the Ethic Committee and the pertinent Competent Authorities.

The investigator should facilitate access to the source documents and data for monitoring and auditing purposes.
The content of the case report forms (CRF), as well as the documents generated during the study will be protected from non-permitted uses by persons not involved in the investigation, and will therefore be considered strictly confidential and not revealed to third parties, except those specified in the previous paragraphs.

11.6. Insurance Policy

The insurance or indemnity in accordance with pertinent regulatory requirements will be provided. All patients in this study are insured through the corresponding insurance policy that satisfies the conditions stipulated by the RD 1090/2015 in Spain.

11.7. End of study definition

The end of study is defined as the Last Patient Last Visit (LPLV) and will be considered at 24 months after last patient first visit (LPFV), Sponsor will ask survival status of all patients at the final clinical trial database closing, in order to maximise the median follow up of patients for overall survival data.

11.8. Early study termination

The clinical trial may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavourable risk benefit judgment for any IMP. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, poor enrolment, or the discontinuation of clinical development of

the IMP or withdrawal of the IMP from the market for safety reasons.

Health Authorities and Independent Ethics Committees (IECs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

In case of early termination of the study, all the study material (study drugs, etc.) must be returned to the Sponsor.

12. STUDY PROCEDURES

12.1. Responsibilities according to Good Clinical Practice

Responsibilities of the principal investigator of each participating center includes what is detailed in section 4 of the Guideline for good clinical practice E6 (R2).

12.2. Instructions for e-CRF completion

The data will be recorded using the Electronic Data Capture software property of MFAR S.L. The MFAR e-CRF environment will be used for data collection in this study. [redacted]. Access to data is secure and restricted for authorised users. Each user requires a username and password for exclusively personal use, as per good clinical practice.

All the EDC users are uniquely identified by name, all the access to the software is made through a secure, encrypted connection and all the activities are logged and audited.

All the EDC forms are designed according to the eCRF defined by the study protocol, and are validated according to the DVP (Data Validation Plan). There will be eCRFs for different visits, and whether these are mandatory (m) and non-mandatory eCRFs (such as laboratory testing and the corresponding validation of variables, rules and extraction).

Data on Adverse Event (AE), Adverse Reactions (AR), Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected SARs (SUSARs) will be undertaken by Sites in the eCRF and are transferred to the study database along with the rest of variables.

Electronic Case Report Form (eCRF) includes the CTCAE version 5.0 terms as a pulldown list in order to categorise the events, additionally when the variable “SAE” is marked as “yes”, an automatic email is sent to the MFAR Staff in order to be aware of the paper based SAE form is expected to be received, for regulatory reporting purposes. As data cleaning procedure, SAE received in paper based form are conciliate with the adverse events data collected in the eCRF and is ensured that all the events reported by means of SAE form are also collected in the eCRF, that is the final destination of any adverse event (whether be AE, AR, SAE, SAR or SUSAR).

12.3. Drug supply

AUREA is an Investigator Initiated Study, Atezolizumab will be supplied by the Sponsor through Roche, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. The treatment for patients not progressing at 24 months will be according to PI criteria, following his/her local normal practice. In case that the site cannot provide the drug for regulatory reasons (for example, the indication is not financed) and always with prior approval by the study sponsor (SOGUG) and by Roche, and if it is thus indicated in the contract between the Sponsor and the Site, the patient could continue in treatment with Atezollizumab participating in a Post-Trial Access (PTA) Program, previously approved by Roche. The maximum duration of the PTA will be 1 year.

If as per Treating Physician criteria, the best option for the patient would be to continue with Atezolizumab, the administration may continue but following Site's supply channels (other than those provided by Sponsor), after managing local administrative approvals Gemcitabine and Cisplatin will be provided by the sites as per standard care criteria.

12.3.1. Packaging and labelling

Packaging and labeling of study treatment will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines.

12.4. Final report and Publications

As stated in article 42 of RD 1090/2015 of clinical trials, the Sponsor is obliged to publish both positive and negative results of the authorized clinical trials in scientific journals and with mention to the Ethical Committee of Clinical Research that approved the study.

The clinical publication will be carried out by the Coordinating Investigator in collaboration and Principal Investigators. Coordinating Investigator and Principal Investigators who contributed with at least 3% of the patients will be the authors. The order of authors will strictly depend on the number of patients included by the Investigators.
The anonymity of the source subjects of the data and biological samples will be maintained at all times.

The results or conclusions of the study will be communicated primarily in scientific publications before being released to the non-health public.

No efficacy study outcome will be reported prematurely or sensationalistically.

Participating investigators should not publish any patient data that is directly related to the study objectives until the trial report is published.

The trial will be registered in the Spanish Registry of Clinical Studies (REEC) and www.clinicaltrials.gov.

12.5. Monitoring

The study will be monitored through local visits, telephone calls and periodic inspection of CRFs. During the study, according to monitoring plan, a monitor from MFAR Clinical Research or a representative will have regular contact with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to MFAR Clinical Research.
- Confirm that AEs and SAEs have been properly documented on eCRFs, all SAEs have been forwarded to MFAR Clinical Research, and all the SAEs that met criteria for reporting have been forwarded to the IEC

The monitor will be available between visits if the investigator(s) or other staff members need information or advice.

12.6. Clinical Study Report

According to local regulation, the summary of results of the trial will be sent to the AEMPS and the CEIm no later than one year after the date of the end of the trial globally. The summary of results will follow the European format required for EudraCT.

12.7. Protocol Amendments

Supplements and changes to the protocol can be performed exclusively by the Sponsor, who must submit them to the Ethics Committee and the local Regulatory Authority protocol amendments.

Relevant safety information will be submitted to the IEC during the course of the trial, in accordance with national regulations and requirements.

Initial IEC positive vote, and all materials approved by the IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

12.8. Data Handling

The data will be recorded using the Electronic Data Capture software property of MFAR S.L., which is developed and maintained with strict observance of the regulatory standards for Clinical EDC systems, with special observance of the guidelines specified at:

- CPMP/ICH/135/95. ICH E6. Note for Guidance on Good Clinical Practice.
- Good Clinical Data Management Practice, Version 4, Society for Clinical Data Management (SCDM), October 2005.
- EMEA. Reflection on expectations for electronic source documents used in clinical trials. London, 17 October 2007.

- Directive 9 Guidance for Industry. Part 11, Electronic Records; Electronic Signatures – Scope and Application (August 2003).
- FDA. Guidance for Industry. Computerised Systems Used in Clinical Investigations (May 2007).
- FDA. Guidance for Industry. Part 11, Electronic Records; Electronic Signatures – Scope and Application (August 2003)
- Organic Law 3/2018, of December 5, Protection of Personal Data and guarantee of digital rights

The EDC database is hosted at a data server located at the Data Centre maintained by Claranet SAU located at [redacted]. The physical access to the Data Centre is restricted to authorised Claranet personnel, and logical access to the database is restricted to named MFAR personnel.

All the EDC users are uniquely identified by name, all the access to the software is made through a secure, encrypted connection and all the activities are logged and audited.

All the EDC forms are designed according to the eCRF defined by the study protocol, and are validated according to the DVP (Data Validation Plan).

12.9. Documentation

The Investigator/Institution should maintain trial documents according to ICH Topic E6 ***Section 8***, and as required by pertinent regulatory requirements. According to RD 1090/2015 on Clinical trial, the archive period for all essential documents is 25 years.

Essential documents should be stored according to ICH GCP guidelines for a longer period of time, if required by pertinent regulations. The original patient data (clinical record) must be kept archived for the time stipulated by the study centre regulations.

All original subject files (medical records) must be stored at the site (hospital, research institution, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer (In Spain 25 years). In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

12.10. Audits and inspections

Authorised representatives of Sponsor, a regulatory authority, an Independent Ethics Committee may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonisation, and any applicable regulatory requirements. The investigator should contact the Sponsor through MFAR immediately if contacted by a regulatory agency about an inspection.

13. TRANSLATIONAL SUBSTUDIES

A key objective of the biomarker analyses that will be performed in this study is to investigate candidate biomarkers that may have predictive value in identifying those patients who may benefit from treatment with the combination of atezolizumab 1 and split dose GC. In addition, analyses of blood biomarkers obtained before, during and after treatment will provide an opportunity to investigate pharmacodynamic effects. Samples collected at the End of Treatment/Withdrawal visit enable investigation of potential mechanisms of resistance to the drug combination.

The following biological samples are required:

- Tumor sample, archive tumor sample in order to evaluate changes in signaling molecules in response to study treatment in tumour tissue.
- Processed blood samples obtained before treatment, at D1C7 of treatment, and at the end of treatment/progression, in order to evaluate changes in signaling molecules in response to study treatment in blood.
- Faecal samples for microbiome analyses.

13.1. Archived Tumor Biospecimens

Somatic alterations in tumours including proteomics, transcriptomics and metabolics will be analyzed. No germinal line determinations will be performed.

Tumor biological specimens from archived tissue samples will be used to analyze candidate DNA, RNA, or protein markers, or relevant signature of markers for their ability to identify those patients who are most likely to benefit from treatment with the study drugs.

Tumor tissue biomarker analyses, including determination of PD-L1 status, will be performed retrospectively in a central laboratory. PD-L1 status will be assessed using a validated PD-L1 IHC test kit manufactured under GMP specifications, in conjunction with a pre-specified scoring algorithm and cutoff defining PD-L1 positive versus negative status that will be established prior to initiation of scoring of PD-L1.

Additional tumor tissue biomarkers that may be analyzed include, but may not necessarily be limited to, gene expression profiles and/or quantitation of tumor-infiltrating CD8+ T lymphocytes by IHC and/or tissue FoxP3, PD-1, or PD-L2.

13.2. Peripheral Blood

Specimens will be processed and retained in local laboratories until Sponsor indications for shipments. It will include whole blood, serum and plasma samples that will be retained in the central laboratory for exploratory assessments.

Samples may be used to identify or characterize cells, DNA, RNA, or protein markers known or suspected to be of relevance to the mechanisms of action, or the development of resistance to study treatment. These include biomarkers that may aid in the identification of those patients who might preferentially benefit from treatment with IMP 1 in combination with IMP 2, which may include but are not limited to biomarkers related to anti-tumor immune response or target modulation, such as (not necessarily be limited to) soluble IL-8 or IFNγ.

Information regarding sample collection, management and shipments are provided in the translational research manual.

13.3. Fecal samples

Specimens will be processed and retained in local laboratories until Sponsor indications for shipments. It will include a total of 3 samples: basal faecal sample collected prior treatment initiation, faecal sample at Cycle 4 Day 1 and after progression. Information regarding sample collection, management and shipments are provided in the translational research manual.

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APPENDICES

Appendix 1. Management of Atezolizumab-specific Adverse Events

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to 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 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.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections.

- Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.
- In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.
- Consider holding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.51 mg/kg/day of prednisone or equivalent) may be administered.
- For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.
- Hold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (12 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.
- In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.
- The investigator should consider the benefit risk balance for a given patient prior to further administration of atezolizumab. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

Guidelines for managing patients who experience selected adverse events are provided in the following sections. Management guidelines are presented by adverse event severity based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

A) Management Guidelines for Pulmonary Events, Including Pneumonitis

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have CT scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies, such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in the next table.

B) Management Guidelines for Pulmonary Events, Including Pneumonitis table

Event	Management
Pulmonary event, Grade 1	● Continue atezolizumab and monitor closely. ● Re-evaluate on serial imaging. ● Consider patient referral to pulmonary specialist. ● For Grade 1 pneumonitis, consider withholding atezolizumab.
Pulmonary event, Grade 2	● Withhold atezolizumab for up to 12 weeks after event onset. [a] ● Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL with or without transbronchial biopsy. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone or equivalent. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] ● For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	● Permanently discontinue atezolizumab and contact Medical Monitor. [c] ● Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. ● Bronchoscopy or BAL with or without transbronchial biopsy is recommended. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully

recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator (or an appropriate delegate).Medical Monitor is available to advise as needed.

[d] In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.

C) Management Guidelines for Hepatic Events

Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in the next table.

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

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

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

AST/ALT is within normal limits at baseline and increases to ≥3 x ULN to ≤10 x ULN or AST/ALT is ≥ ULN to ≤ 3 x ULN at baseline and increases to ≥5 x ULN to ≤10 x ULN or AST/ALT is ≥3xULN to ≤ 5 x ULN at baseline and increases to ≥ 8 x ULN to ≤ 10 x ULN	• Monitor LFTs more frequently until return to baseline values. • Withhold atezolizumab for up to 12 weeks after event onset. a Events of > 5 days' duration: • Consider initiating treatment with corticosteroids equivalent to 12 mg/kg/day oral prednisone. • If event resolves to baseline or to Grade 1 or better, resume atezolizumab. b • If event does not resolve to baseline or to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. c
AST or ALT increases to ≥ 10 x ULN or total bilirubin increases to ≥ 3 x ULN	Permanently discontinue atezolizumab and contact the Medical Monitor. c Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to baseline, taper corticosteroids over ≥ 1 month.

GI=gastrointestinal; HCC=hepatocellular carcinoma; LFT=liver function test; ULN=upper limit of normal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.
[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

D) Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Management guidelines for diarrhea or colitis are provided in the next table.

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

Event	Management
Diarrhea or colitis, Grade 1	● Continue atezolizumab. ● Initiate symptomatic treatment. ● Endoscopy is recommended if symptoms persist for 7 days. ● Monitor closely.
Diarrhea or colitis, Grade 2	● Withhold atezolizumab for up to 12 weeks after event onset. [a] ● Initiate symptomatic treatment. ● If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis. ● Patient referral to GI specialist is recommended. ● For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	● Withhold atezolizumab for up to 12 weeks after event onset. [a] ● Refer patient to GI specialist for evaluation and confirmatory biopsy. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 4	● Permanently discontinue atezolizumab and contact Medical Monitor. [c] ● Refer patient to GI specialist for evaluation and confirmation biopsy. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, taper corticosteroids over 1 month.

GI=gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk

assessment and in alignment with protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

E) Management Guidelines for Endocrine Events

Management guidelines for endocrine events are provided in the next table.

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

Event	Management
Grade 1 hypothyroidism	● Continue atezolizumab. ● Initiate treatment with thyroid replacement hormone. ● Monitor TSH closely.
Grade 2 hypothyroidism	● Consider withholding atezolizumab. ● Initiate treatment with thyroid replacement hormone. ● Monitor TSH closely. ● Consider a patient referral to an endocrinologist. ● Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Grade 3 and 4 hypothyroidism	● Withhold atezolizumab. ● Initiate treatment with thyroid replacement hormone. ● Monitor TSH closely. ● Refer to an endocrinologist. ● Admit patient to the hospital for developing myxedema (bradycardia, hypothermia and altered mental status). ● Resume atezolizumab when symptoms are controlled and thyroid function is improving. ● Permanently discontinue atezolizumab and contact the Medical monitor for life-threatening immune-mediated hypothyroidism.
Grade 1 hyperthyroidism	TSH ≥ 0.1 mU/L and < 0.5 mU/L: ● Continue atezolizumab. ● Monitor TSH every 4 weeks. ● Consider patient referral to endocrinologist. TSH < 0.1 mU/L: ● Follow guidelines for symptomatic hyperthyroidism. ● Consider patient referral to endocrinologist.
Grade 2	● Consider withholding atezolizumab.

hyperthyroidism	● Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. ● Consider patient referral to endocrinologist. ● Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Grade 3 and 4 hyperthyroidism	● Withhold atezolizumab. ● Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. ● Refer to endocrinologist. ● Resume atezolizumab when symptoms are controlled and thyroid function is improving. ● Permanently discontinue atezolizumab and contact the Coordinating Investigator for life-threatening immune-mediated hyperthyroidism. [c]
Symptomatic adrenal insufficiency, Grade 2 - 4	● Withhold atezolizumab for up to 12 weeks after event onset. [a] ● Refer patient to endocrinologist. ● Perform appropriate imaging. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ● If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	● Continue atezolizumab. ● Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. ● Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	● Withhold atezolizumab. ● Initiate treatment with insulin. ● Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. ● Monitor for glucose control. ● Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	● Withhold atezolizumab for up to 12 weeks after event onset. a ● Refer patient to endocrinologist. ● Perform brain MRI (pituitary protocol). ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ● Initiate hormone replacement if clinically indicated. ● If event resolves to Grade 1 or better, resume atezolizumab. b ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] ● For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	● Permanently discontinue atezolizumab and contact Medical Monitor. c ● Refer patient to endocrinologist. ● Perform brain MRI (pituitary protocol). ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2

	mg/kg/day oral prednisone or equivalent upon improvement. ● Initiate hormone replacement if clinically indicated.

MRI magnetic resonance imaging; TSH thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

F) Management Guidelines for Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in the next Table.

Event	Management
Ocular event, Grade 1	● Continue atezolizumab. ● Patient referral to ophthalmologist is strongly recommended. ● Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. ● If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	● Withhold atezolizumab for up to 12 weeks after event onset.a ● Patient referral to ophthalmologist is strongly recommended. ● Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. ● If event resolves to Grade 1 or better, resume atezolizumab.b ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	● Permanently discontinue atezolizumab and contact Medical Monitor. c Refer patient to ophthalmologist. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. ● If event resolves to Grade 1 or better, taper corticosteroids over 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

G) Management Guidelines for Immune-Mediated Cardiac Events

Management guidelines for cardiac events are provided in the following table.

Immune-Mediated Myocarditis

Immune-related myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis and should be managed accordingly. 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 preexisting cardiac conditions, or progression of malignancy.

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

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

Immune-mediated pericardial disorders

Immune-Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis.

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted.

Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in the next Table.

Event	Management
Immune-mediated myocarditis, Grade 2-4	● Permanently discontinue atezolizumab and contact Medical Monitor. ● Refer patient to cardiologist. ● Initiate treatment as per institutional guidelines and consider

Immune-mediated pericardial disorders, Grades 2-4	antiarrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ● If 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.

H) Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab.
However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-L1 or PD-1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for the medical management of IRRs and CRS are provided in the next Table.

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

Event	Management
Grade 1 [a] Fever [b] with or without constitutional	● Immediately interrupt infusion. ● Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.

symptoms	● If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. ● If symptoms recur, discontinue infusion of this dose. ● Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. ● In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. ● For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medication, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors and/or Hypoxia requiring low-flow oxygen d by nasal cannula or blow-by	● Immediately interrupt infusion. ● Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. ● If symptoms recur, discontinue infusion of this dose. ● Administer symptomatic treatment. [c] ● For hypotension, administer IV fluid bolus as needed. ● Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. ● Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy. [e] ● Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor. ● If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medication, and/or analgesics and monitor closely for IRRs and/or CRS. ● If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen d by nasal cannula, face mask, non-rebreather mask, or venturi mask	● Permanently discontinue atezolizumab and contact Medical Monitor. [f] ● Administer symptomatic treatment. [c] ● For hypotension, administer IV fluid bolus and vasopressor as needed. ● Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. ● Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy. [e] ● Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring,

	mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	● Permanently discontinue atezolizumab and contact Medical Monitor. [f] ● Administer symptomatic treatment. [c] ● Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. ● Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy. [e] For patients who are refractory to anti-cytokine therapy, experimental treatments [g] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. ● Hospitalize patient until complete resolution of symptoms.

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI National Cancer Institute.
Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT Consensus Grading Scale for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
[b] Fever is defined as temperature ≥ 38ºC not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
[c] Symptomatic treatment may include oral or IV antihistamines, antipyretic medications, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.
[e] There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors/ICI (*Rotz et al. 2017*; *Adashek and Feldman 2019*), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
[f] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit-risk ratio.
[g] Refer to *Riegler et al. (2019)*.

I) Management Guidelines for Pancreatic Events, Including Pancreatitis

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 the next Table.

Event	Management
Amylase and/or lipase elevation, Grade 2	Amylase and/or lipase > 1.5 - 2.0 ULN: ● Continue atezolizumab. ● Monitor amylase and lipase weekly. ● For prolonged elevation (e.g., > 3 weeks), consider treatment ● with corticosteroids equivalent to 10 mg/day oral prednisone. Asymptomatic with amylase and/or lipase > 2.0 - 5.0 x ULN: ● Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	● Withhold atezolizumab for up to 12 weeks after event onset.[a] ● Refer patient to GI specialist. ● Monitor amylase and lipase every other day. ● If no improvement, consider treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] ● For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 2 or 3	● Withhold atezolizumab for up to 12 weeks after event onset.[a] ● Refer patient to GI specialist. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] ● For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	● Permanently discontinue atezolizumab and contact Medical Monitor. [c] ● Refer patient to GI specialist. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab

should be based on the investigator's benefit-risk assessment and documented by the investigator. Medical Monitor is available to advise as needed.

J) Management Guidelines for Dermatologic Events

The majority of cases of rash reported with the use of atezolizumab were mild in severity and self limited, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in the next Table.

Event	Management
Dermatologic event, Grade 1	● Continue atezolizumab. ● Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	● Continue atezolizumab. ● Consider patient referral to dermatologist for evaluation and, if indicated, biops. ● Initiate treatment with topical corticosteroids. ● Consider treatment with higher-potency topical corticosteroids if event does not improve. ● If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	● Withhold atezolizumab for up to 12 weeks after event onset.[a] ● Refer patient to dermatologist for evaluation and, if indicated, biopsy. ● Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	● Permanently discontinue atezolizumab and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis, (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: ● Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. ● Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy. ● Follow the applicable treatment and management guidelines above. ● If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.
[b] If corticosteroids have been initiated, they must be tapered over 1 month to the equivalent of 10 mg/day oral prednisone before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed..

K) Management Guidelines for 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 the next Table.

Event	Management
Immune-mediated neuropathy, Grade 1	● Continue atezolizumab. ● Investigate etiology
Immune-mediated, including facial paresis, neuropathy, Grade 2	● Withhold atezolizumab for up to 12 weeks after event onset.[a] ● Investigate etiology and refer patient to neurologist. ● Initiate treatment as per institutional guidelines. ● For general immune-mediated neuropathy o If event resolves to Grade 1 or better, resume atezolizumab. [b] o If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinueatezolizumab and contact the Medical Monitor. [c] ● For facial paresis: o If event resolves fully, resume atezolizumab [b] o If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor.[c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	● Permanently discontinue atezolizumab and contact Medical Monitor. [c] ● Refer patient to neurologist ● Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	● Permanently discontinue atezolizumab and contact Medical Monitor. [c] ● Refer patient to neurologist. ● Initiate treatment as per institutional guidelines. ● Consider initiation of corticosteroids equivalent to 1-2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.
[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10

mg/day oral prednisone before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab based on the investigator's benefit-risk assessment and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

L) Management Guidelines for Immune-Mediated 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 the next Table.

Event	Management
Immune-mediated meningoencephalitis, all grades	● Permanently discontinue atezolizumab and contact Medical Monitor. [a] ● Refer patient to neurologist. Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ● If 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

M) Management Guidelines for Renal Events

Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

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

Event	Management
Renal event, Grade 1	● Continue atezolizumab. ● Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	● Withhold atezolizumab for up to 12 weeks after event onset. [a] ● Refer patient to renal specialist. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue

	atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	● Permanently discontinue atezolizumab and contact Medical Monitor. ● Refer patient to renal specialist and consider renal biopsy. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

N) Management Guidelines for Immune-Mediated Myositis

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

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

Event	Management
Immune-mediated myositis, Grade 1	● Continue atezolizumab. ● Refer patient to rheumatologist or neurologist. ● Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	● Withhold atezolizumab for up to 12 weeks after event onset a and contact Medical Monitor. ● Refer patient to rheumatologist or neurologist. ● Initiate treatment as per institutional guidelines. ● Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ● If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated myositis, Grade 3	● Withhold atezolizumab for up to 12 weeks after event onset a and contact Medical Monitor. ● Refer patient to rheumatologist or neurologist. ● Initiate treatment as per institutional guidelines. ● Respiratory support may be required in more severe cases. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, resume atezolizumab. b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] ● For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4 (CTCAE v5.0 guidelines only)	● Permanently discontinue atezolizumab and contact Medical Monitor. [c] ● Refer patient to rheumatologist or neurologist. ● Initiate treatment as per institutional guidelines. ● Respiratory support may be required in more severe cases. Initiate treatment with corticosteroids equivalent to 1-2

	mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 12 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] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's benefit-risk assessment and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. Medical Monitor is available to advise as needed.

O) Management Guidelines for Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
    - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
    - Platelet count < 100 x 109/L (100,000/µL)
    - ANC < 1.0 x 109/L (1000/µL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

Ferritin > 684 mg/L (684 ng/mL)

At least two of the following:

- Platelet count ≤181 x 109/L (181,000µ/L)
- AST ≥ 48 U/L
- Triglycerides > 1.761 mmol/L (156 mg/dL)
- Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in the next Table.

Event	Management
Suspected HLH or MAS	● Permanently discontinue atezolizumab and contact the Medical Monitor. ● Consider patient referral to hematologist. ● Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. ● Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. ● If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines. ● If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH=hemophagocytic lymphohistiocytosis; IV=intravenous; MAS=macrophage activation syndrome.

P) Management Guidelines for Immune-Mediated Myelitis

Event	Management
Immune-mediated myelitis, Grade 1	● Continue atezolizumab unless symptoms worsen or do not improve. ● Investigate etiology and refer patient to a neurologist
Immune-mediated myelitis, Grade 2	● Permanently discontinue atezolizumab and contact the Medical Monitor. ● Investigate etiology and refer patients to a neurologist. ● Rule out infection. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone
Immune-mediated myelitis, Grade 3 or 4	● Permanently discontinue atezolizumab and contact the Medical Monitor. ● Refer a patient to a neurologist. ● Initiate treatment as per institutional guidelines

Clinical Trial Protocol

Protocol Number:	SOGUG-2020-IEC(VEJ)-1
Title:	Phase II, multicenter, non-randomized, single-arm, open-label trial of atezolizumab in combination of split-doses of gemcitabine plus cisplatin in patients with locally advanced or metastatic urothelial carcinoma
Short title:	Study of atezolizumab combined with split-dose gemcitabine plus cisplatin in urothelial carcinoma
Acronym:	AUREA
Nº EudraCT:	2020-001326-65
Sponsor:	Spanish Oncology Genitourinary Group (SOGUG) [redacted]
Coordinating: Investigator:	Guillermo de Velasco, M.D., PhD. [redacted]

VERSION 2.0 - 08MAR2022

Confidentiality Statement

The information contained in this document is the property of the sponsor and therefore is provided confidentially for review by you, your investigative team, the Investigational Ethics Committee, and the competent authorities. This information must not be revealed to any other party without previous authorization in writing by the sponsor, except as needed to obtain the informed consent of the subjects who may be given the medicinal product.

SPONSOR'S PROTOCOL SIGNATURE PAGE

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonization Good Clinical Practice, and all applicable Health Authority requirements and national laws.

[redacted]

SOGUG Chairman	**Signature**	**Signature date (DD-mm-YYYY)**

Dr. Guillermo de Velasco

Coordinating Investigator	**Signature**	**Signature date (DD-mm-YYYY)**

PRINCIPAL INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

I have read this protocol and agree to conduct this clinical trial in accordance with all the provisions of the Protocol, any approved protocol amendments, International Conference on Harmonization Good Clinical Practice, Helsinki Declaration and all applicable Health Authority requirements and national laws

Site: _____

Name: _____

Date:_____

Principal Investigator Signature:_____

1. SUMMARY

1.1. Type of application

Clinical trial with approved medications with a potential better regimen.

1.2. Study Title

Phase II, multicenter, non-randomized, single-arm, open-label trial of atezolizumab in combination of split-doses of gemcitabine plus cisplatin in patients with locally advanced or metastatic urothelial carcinoma

1.3. Protocol Number and Version

SOGUG-2020-IEC(VEJ)-1 - VERSION 2.0 08MAR2022

1.4. Nº EudraCT

2020-001326-65

1.5. Sponsor Data

Spanish Oncology Genitourinary Group (SOGUG)

[redacted]

1.6. Coordinating Investigator

Guillermo de Velasco, M.D., PhD.

[redacted]

1.7. Principal Investigators

The list of sites and the corresponding Principal Investigators is provided in the attached document.

1.8. Study Sites

It is expected the participation of 12 Sites in Spain.

1.9. Monitoring Organization

MFAR Clinical Research

[redacted]

1.10. Disease under study

Locally advanced and metastatic urothelial carcinoma (mUC)

1.11. Study Phase

Phase II clinical trial; Investigator Initiated Study (IIS)

1.12. Study Treatments

All study treatments are intended for administration as described below (regarding maximum treatment duration as per protocol), until PD, unacceptable toxicity, investigator's decision or patient's consent withdrawal (whichever occurs first).

- **Atezolizumab** at a fixed dose of 1200 mg/m^2 by intravenous (IV) infusion on D1 of each cycle up to disease progression, unacceptable toxicity or absence of clinical benefit. AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation.

- **Gemcitabine** 1000 mg/m^2 IV on D1 and 1000 mg/m^2 IV on D8 of each 21-day cycle *plus* **Cisplatin** 70 mg/m^2 by IV on split-dose schedule of 35 mg/m^2 on day 1 (D1) and 35 mg/m^2 on day 8 (D8) <u>for up to 6 cycles.</u>

1.13. Objectives

Primary Objective:

To evaluate the preliminary efficacy of atezolizumab plus split-dose gemcitabine and cisplatin (GC) for the first-line setting, in patients with histologically confirmed advanced (locally advanced and metastatic) urothelial cancer in terms of overall response rate (ORR) assessed by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Secondary Objectives

Efficacy:

- To evaluate the *duration of response (DoR)* associated with the study treatment, understood as the time from first confirmed response (CR or PR) to the date of the documented progressive disease as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.
- To determine the *overall survival (OS)* of patients with locally-advanced or mUC treated with the intended treatment regimen, understood as the time from first dosing date to the date of death. A subject who has not died will be censored at last known date alive.
- To evaluate the *time to response (TtR)* associated with the study treatment, understood as the time from the first dose of the study treatment and confirmed response (CR or PR) based on RECIST 1.1 criteria.
- To evaluate the *clinical benefit rate (CBR)*, defined as the percentage of patients who have achieved complete response, partial response and stable disease. Stable disease should be maintained for at least 6 months to be considered as CBR event.
- To determine the *progression-free survival (PFS)* of patients with locally-advanced or mUC treated with the intended treatment regimen, defined as the time from first dosing date until disease progression or death from any cause. Patients who have not progressed and start a new line of treatment will be censored.

Safety:

- To evaluate *safety* of the intended treatment regimen based on the frequency and severity of adverse events assessed by NCI CTCAE v5.0.

Exploratory objectives

- To explore potential correlation of efficacy with relevant potential prognostic factors/stratification factors

- To evaluate the relationship between the expression of PD-L1 and microbiome with ORR and PFS during experimental treatment.

1.14. Endpoints

Primary endpoint:

- *Overall Response Rate (ORR)*

Secondary endpoints

- *Duration of response* (DoR)
- *Overall Survival* (OS)
- *Time to response* (TtR)
- *Clinical benefit* (CB)
- *Progression-Free Survival* (PFS)

Safety endpoints

- *Adverse events* (AE)
- *Treatment-related AEs* (TRAEs)

Exploratory endpoints

- Biomarkers expression

1.15. Sample Size

A minimum of 66 patients will be included in the trial.

1.16. Eligibility and withdrawal criteria

Inclusion criteria

1. Male or female subjects ≥ 18 years old.
2. Written informed consent approved by the Independent Ethics Committee (IEC), prior to the performance of any trial activities.
3. Patients with histologically documented, locally advanced (T4B, any N; or any T, N2-3) or metastatic urothelial carcinoma (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).*
4. Patients should not be eligible (unfit) for full dose of cisplatin, in the investigator's judgement, based on:
   a. Age older than 70 years.
   b. ECOG Performance status (PS) 2 or Karnofsky PS of 60 - 70% (only 15 patients will be included with ECOG 2).
   c. Measured creatinine clearance (ClCr) > 30 and < 60 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for the determination of creatinine clearance:

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

   d. Any other reason the physician considers but should specify in the CRF and discussed with the PI.

5. At least one measurable lesion through radiographic tumor evaluation (CT scan or magnetic resonance imaging/MRI) as defined by RECIST version 1.1, that has not been previously irradiated within 4 weeks prior to the study enrolment.

6. Patients with an archival or *de novo* tumor biopsy (representative formalin-fixed paraffin-embedded/FFPE paraffin block obtained as close as possible to the patient inclusion) with an associated pathology report, for testing of PD-L1 expression, prior to study enrollment. Samples in unstained slides could be acceptable (at least 15 slides).

7. Patients with adequate normal organ and marrow function as defined below:

   a. Haemoglobin ≥ 9.0 g/dL.
   b. Absolute neutrophil count (ANC) ≥ 1500 per mm^3.
   c. Platelet count ≥ 100,000 per mm^3.
   d. Serum bilirubin ≤ 1.5 X institutional upper limit of normal (ULN) unless liver metastases are present, in which case it must be ≤ 2X ULN. This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology); however, they will be allowed only in consultation with their physician.
   e. Serum transaminases (ALT, AST and GGT) ≤ 2.5X institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 3X ULN.

8. No major active bleeding.

9. Female subjects of childbearing potential (not surgically sterile or at least 2 years postmenopausal) must provide a negative urine pregnancy test at screening, and use a medically accepted double barrier method of contraception (i.e. condom with spermicide + IUD or cervical caps). In addition, they must agree to continue the use of this double barrier method for the duration of the study and for 6 months after participation in the study.

10. Males should agree to abstain from sexual intercourse with a female partner or agree to use a double barrier method of contraception (i.e. condom with spermicide, in addition to having their female partner use some contraceptive measures such as oral contraceptive drugs, intrauterine device (IUD) hormonal contraception, or cervical caps), for the duration of the study and for 6 months after participation in the study

11. Willingness and ability of patients to comply with the protocol for the duration of the study including undergoing treatment as well as availability for scheduled visits and examinations including follow up.

Exclusion criteria

1. Prior treatment with any immune checkpoint inhibitor therapy (e.g., CTLA4, PD-1, or PD-L1 targeting agent).*

   **Note*: Prior adjuvant or neoadjuvant treatment with targeted therapy/checkpoint inhibitors is allowed, as long as the last dose was administered at least 12 months prior to the patient inclusion in this trial.

2. Presence of active second malignancy and/or prior malignancy in the last 2 years is allowed except for the following:
   a. adequately treated basal cell or squamous cell skin cancer,
   b. adequately treated Stage I or II cancer from which the patient is currently in complete remission per investigators' clinical judgment.
3. Patient receiving radiation therapy within 4 weeks before inclusion.
4. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
5. Active or prior documented inflammatory bowel disease (e.g.., Crohn's disease and ulcerative colitis).
6. History of allogeneic organ transplant.
7. Subjects having a diagnosis of immunodeficiency or are receiving systemic steroid therapy or any other form of immunosuppressive therapy within 28 days prior to the first dose of trial treatment.
8. Current or prior use of immunosuppressive medication within 7 days prior to enrolment, except the following:
   a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);
      i. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;
      ii. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
9. The subject has uncontrolled, significant intercurrent or recent illness (within 6 months prior to inclusion) including, but not limited to, the following conditions:
   a. Cardiovascular disorders:
      i. Class 3 or 4 congestive heart failure as defined by the New York Heart Association, unstable angina pectoris, and serious cardiac arrhythmias.
      ii. Uncontrolled hypertension defined as sustained blood press > 150 mm hg systolic or > 100 mm hg diastolic despite optimal antihypertensive treatment.
      iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction, other ischemic event, or thromboembolic event (e.g., deep venous thrombosis [DVT] and pulmonary embolism) within 6 months

before inclusion. Subjects with a more recent diagnosis of DVT are allowed if stable, asymptomatic, and treated with LMWH for at least 6 weeks before study treatment.

b. Gastrointestinal disorders (e.g., malabsorption syndrome or gastric outlet obstruction) including those associated with a high risk of perforation or fistula formulation:
    i. Tumours invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.
    ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before inclusion. Note: complete healing of an intra-abdominal abscess must be confirmed prior to start of the treatment.

c. Clinically significant hematemesis or hemoptysis of > 0.5 teaspoon (> 2.5 ml) of red blood or history of other significant bleeding within 3 months before treatment.

d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation.

e. Lesions invading major pulmonary blood vessels.

f. Other clinically significant disorders such as:
    i. Active infection requiring systemic treatment, infection with human immunodeficiency virus or acquired immunodeficiency syndrome-related illness, or chronic hepatitis B or C infection.
    ii. Serious non-healing wound/ulcer/bone fracture.
    iii. Malabsorption syndrome.
    iv. Moderate to severe hepatic impairment (child-pugh B or C).
    v. Requirement for hemodialysis or peritoneal dialysis.
    vi. Uncontrolled diabetes mellitus.

10. Major surgery (e.g., GI surgery and removal or biopsy of brain metastasis) within 8 weeks before inclusion. Complete wound healing from major surgery must have occurred 4 weeks before study treatment and from minor surgery (e.g., simple excision, tooth extraction) at least 10 days before study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

11. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

12. Any test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or chronic infection.

13. Women who are pregnant or are breastfeeding.

14. Male patients must be surgically sterile or must agree to use effective contraception during the period of therapy.

15. Any of the following within 6 months prior to study entry: myocardial infarction, uncontrolled angina, uncontrolled hypertension, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack.

16. Previously identified allergy or hypersensitivity to components of the study treatment formulations.

1.17. Planned trial period

- Enrolment/recruitment period: 12 months
- First patient first visit (FPFV): 8ENE2021
- Last patient last visit (LPLV): FPFV + 24 months
- Treatment period: Up to 24 months of LPFV
- Follow-up period: 24 months
- Planned end of study date: FPFV + up to 36 months

GLOSSARY OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ADR	**Adverse drug reaction**
AE	**Adverse event**
aUC	**Advanced urothelial cancer**
BMI	**Body Mass Index**
BP	**Blood Pressure**
CIs	**Confidence intervals**
CK	**Creatine kinase (CK), also known as creatine phosphokinase (CPK) or phosphocreatine kinase**
CB	**Clinical benefit**
CR	**Complete Response**
CRA	**Clinical Research Associate**
CTCAE	**Common Terminology Criteria for Adverse Events**
CT Scan	**Computed Tomography Scan**
DMP	**Data Management Plan**
CYP	**Cytochromes P450 enzymes**
DoR	**Duration of response**
DVP	**Data Validation Plan**
ECHO	**Echocardiogram**
ECG	**Electrocardiogram**
ECOG	**Eastern Cooperative Oncology Group**
eCRF	**Electronic Case Report Form**
EDC	**Electronic Data Capture**
ECG	**Electrocardiogram**
EMA	**European Medicines Agency**
ESMO	**European Society of Medical Oncology**
FBE	**Full blood examination**
FDA	**US Food and Drug Administration**
FFPE	**Formalin-fixed paraffin-embedded**

FPFV	**First patient first visit**
FU	**Follow-up**
GC	**Gemcitabine plus cisplatin**
GCP	**Good Clinical Practice**
G-CSF	**Granulocyte colony-stimulating factor**
GH	**Growth hormone**
Hb	**Haemoglobin**
IB	**Investigator Brochure**
ICF	**Informed Consent Form**
ICH	**International Conference on Harmonization**
ICI	**Immune Checkpoint Inhibitors**
IEC	**Independent Ethics Committee**
IgG1	**Immunoglobulin G1**
IIS	**Investigator Initiated Study**
IMP	**Investigational Medicinal Product**
ISF	**Investigator Site File**
ITT	**Intention To Treat**
IUD	**Intrauterine device**
LPLV	**Last visit Last patient**
MedDRA	**Medical Dictionary for Regulatory Activities**
MRI	**Magnetic Resonance Imaging**
mUC	**Metastatic urothelial cancer**
MUGA	**Multigated Acquisition Scan**
MVAC	**Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin**
NCI	**National Cancer Institute (USA)**
ORR	**Overall response rate**
OS	**Overall Survival**
PD	**Progression disease**
PE	**Physical Examination**
PFS	**Progression Free Survival**
PI	**Principal Investigator**

PP	**Per Protocol**
PR	**Partial Response**
PS	**Performance Status**
QD	**Quaque die, every day “once daily”**
QxW	**Every X weeks**
RECIST	**Response Evaluation Criteria In Solid Tumours**
REEC	**Registro Español de Estudios Clínicos (Spanish Registry of Clinical Studies)**
Rx	**Radiography**
SAE	**Serious adverse event**
SAP	**Statistical Analysis Plan**
SAR	**Serious adverse reaction**
SC	**Subcutaneous**
SD	**Stable disease**
SDV	**Source Data Verification**
SmPC	**Summary of Product Characteristics**
SP	**Safety Population**
SUSAR	**Suspected unexpected serious adverse reaction**
PD-1	**Programmed death-1**
PD-L1	**Programmed death ligand-1**
TR	**Translational Research**
UC	**Urothelial cancer**
ULN	**Upper Limit of Normality**
VS	**Vital Signs**
WBC	**White Blood Count**
wGC	**weekly Gemcitabine plus cisplatin**
WHO	**World Health Organization**

2. GENERAL INFORMATION

2.1. Study Identification

Short title: Study of atezolizumab and split-dose cisplatin/gemcitabine and in urothelial carcinoma

Protocol number: SOGUG-2020-IEC (VEJ-1)

EudraCT No.: 2020-001326-65

2.2. Monitoring Organization

MFAR Clinical Research
[redacted]

2.3. Sponsor information

Spanish Oncology Genitourinary Group (SOGUG)
[redacted]

2.4. Coordinating investigator

Guillermo de Velasco M.D., PhD.
[redacted]

2.5. Investigators and study centres

It is expected the participation of 12 Sites in Spain. The list of Sites and the corresponding Principal Investigators is provided in a separated document.

3. INVESTIGATIONAL MEDICINAL PRODUCT (IMP) DESCRIPTION

3.1. Study medication

Atezolizumab:

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01XC

Presentation: 60 mg/mL glass vials of 20-mL, nominal atezolizumab amount per vial, 1200 mg. Commercial medication labeled for clinical trial.

Pharmaceutical form: Concentrate for solution for infusion. Clear, colourless to slightly yellowish liquid.

Supply: Roche Pharma will supply atezolizumab to the Sponsor that will supply this product to the sites pharmacy.

Gemcitabine

Pharmacotherapeutic group: Antineoplastic agents - Alkylating agents - Antimetabolites - Pyrimidine analogues, ATC code: L01BC05

Presentation:; Glass vial: *200 mg/5.3 mL *or* 200 mg/2 mL; 1000 mg/10 mL or 1000 mg/26.3mL; 1500 mg/15 mL and *2000 mg/52.6 mL *or* 2000 mg/20 mL. Commercial medication not-labeled for clinical trial.

Pharmaceutical form: *Concentrate for solution for infusion according to different commercial presentations authorized in Spain.

Supply: By participating sites under standard treatment criteria

Cisplatin

Pharmacotherapeutic group: Antineoplastic agents - Other antineoplastic agents, ATC code: L01XA01

Presentation: 1 mg/mL glass vials of 10-mL, 50-mL and 100-mL. Commercial medication not-labeled for clinical trial.

Pharmaceutical form: Concentrate for solution for infusion.

Supply: By participating sites under standard treatment criteria.

4. RATIONALE AND OBJECTIVES

4.1. Rationale

4.1.1. Current state of the art

Cisplatin-based chemotherapy (70 mg/m^2) has been the standard of care for first-line treatment for surgically unresectable and metastatic patients fit enough to tolerate cisplatin for more than 30 years (*Saxman SB, et al. 1997; Von der Maase, et al. 2000; Bellmunt J, et al. 2016*). However, a standard dose schedule is not feasible for a significant number of patients (about 50%). Age-related physiological changes and comorbidities are common in the uro-oncology field and, as expected, affect treatment choices and outcomes. Renal function impairment, cardiovascular disease, neuropathy, hearing loss are commonly reported in patients with bladder cancer (*Bellmunt J, et al. 2016*; *Katz H, et al. 2017*); but its toxicity (*van Leenders GJLH, 2019*).

According to the most recent update on cumulative evidence and as summarized in the most recent ESMO Bladder Cancer Treatment Recommendations published on 16 December 2019, a number of cisplatin-containing regimens are acceptable although gemcitabine and cisplatin [I, A] is the most widely accepted (*Von der Maase, et al. 2000*). Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) [I, B], MVAC with granulocyte colony-stimulating factor (G-CSF) [I, B], and gemcitabine, cisplatin and paclitaxel [I, C] are alternatives which have established themselves as options over time (*Loehrer PJ, et al. 1992; Sternberg CN, et al 2006; Bellmunt J, et al. 2012; Grande E, et al. 2019*). Although these specific regimens may lack proven advantage or non-inferiority compared with gemcitabine and cisplatin, they can be considered as options in selected patients.

4.1.2. Split-Dose Cisplatin

For those patients with mUC cisplatin-ineligible or who have progressed on a platinum-based regimen treatment options are limited (*Koshkin VS, et al. 2018*) and are usually palliated with carboplatin-based regimen, single-agent taxane or gemcitabine, or split-dose cisplatin-based regimens may be employed. In fact, some studies have presented data on up to 50% of patients eligible for cisplatin might be treated with carboplatin-based chemotherapy based on physician criteria (ie. IMvigor 130; *Grande E, et al. 2019*).

The difficult-to-treat concept of this disease entails the undoubtedly high age of most of around 80% of patients with UC (*Gore JL, et al. 2010*).

Administration of cisplatin 35 mg/m2 on day 1 + 8 or 1 + 2 (i.e., split schedule) is a commonly used alternative. Several studies have reported that split dose GC has comparable response rates in metastatic disease to other platinum containing regimens (*Morales-Barrera R, et al. 2012*), but has a favourable toxicity profile and considerably less time burden on day care facilities (*Sellers LE, et al. 2016*). These led us to consider that split dose GC should be a feasible alternative to the longer more toxic regimens, particularly in metastatic disease.

4.1.3. PD-L1 and the role of atezolizumab in mUC

Expression of programmed death ligand-1 (PD-L1) is prevalent among many human tumors (*Dong et al. 2002*), and its overexpression is associated with poor prognosis for patients with certain cancers (*Thompson et al. 2006; Hamanishi et al. 2007; Okazaki T and Honjo T, 2007;*

Hino et al. 2010, Mu et al. 2011). Therefore, interruption of the PD-L1/PD 1 pathway represents an attractive strategy to reinvigorate tumor-specific T cell immunity.

Since May 2016, five different agents targeting the PD-1/PD-L1 pathway (atezolizumab, pembrolizumab, nivolumab, avelumab, durvalumab) have received FDA approval for the treatment of aUC in the platinum-refractory setting, while pembrolizumab and atezolizumab are FDA-approved for cisplatin-ineligible patients in the first-line setting (*Koshkin VS 2018*). For platinum or chemotherapy-ineligible patients with mUC, immune checkpoint inhibitors (ICI) such as inhibitors of programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) are approved regardless of PD-L1 expression, including pembrolizumab and atezolizumab (*Einstein and Sonpavde, 2019*).

Atezolizumab is a humanized immunoglobulin (IgG1) monoclonal antibody that is produced in Chinese hamster ovary (CHO) cells. Atezolizumab targets programmed death-ligand 1 (PD-L1) on tumor-infiltrating immune cells (ICs) or tumor cells (TCs) and prevents interaction with the programmed death-1 (PD-1) receptor and B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells and other immune cells. The PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T cell response through increased T cell priming, expansion, and/or effector function. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc effector function. By eliminating Fc-effector function and antibody-dependent cell-mediated cytotoxicity, antibody-mediated clearance of activated effector T cells is also eliminated.

Atezolizumab has demonstrated efficacy and a tolerable safety profile in a range of cancers, including locally advanced or mUC (*Herbst RS, et al. 2014; Powles T, et al. 2014, Fehrenbacher L et al. 2016; McDermott DF, et al. 2016; Rosenberg JE, et al. 2016*). Cumulative data on efficacy at the time of this study design (March 2020) suggest that atezolizumab as a single-agent for first-line in patients with mUC entails clinical benefit in terms of objective responses, durable responses, and OS.

Clinical data from the first-line cisplatin-ineligible IMvigor210 cohort—the first report of an anti–PD-L1/PD-1 checkpoint inhibitor in this setting— atezolizumab conferred significant clinical benefit (*Rosenberg JE, et al. 2016*), leading to accelerated regulatory approval, and several biomarkers associated with response were identified. Furthermore, encouraging durable response rates, survival and tolerability (*Balar AV, et al. 2017*) have been also reported.

Interim results (2018) from the ongoing IMvigor 130 trial (atezolizumab *vs* atezolizumab plus platinum-based chemotherapy in locally advanced/mUC not previously treated) has shown a reduction on survival for those patients treated with atezolizumab alone when compared to those who received platinum-based chemotherapy (carbo- or cis- at physician discretion), not previously treated and with tumors showing a low-PD-L1 expression (<5% of immune cells with positive staining) (*EMA Tecentriq Assessment Report*).

4.2. Hypothesis

The results of trials combining checkpoint inhibitors or platinum-based chemotherapy plus PD-1/PD-L1 inhibitors are eagerly awaited. The combination of split cisplatin with

atezolizumab is a feasible treatment that may provide better outcomes than carboplatin/based combinations.

In the IMvigor130, 52% of patients considered cisplatin eligible at the entry of the study were treated with carboplatin. Subanalysis presented at ESMO 2019 (*Grande E, et al. 2019*) has also shown a longer median OS are achieved with cisplatin-based chemotherapy combined with atezolizumab (21.7 months) when compared to the carboplatin-based chemotherapy plus atezolizumab (14.2 months), with similar findings when it comes to PFS 8.8 months with cisplatin/gemcitabine/atezolizumab vs 7.1 months carboplatin/gemcitabine/atezolizumab.

A reasonable strategy may be the use of split cisplatin with atezolizumab to increase the number of patients receiving cisplatin.

4.3. Rationale for dose selection

As per Atezolizumab Investigator's Brochure (IB) at the time of this study design (*version 15, July 2019*), the standard fixed dose of 1200, equivalent to 15mg/kg in a typical patient. No dose-limiting toxicities were observed at the 20 mg/kg dose level and the incidence and intensity of AEs reported have not been shown to be dependent on dose. A maximum tolerated dose has not been established. Atezolizumab is supplied in vials containing the fixed 1200 mg dose of drug substance, which minimizes the chance of overdose. Because the dose per patient is not based on weight or body surface area, and no dose calculation is required, the risk of overdose due to medication errors is minimal. The data available to date suggest that the potential for harm from overdose is very low.

Weekly gemcitabine with GC every 3-4 weeks is considered conventional first-line chemotherapy for aUC. Weekly split-dose cisplatin with wGC might be less toxic and have similar activity. Considering the probable lower nephrotoxicity of fractionated cisplatin, prospective evaluation of wGC might be warranted across cisplatin-eligible and -ineligible patients to develop a single chemotherapy template for the development of combinations with biological agents in a broad population of patients (*Maughan BL, et al. 2013*).

In conclusion, the proposed scientific rationale and the preliminary benefit-risk profile of the study treatments observed in previous trials support the further investigation of the combination in the patient population and dosification regimen chosen for this study.

4.4. Study Objectives

4.4.1. Primary Objectives

To evaluate the preliminary efficacy of atezolizumab plus split-dose gemcitabine and cisplatin (GC) for the first-line setting, in patients with histologically confirmed advanced (locally advanced and metastatic) urothelial cancer in terms of overall response rate (ORR) assessed by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

4.4.2. Secondary Objectives

Efficacy:

- To evaluate the *duration of response (DoR)* associated with the study treatment,

understood as the time from first confirmed response (CR or PR) to the date of the documented progressive disease as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.

- To determine the *overall survival (OS)* of patients with locally-advanced or mUC treated with the intended treatment regimen, understood as the time from first dosing date to the date of death. A subject who has not died will be censored at the last known date alive.
- To evaluate the *time to response (TtR)* associated with the study treatment, understood as the time from the first dose of the study treatment and confirmed response (CR or PR) based on RECIST 1.1 criteria.
- To evaluate the *clinical benefit rate (CBR)*, defined as the percentage of patients who have achieved complete response, partial response and stable disease. Stable disease should be maintained for at least 6 months to be considered as a CBR event.
- To determine the *progression-free survival (PFS)* of patients with locally-advanced or mUC treated with the intended treatment regimen, defined as the time from first dosing date until disease progression or death from any cause. Patients who have not progressed and start a new line of treatment will be censored.

Safety:

- To evaluate *safety* of the intended treatment regimen based on the frequency and severity of adverse events assessed by NCI CTCAE v5.0.

4.4.3. Exploratory objectives

- To explore potential correlation of efficacy with relevant potential prognostic factors/stratification factors
- To evaluate the relationship between the expression of PD-L1and microbiome with ORR and PFS during experimental treatment.

5. STUDY DESIGN

5.1. Study design

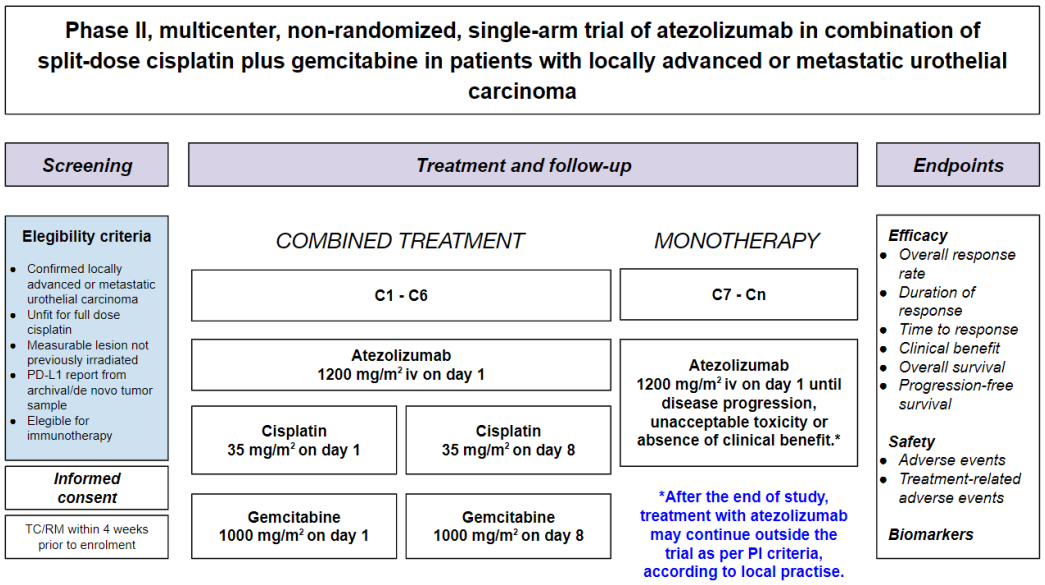
The AUREA study is a multicenter, open labelled, single arm, Phase II clinical trial of of atezolizumab in combination of split-dose cisplatin plus gemcitabine in patients with locally advanced or metastatic urothelial carcinoma (additional details on the eligibility criteria of the study are found in section 6 of this protocol).

The design includes screening phase, combined treatment initial phase, monotherapy treatment phase, follow-up phase and translational research with biopsies, blood samples and faecal samples.

The dose scheme includes the initial dose of atezolizumab (1200 mg) intravenously administered every 21 days (one cycle) up to disease progression, unacceptable toxicity or absence of clinical benefit. Dose adjustment or dose reductions of atezolizumab are not expected. Additional information on the treatment, modifications, and dose delays is available in section 7 of this protocol. AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation.

Study treatment will begin as soon as possible after signing the informed consent (as per ***section 5.2*** of this protocol) and inclusion will be completed as per ***section 5.3*** of this protocol.

Figure 1. Study design



5.2. Patient selection

Once all regulatory and sponsor requirements are completed confirming that the study is fully active in the corresponding site, informed consents can be offered to potential patients, and patient selection can start in this site.

5.3. Screening period and screening failure

Informed consent will be obtained prior to the start of the specified screening window. Procedures conducted as part of the subject's routine clinical management (e.g.., blood count determinations and imaging studies) prior to signing of ICF may be used for screening or for defining baseline data, provided these procedures are conducted as specified in the protocol.

Other procedures (such as the faecal sample collection) must be developed once the patient has provided the signed consent for participation.

Once ICFs are signed, a trial screening number will be assigned to each patient after registering at Electronic Data Capture (EDC) platform. Each site will receive access to the EDC platform to register each screened case because as per GCP guidelines, it is mandatory to register every patient who signs a consent form.

Furthermore, within the Investigator Site File (ISF), a Patient Identification List will be included in order to identify patients according to local normal practice. This document will allow for immediate and unequivocal identification of patients participating in this clinical trial.

This document will always be stored under Investigator staff custody at the site. The screening number will identify patients throughout the screening period while procedures needed to confirm the subjects' suitability for the trial protocol, such as clinical laboratory tests, imaging, and others are performed.

Screening determinations should be performed as per indications specified in ***Table 4*** include ICF signature, eligibility assessments, tumour characteristics, ECG, clinical evaluation (AE, PE, ECOG, VS, BMI, and symptom control), laboratory determinations (FBE, Biochemistry,

electrolytes, liver panel TF), Pancreatic enzymes, serology, urinalysis, pregnancy test, concomitant medication, biological samples (tumour sample, biomarkers), CT Scan / MRI. Availability of archival tumor blocks should be verified. Additional information about screening procedures can be found in ***Section 8.4*** of this protocol.

5.4. Patient registration/enrollment

After confirming that a patient fulfils all eligibility criteria of the study (***Section 6***, *study population*), site staff will initiate the electronic case report form (eCRF) registration procedure. Once registration has been completed, the site staff will receive the "Inclusion confirmation communication", and study treatment can be initiated as per ***Section 7*** *(treatment description*).

5.5. Treatment description, doses and schedules

During treatment, patients should be visited at baseline for administration of the study treatment (Day 1 of each cycle) as follows: Atezolizumab 1200 mg, gemcitabine 1000 mg/m^2 and cisplatin 35 mg/m^2. A second visit on day 8 (D8) should be compiled in order to administer the second dose of gemcitabine 1000 mg/m^2 and cisplatin 35 mg/m^2 cisplatin.

Atezolizumab will be administered first as a IV infusion according to what is detailed in section 7.4 of this protocol, followed by the cisplatin infusion and then the gemcitabine infusion. The GC infusion will start at least 30 minutes after completion of the atezolizumab infusion. At the investigator's discretion, atezolizumab may be administered over a longer infusion time (60 minutes) if the participant developed a prior infusion reaction.

This regimen will be repeated every three weeks (q3w) for up to 6 cycles. Once cycle 6 is done, Atezolizumab 1200 mg/m^2 will be administered as monotherapy every 3 weeks until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent or absence of clinical benefit. AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation.

All chemotherapy agents' preparation, premedication, administration, monitoring, and management of complications are to follow local prescription guidelines and regulations. The dose of chemotherapy may be capped per local standards.
All participants will be monitored continuously for adverse events (AEs) while on study treatment. Treatment modifications (eg, dose delay, reduction, retreatment, or discontinuation) will be based on specific laboratory and adverse event criteria, as described in ***Section 5.2*** and ***Section 5.3***.

Table 1. AUREA's trial treatment schedule

Drug	Drug	Frequency	Administration	Treatment period	Use

Atezolizumab	**1200 mg**	**Q3W**	**IV infusion**	**Day 1 of each cycle**	**Experimental**
Gemcitabine	**1000 mg/m^2/day**	**Q3W**	**IV infusion**	**Day 1 and Day 8 of each cycle up to 6 cycles**	**Experimental**
Cisplatin	**35 mg/m^2/day**	**Q3W**	**IV infusion**	**Day 1 and Day 8 of each cycle up to 6 cycles**	**Experimental**

5.6. Duration of study, recruitment, treatment and follow-up

- Enrolment/recruitment period: 12 months
- First patient first visit (FPFV): 8ENE2021
- Last patient last visit (LPLV): FPFV + 24 months
- Treatment period: Up to 24 months from LPFV
- Follow-up period: 24 months
- Planned end of study date: FPFV + up to 36 months

5.7. Determinations during the study

Determination during the study will be performed as per ***Table 4*** and ***Section 8.3*** of this protocol.

5.7.1. Screening phase

The baseline assessments and procedures should be performed within 28 days before inclusion, and when applicable, as close as possible to the start of study treatment.

5.7.2. Treatment phase

Before each treatment administration chemotherapy/atezolizumab administration laboratory, medical consulting and other determinations will be performed according to ***Table 4*** and ***Section 8.5*** to ensure that treatment can be safely administered.

A CT Scan or MRI will be performed at baseline, on week 9, week 18 and then every 12 weeks (q12w) ± 1w until objective disease progression as per PI's criteria or death (whichever comes first). Blood samples for biomarkers studies should be collected before administration of cycle 4 and at the time of PD (end of treatment if applicable).

For patients with progression reported as per RECIST criteria at week 9, continuity of treatment with atezolizumab should be evaluated by the PI of each site as per clinical benefit criteria.

5.7.3. Safety visit (after the end of treatment by any reason)

Safety follow-up visits will be scheduled up to 30 days after the last dose of study treatment (end of treatment).

5.7.4. Follow up until progression

After the end of the combined treatment with atezolizumab and split dose of gemcitabine and cisplatin, if the patient has finished treatment without progression and does not start a new treatment line, will be visited every 12 weeks. At the time of progression blood samples should be collected for biomarkers studies.

5.7.5. Follow up after progression

Overall, after progression, patients will continue the long-term follow up every 6 months until death or end of study. Sponsor will ask the survival status of all patients at the final clinical trial database closing, in order to maximise the median follow up of patients for overall survival data.

In cases where atezolizumab treatment has been maintained because of clinical benefit, follow up will comply with the "Follow up until progression" conditions, with visits every 12 weeks along with radiological evaluation/assessment of the disease.

5.8. End of study (EoS)

The end of study is defined as the Last Patient Last Visit (LPLV) and will be considered at 24 months after last patient first visit (LPFV), Sponsor will ask survival status of all patients at the final clinical trial database closing, in order to maximise the median follow up of patients for overall survival data.

5.9. Outcome assessments

5.9.1. Response evaluation according RECIST 1.1

All patients will have their best response according to RECIST criteria 1.1 from the start of study treatment until the end of treatment classified as outlined below:

- Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later.
- Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of tumour markers. Pathological lymph nodes must have short axis

measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Tumour markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.

- Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.
- Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment, for example where the tumour burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

5.9.2. Safety assessments

Safety parameters are AE, SAE, AESI, pregnancy, medication error, overdose. Additional safety information could be derived from ECG, lab test, pregnancy test, or vital sign exam. The assessment of adverse events will include the type of event (including symptoms, physical exam findings and laboratory abnormalities), the incidence, severity, timing, seriousness, and relatedness regarding the treatment under study. Adverse events will be recorded and reported in the corresponding section of the case report form. The grade of adverse events will be coded according to the National Cancer Institute's Common Toxicity criteria (NCI-CTCAE v5.0 scoring system). The worst toxicity score will be recorded. In case of SAE and AESI the investigator should immediately fill in the dedicated SAE form and send it by as detailed in ***Section 9.2***

6. STUDY POPULATION

6.1. Inclusion criteria

1. Male or female subjects ≥ 18 years old.

2. Written informed consent approved by the Independent Ethics Committee (IEC), prior to the performance of any trial activities.

3. Patients with histologically documented, locally advanced (T4B, any N; or any T, N2-3) or metastatic urothelial carcinoma (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).*

4. Patients should not be eligible (unfit) for full dose of cisplatin, in the investigator's judgement, based on:

   a. Age older than 70 years

   a. ECOG Performance status (PS) 2 or Karnofsky PS of 60 - 70% (only 15 patients will be included with ECOG 2)

   b. Measured creatinine clearance (ClCr) > 30 and < 60 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for the determination of creatinine clearance:

      Males:

      $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

      Females:

      $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

   c. Any other reason the physician considers but should specify in the CRF and discussed with the PI.

5. At least one measurable lesion through radiographic tumor evaluation (CT scan or magnetic resonance imaging) as defined by RECIST version 1.1, that has not been previously irradiated within 4 weeks prior to the study enrolment.

6. Patients with an archival or *de novo* tumor biopsy (representative formalin-fixed paraffin-embedded/FFPE paraffin block obtained as close as possible to the patient inclusion) with an associated pathology report, for testing of PD-L1 expression prior to study enrollment. Samples in unstained slides could be acceptable (at least 15 slides).

7. Patients with adequate normal organ and marrow function as defined below:

   a. Haemoglobin (Hb) ≥ 9.0 g/dL.
   b. Absolute neutrophil count (ANC) ≥ 1500 per mm^3.
   c. Platelet count ≥ 100,000 per mm^3.
   d. Serum bilirubin ≤ 1.5 X institutional upper limit of normal (ULN) unless liver metastases are present, in which case it must be ≤ 2X ULN. This will not

apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology); however, they will be allowed only in consultation with their physician.

e. Serum transaminases (ALT, AST and GGT) ≤ 2.5X institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 3X ULN.

8. No major active bleeding.

9. Female subjects of childbearing potential (not surgically sterile or at least 2 years postmenopausal) must provide a negative urine pregnancy test at screening, and use a medically accepted double barrier method of contraception (i.e. condom with spermicide + IUD or cervical caps). In addition, they must agree to continue the use of this double barrier method for the duration of the study and for 6 months after participation in the study.

10. Males should agree to abstain from sexual intercourse with a female partner or agree to use a double barrier method of contraception (i.e. condom with spermicide, in addition to having their female partner use some contraceptive measures such as oral contraceptive drugs, intrauterine device (IUD) hormonal contraception, or cervical caps), for the duration of the study and for 6 months after participation in the study

11. Willingness and ability of patients to comply with the protocol for the duration of the study including undergoing treatment as well as availability for scheduled visits and examinations including follow up.

6.2. Exclusion criteria

1. Prior treatment with any immune checkpoint inhibitor therapy (e.g., CTLA4, PD-1, or PD-L1 targeting agent).*

   **Note*: Prior adjuvant or neoadjuvant treatment with targeted therapy/checkpoint inhibitors is allowed, as long as the last dose was administered at least 12 months prior to the patient inclusion in this trial.

2. Presence of active second malignancy and/or prior malignancy in the last 2 years is allowed except for the following:
   a. adequately treated basal cell or squamous cell skin cancer,
   b. adequately treated Stage I or II cancer from which the patient is currently in complete remission per investigators' clinical judgment.

3. Patient receiving radiation therapy within 4 weeks before inclusion.

4. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

5. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis).

6. History of allogeneic organ transplant.

7. Subjects having a diagnosis of immunodeficiency or are receiving systemic steroid therapy or any other form of immunosuppressive therapy within 28 days prior to the first dose of trial treatment.

8. Current or prior use of immunosuppressive medication within 7 days prior to enrolment, except the following:
    a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);
        i. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;
        ii. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
9. The subject has uncontrolled, significant intercurrent or recent illness (within 6 months prior to inclusion) including, but not limited to, the following conditions:

    a. Cardiovascular disorders:
        i. Class 3 or 4 congestive heart failure as defined by the New York Heart Association, unstable angina pectoris, and serious cardiac arrhythmias.
        ii. Uncontrolled hypertension defined as sustained blood press > 150 mm hg systolic or > 100 mm hg diastolic despite optimal antihypertensive treatment.
        iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction, other ischemic event, or thromboembolic event (e.g., deep venous thrombosis [DVT] and pulmonary embolism) within 6 months before inclusion. Subjects with a more recent diagnosis of DVT are allowed if stable, asymptomatic, and treated with LMWH for at least 6 weeks before study treatment.

    b. Gastrointestinal disorders (e.g., malabsorption syndrome or gastric outlet obstruction) including those associated with a high risk of perforation or fistula formulation:
        i. Tumours invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.
        ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before inclusion. Note: complete healing of an intra-abdominal abscess must be confirmed prior to start of the treatment.

    c. Clinically significant hematemesis or hemoptysis of > 0.5 teaspoon (> 2.5 ml) of red blood or history of other significant bleeding within 3 months before treatment.

    d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation.

    e. Lesions invading major pulmonary blood vessels.

f. Other clinically significant disorders such as:
    i. Active infection requiring systemic treatment, infection with human immunodeficiency virus or acquired immunodeficiency syndrome-related illness, or chronic hepatitis B or C infection.
    ii. Serious non-healing wound/ulcer/bone fracture.
    iii. Malabsorption syndrome.
    iv. Moderate to severe hepatic impairment (child-pugh B or C).
    v. Requirement for hemodialysis or peritoneal dialysis.
    vi. Uncontrolled diabetes mellitus.

10. Major surgery (e.g., GI surgery and removal or biopsy of brain metastasis) within 8 weeks before inclusion. Complete wound healing from major surgery must have occurred 4 weeks before study treatment and from minor surgery (e.g., simple excision, tooth extraction) at least 10 days before study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

11. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

12. Any test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or chronic infection.

13. Women who are pregnant or are breastfeeding.

14. Male patients must be surgically sterile or must agree to use effective contraception during the period of therapy.

15. Any of the following within 6 months prior to study entry: myocardial infarction, uncontrolled angina, uncontrolled hypertension, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack.

16. Previously identified allergy or hypersensitivity to components of the study treatment formulations.

6.3. Criteria for withdrawal from the treatment and study

6.3.1. Permanent Interruption of study treatments

Any reason for discontinuing investigational products must be clearly recorded on the electronic case report forms (eCRF).

Patients will receive the product under investigation as per schedule described in section 5.5 of this protocol or until any of the following occurs:

- *Objective disease progression*. However, patients with disease progression at week 9 who are continuing to derive clinical benefit from the study treatment will be eligible to continue with single-agent atezolizumab, provided that the treating physician has determined that the benefit/risk for doing so is favorable;
- *Global deterioration of health status requiring discontinuation*;

- Unacceptable toxicity. If the unacceptable toxicity is attributed to one of the two study treatments, the investigator (in discussion with the sponsor) may continue treatment with the other study treatment;
- Investigator's decision;
- Pregnancy;
- Protocol violation, only when non-compliance might significantly impact in patients safety and/or trial results validity, as per case by case Sponsor assessment/criteria;
- Lost to follow-up;
- Patient refused further treatment (follow-up permitted by patient);
- Study terminated by sponsor;
- Death.

For all participants, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration' in the source data and in the eCRF.

A temporary interruption in study medication due to an AE is not considered to be permanent discontinuation from investigational product.

Tumor assessments for participants, who discontinue study treatment without radiographic progression, should continue as per protocol until radiographic progression is determined.

Chemotherapy dose reduction is allowed in study. Any participant with two prior dose reductions to one agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent. A participant who is discontinued from the chemotherapy treatment will remain on the study and receive atezolizumab.

If a participant meets criteria for discontinuation and the investigator is unable to determine whether the event is related to atezolizumab or chemotherapy, the participant should discontinue all treatments.

The assessment for discontinuation of atezolizumab should be made separately from the assessment made for discontinuation of chemotherapy. If criteria for discontinuation for atezolizumab are met before the first 6 atezolizumab + split-doses of gemcitabine and cisplatin chemotherapy cycles have been completed, the split-dose GC chemotherapy may continue until 6 cycles have been completed.

6.3.2. Withdrawal from the study

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw at any time.

The investigator may also, at his/her discretion, withdraw the subject from participating in this study at any time, or the sponsor may discontinue the study.

Reasons for early withdrawal from the study should be documented in the eCRF as:

- Study closed/terminated by sponsor;
- Lost to follow-up;
- Investigator's decision;
- Subject withdrew consent (refused further follow-up);
- Major protocol non-compliance. Protocol violation, only when non-compliance might significantly impact in patients safety and/or trial results validity, as per case by case Sponsor assessment/criteria;

- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstances, every effort should be made to document patient outcomes, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Date of withdrawal from the study, with reason for withdrawal, will be recorded on the eCRF. In the case of death, a death certificate should be obtained if possible, with the cause of death evaluated and documented.

Note: Patients withdrawn the trial for any reason, cannot enter again.

7. TREATMENT DESCRIPTION

For the purpose of this study, the investigational products as defined by (ICH E6 1.33) are atezolizumab, cisplatin and gemcitabine.

7.1. Study medication

7.1.1. Atezolizumab

Atezolizumab will be supplied as 60 mg/mL glass vials of 20-mL, nominal atezolizumab amount per vial, 1200 mg.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines.

The information on the study treatment will be in accordance with approved submission documents.

AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation.

7.1.2. Gemcitabine and Cisplatin

Gemcitabine and cisplatin will be supplied as per site clinical standards.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines, under commercial presentation and each site availability.

The information on the study treatment will be in accordance with approved submission documents.

7.2. Treatment accountability and compliance

According to local legislation, the investigator will record in the medical history that the patient is taking the medication as prescribed for each new cycle in the study.

7.2.1. Atezolizumab accountability and compliance

Atezolizumab will be dosed at the investigational site, compliance will be assessed by reviewing the consistency of information in the IWRS, the eCRF, patient records, nurse sheets, and in the pharmacy source documentation.

7.2.2. Gemcitabine and Cisplatin accountability and compliance

Compliance of the split-dose GC chemotherapy will be assessed by reviewing the consistency of information in the eCRF, patient records, nurse sheets, and in the pharmacy source documentation.

7.3. Preparation and Dispensing

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

Investigational products should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

7.3.1. Atezolizumab preparation and dispensing

Atezolizumab will be dosed at the investigational site. Atezolizumab must not be used for any purpose other than the trial. The administration of trial investigational products to patients who have not been enrolled into the trial is not covered by the trial insurance.

7.3.2. Gemcitabine plus cisplatin preparation and dispensing

The GC treatment will be administered in quantities appropriate for the study visit schedule and according to local practice. A qualified staff member will record all the study treatment using the local practise. Procedures described in each institution's pharmacy or hospital standard operating procedure manual should be followed when handling hazardous drugs.

7.4. Investigational Medical Products Administration

7.4.1. Atezolizumab administration

Atezolizumab will be administered after all procedures/assessments have been completed as described in the Schedule of Activities (***Table 4***), as a 1-hour IV infusion once every 3 weeks until disease progression, unacceptable toxicity or absence of clinical benefitt. AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation.

The infusions must not be administered as an intravenous push or bolus. The initial dose of atezolizumab must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Atezolizumab will be administered in IV infusion bags containing 0.9% sodium chloride (NaCl) and infusion lines equipped with 0.2 or 0.22 m in-line filters. The IV bag may be constructed of polyvinyl chloride, polyolefin, polyethylene, or polypropylene. The IV infusion line may be constructed of polyvinyl chloride, polyethylene, polybutadiene, or polyurethane and the 0.2 or 0.22 m in-line filter may be constructed of polyethersulfone or polysulfone. The use of administration supplies composed of materials other than those listed should be avoided if possible. Atezolizumab can be diluted to concentrations between 3.2 mg/mL and 16.8 mg/mL in IV bags containing 0.9% NaCl. Atezolizumab must be prepared/diluted under appropriate aseptic conditions as it does not contain antimicrobial preservatives.

The prepared solution for infusion should be used immediately to limit microbial growth in case of potential accidental contamination. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user. For flat or fixed dosing (1200 mg for

this clinical trial) in IV infusion bags, the dose solution may be stored at 2°C–8°C (36°F – 46°F) for 24 hours or at ambient temperature ≤ 25°C (77°F) for 8 hours. This time includes storage and time for administration for infusion.. Do not shake or freeze infusion bags containing the dose solution.

Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the Dosage and Administration Instruction contained in the Summary of Product Characteristics, and when applicable, the corresponding Pharmacy Guidelines.

Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. See more information in ***Appendix 1***.

7.4.1.1. Intrapatient Atezolizumab Dose Reduction

The dose amount required to prepare the atezolizumab infusion solution will be based on the corresponding flat dose of 1200 mg established in this protocol. Overall, Atezolizumab dose reduction for toxicity management is not permitted. Toxicity management (dose delay or discontinuation) in case of immune-mediated events is described in ***Appendix 1***.

7.4.2. Gemcitabine and cisplatin administration

The infusions must not be administered as an intravenous push or bolus. The estimated total infusion time for this treatment takes up to two hours for Day 1 and Day 8 of each 21-days cycle. Typically, IV hydration is given both before and after cisplatin and can add up to two hours on administration days. Infusion times may vary depending on physician preference or patient tolerability.

7.4.2.1. Gemcitabine administration

Gemcitabine will be administered after all procedures/assessments have been completed as described in the Schedule of Activities (***Table 4***), as a 30-minutes IV infusion on days 1 and 8 once every 3 weeks for a maximum of 6 cycles.

Gemcitabine is tolerated well during infusion and may be administered ambulant. If extravasation occurs, generally the infusion must be stopped immediately and started again in another blood vessel. The patient should be monitored carefully after the administration. Treatment omitted will not be reinstated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 ($x10^6$/l) and the platelet count reaches 100,000 ($x10^6$/l).

7.4.2.2. Cisplatin administration

Cisplatin should be administered by intravenous infusion over a period of 2 hours (up to 8 hours) on days 1 and 8 once every 3 weeks for a maximum of 6 cycles. Adequate hydration must be maintained from 2 to 12 hours prior to administration until minimum 6 hours after the

administration of cisplatin. Hydration is necessary to cause sufficient diuresis during and after treatment with cisplatin. It is realised by intravenous infusion of one of the following solutions specified on the SmPC.

7.4.2.3. Intrapatient Gemcitabine and Cisplatin Dose Reduction

According to the current version of Gemcitabine Summary of Product Characteristics (*Gemcitabine SmPC*) at the time of this study design (March 2020), dose modifications are considered in case of ***haematological toxicity*** as described below. For the matter of this study, information on dose modification recommendations for gemcitabine given in monotherapy or in combination with cisplatin for bladder cancer are described.

Dose modifications due to haematological toxicity: Initiation of a cycle
For all indications, the patient must be monitored before each dose for platelet and granulocyte counts. Patients should have an absolute granulocyte count of at least 1,500 (x 10^6 /l) and platelet account of 100,000 (x 10^6 /l) prior to the initiation of a cycle.

Dose modifications due to haematological toxicity: Within a cycle
Dose modifications of gemcitabine within a cycle should be performed according to ***Table 2***:

Table 2. Dose modification of gemcitabine within a cycle for bladder cancer, NSCLC and pancreatic cancer, given in monotherapy or in combination with cisplatin

Absolute granulocyte count (x 10^6/l)		**Platelet count (x 10^6/l)**	**Percentage of standard dose of Gemcitabine (%)**
> 1,000	**and**	**> 100,000**	**100**
500 - 1,000	**or**	**50,000-100,000**	**75**
<500	**or**	**< 50,000**	**Omit dose***

*Treatment omitted will not be reinstated within a cycle before the absolute granulocyte count reaches at least 500 (x106 /l) and the platelet count reaches 50,000 (x10^6 /l).

Dose modifications due to haematological toxicity: Subsequent cycles for all indications
The gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following hematologic toxicities (***Table 3***):

Table 3. Dose modification of gemcitabine in subsequent cycles for all indications

	Count (x 10^6/l)	**Time**	**Percentage of standard dose of Gemcitabine (%)**
Absolute granulocyte	**< 500**	**> 5 days**	**75**
	< 100	**> 3 days**	**75**
Platelet count	**< 25,000**	**Not applicable**	**75**
Febrile neutropenia	**-**	**-**	**75**
Cycle delay > 1 week to toxicity	**-**	**-**	**75**

Patients will be monitored closely for toxicity; Gemcitabine may be adjusted by dosing

interruption with or without dose reduction as indicated in ***Table 2*** and ***Table 3.***

Management of patients requiring more than 2 dose reductions of any of the IMPs (one dose level decrease at a time) should be discussed with the Coordinating Investigator.

Patients who have undergone dose reduction may also undergo dose re-escalation back to the previous dose level at the discretion of the Investigator in the absence of Grade ≥2 non-hematologic treatment-related toxicity for at least 28 days.

Cisplatin reduction will be followed as indicated for Gemcitabine reduction following the current version of Cisplatin Summary of Product Characteristics (Cisplatin SmPC).

No chemotherapy reduction as allowed in Cycle 1 Day 1.

7.5. Special Precautions for Investigational Medical Products

7.5.1. Special Precautions for Atezolizumab

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Pneumonitis secondary to PD1/PDL1 inhibitor drugs is a rare but potentially serious side effect, patients should be monitored for signs and symptoms of pneumonitis during physical examination (PE), and causes other than immune-mediated pneumonitis should be ruled out in the case of findings during PE.

7.5.1.1. Hepatic impairment

No dedicated studies of atezolizumab have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of atezolizumab between patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin 1.0 to 1.5 ULN and any AST, n=71) and normal hepatic function (bilirubin and AST ≤ ULN, n=401). No data are available in patients with either moderate (bilirubin > 1.5 to 3.0 x ULN and any AST) or severe (bilirubin > 3.0 ULN and any AST) hepatic impairment. Hepatic impairment was defined by the National Cancer Institute criteria of hepatic dysfunction. More information available in the current version of Atezolizumab Investigator's Brochure.

7.5.1.2. Renal impairment

No dedicated studies of atezolizumab have been conducted in patients with renal impairment. More information available in the current version of Atezolizumab Investigator's Brochure.

7.5.1.3. Reproductive and Developmental Toxicity

Reproductive and developmental toxicity studies with atezolizumab have not been conducted. The PD-L1/ programmed death 1 (PD-1) signaling pathway is well established as essential in maternal/fetal tolerance and embryo-fetal survival during gestation (*Guleria et al. 2005; Habicht et al. 2007; D'Addio et al. 2011*). Administration of atezolizumab is expected to have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality.

7.5.1.4. Immune-mediated adverse reactions

Most immune-mediated adverse reactions that occur during treatment with atezolizumab are reversible with the interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-mediated adverse reactions affecting more than one body system have been observed; these may occur after the last dose of atezolizumab.

For suspected immune-mediated adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical studies in patients whose immune-mediated adverse reactions could not be controlled with systemic corticosteroid use, the administration of other systemic immunosuppressants may be considered.

Atezolizumab must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones. Specific guidelines for the management of atezolizumab-specific adverse events is available in ***Appendix 1***.

1) Pulmonary events

Pneumonitis secondary to PD1/PDL1 inhibitor drugs is a rare but potentially serious side effect, patients should be monitored for signs and symptoms of pneumonitis during physical examination (PE), and causes other than immune-mediated pneumonitis should be ruled out in the case of findings during PE.

Cases of pulmonary events, including dyspnea, cough, fatigue and pulmonary infiltrates, have been observed in clinical trials with atezolizumab. Patients should be monitored for pulmonary signs and symptoms.

Treatment with atezolizumab should be withheld for Grade 2 pulmonary event , and corticosteroids equivalent 1 to 2 mg/kg/day oral prednisone should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 pulmonary events.

2) Hepatic events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in ***Appendix 1***.

3) Gastrointestinal events

Immune-mediated colitis has been associated with the administration of atezolizumab. All events of diarrhea or colitis should be thoroughly evaluated for other common etiologies. For events of significant duration or or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or

bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis. More information provided in ***Appendix 1***.

4) Endocrine events

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected.

Thyroid-stimulating hormone (TSH) and free triiodothyronine (T3) and thyroxine (T4) levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, GH, 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. More information provided in ***Appendix 1***.

5) Ocular events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). More information provided in ***Appendix 1***.

6) Immune-Mediated Myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab and should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type Natriuretic Peptide]) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope.

Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of 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 ***Appendix 1***.

7) Infusion-Related Reactions and Cytokine-Release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics, and/or

analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated infusion-related reactions, due to IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end -organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (*Rotz et al. 2017*; *Adashek and Feldman 2019*), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs during Cycle 1 and CRS are provided in ***Appendix 1***.

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

8) 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 ***Appendix 1***.

9) Dermatologic events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in ***Appendix 1***.

10) Neurologic Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor

neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in ***Appendix 1***.

11) Immune-Mediated Meningoencephalitis

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness.

Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process. All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in ***Appendix 1***

12) Renal events

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in ***Appendix 1***.

13) Immune-Mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase/CK increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

14) Severe Cutaneous Adverse Reactions (SCAR)

SCARs are a heterogeneous group of immunologically mediated drug eruptions. Although rare, these events are potentially fatal, and mainly constituted by erythema multiforme, acute generalised exanthematous pustulosis, Stevens-Johnson syndrome (SJS), Toxic Epidermal

Necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS). As per epidemiology data, the incidence of SJS and TEN ranges from 0.8 to 5.3 and 1.2 to 6 per million person-years respectively.

A cumulative analysis of the company safety database across the TECENTRIQ (atezolizumab) program identified at total of 99 cases of SCARs, of which 36 were confirmed by histopathology or specialist diagnosis, in patients who have received TECENTRIQ (atezolizumab). Approximately 23,654 clinical trial patients and 106,316 patients in post-marketing settings have been exposed to TECENTRIQ (atezolizumab) as of 17 May 2020. The incidence rates of SCAR, regardless of severity, from pooled atezolizumab monotherapy (N=3178) and combination therapy (N=4371) company sponsored clinical studies were 0.7% and 0.6% respectively. One fatal case of TEN was reported in a 77 year old female patient who received atezolizumab monotherapy.

Patients with signs and symptoms of SCAR should be treated according to the guidelines in ***Appendix 1***.

7.5.2. Special Precautions for Gemcitabine

Prolongation of the infusion time and increased dosing frequency have been shown to increase toxicity. Further information on particular risk for toxicity (including haematological toxicity, hepatic insufficiency, concomitant radiotherapy, live vaccinations, cardiovascular risk, pulmonary effects, renal, fertility or sodium control are displayed in the Gemcitabine SmPC.

7.5.3. Special Precautions for Cisplatin

This agent should only be administered under the direction of oncologists in specialist units under conditions permitting adequate monitoring and surveillance. Supportive equipment should be available to control anaphylactic reactions.

Cisplatin reacts with metallic aluminium to form a black precipitate of platinum. All aluminium containing IV sets, needles, catheters and syringes should be avoided. The solution for infusion should not be mixed with other drugs or additives.

Appropriate monitoring and management of the treatment and its complications are only possible if adequate diagnosis and exact treatment conditions are available.

Further information on particular risks including nephrotoxicity, neuropathies, ototoxicity, allergic reactions, hepatic function and haematological formula, carcinogenic potential, injection site reactions are displayed in the Cisplatin SmPC.

7.6. Investigational Product Storage

The investigational products should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational products are only dispensed to study participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Storage conditions stated in the SRSD (ie, IB) will be superseded by the storage conditions stated on the label. Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery.

The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct patients on the proper storage requirements for take-home investigational products.

7.6.1. Atezolizumab storage

Atezolizumab must be refrigerated at 2°C - 8°C (36°F - 46°F) upon receipt until use. Atezolizumab and the diluent vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab Drug Product or the diluent; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial. Vial contents should not be frozen or shaken and should be protected from light by keeping the vial in the outer carton. This information is also available in the pharmacy manual.

7.6.2. Gemcitabine and cisplatin storage

Gemcitabine and cisplatin must be stored and controlled as specified in the product label.

7.7. Investigational Product Accountability

The delegated investigation site staff must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All bottles of study drug

must be returned to the investigator by the patient at the end of each cycle and at the end of the trial, the sponsor will provide instructions as to the disposition of any unused investigational product if the investigative site is unable to destroy at site per local procedures.

7.8. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product Atezolizumab (e.g., at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor, and all destruction must be adequately documented.

7.9. Concomitant Treatments

Medications or vaccinations specifically prohibited in the Exclusion Criteria are also not allowed during the active treatment period, except for the administration of inactivated influenza vaccine.

If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from study therapy or medication/vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication/vaccination schedule requires the mutual agreement of the investigator, the sponsor, and the patient.

Concomitant treatment considered necessary for the patient's wellbeing may be given at the discretion of the treating physician. All concomitant treatments, blood products, as well as non-drug interventions received by patients from screening until the end of study visit will be recorded on the CRF.

Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (e.g., antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (e.g., transfusions).

Concurrent anticancer therapy with agents other than atezolizumab and GC are not allowed. Medications intended solely for supportive care (i.e., antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

7.9.1. Inhibitors and Inducers of CYP Enzymes

Because antibodies are cleared principally by catabolism (i.e., cleavage to small peptides and amino acids), atezolizumab is not expected to show pharmacokinetic interactions with other drugs, and is therefore not expected to interact with other drugs through protein binding, effects on cytochrome P450 activity, renal excretion or competition for common drug transporter proteins. No formal pharmacokinetic drug interaction studies have thus been undertaken with atezolizumab.

7.9.2. Concomitant Surgery

No specific information on the effect of Atezolizumab on wound healing are reported in the current version of IB nor SmPC.

7.9.3. Concomitant Radiotherapy

Toxicity of concurrent administration of gemcitabine (simultaneous or ≤ 7 days apart) depends on many different factors, including the dose of gemcitabine, the frequency of gemcitabine administration, radiation dose, radiotherapy planning technique, tissue to radiate and the theoretical irradiation volume. For the matter of this study, radiotherapy within 4 weeks prior to inclusion is considered an exclusion criteria.

For non-concurrent gemcitabine administration (administered> 7 days apart), data analysis does not indicate an increased toxicity when gemcitabine is administered at least 7 days before

or after radiotherapy, except for late skin toxicity. The data that can be started administration of gemcitabine when the acute effects of radiation therapy have resolved or at least one week after radiation therapy. Radiation injury has been detected in irradiated tissues (e.g. esophagitis, colitis, and pneumonitis) in association with both concurrent and non-concurrent use of gemcitabine. Further information can be obtained in the current version of Gemcitabine SmPC.

7.9.4. Other Prohibited Concomitant Medications and Therapies

Clarifications about Steroid Use: Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes (*Schleimer RP, et al. 1984; Khan MM, 2008*).

Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressants such as steroids will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA4 compounds indicate that short-term use of steroids may be employed without compromising clinical outcomes (*Weber JS, et al. 2012*).

Therefore, the use of steroids during this trial is restricted as follows:

- *Therapeutic use:* for the treatment of infusion-related reactions and short-term treatment of irAEs, steroids are permitted according to the modalities indicated in ***Appendix 1***.
- *Physiologic use:* steroid replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.
- *Prophylactic use*, e.g., for the prevention of acute infusion-related reactions, is prohibited, ***except*** prior to CT or MRI.

7.10. Rescue Medications and Supportive Care

7.10.1. Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- *Diarrhea:* All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- *Nausea/Vomiting*: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

- *Anti-infectives:* Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice. Prophylactic administration should be considered for the cases outlined in ***Appendix 1***.

- *Anti-inflammatory or narcotic analgesics* may be offered as needed. Acetaminophen/paracetamol to a maximum total daily dose of 2 g is permitted. Daily

intake over 2 g is prohibited.

- Patients who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, coumadin or other coumarin derivatives or other anticoagulants (including direct Xa inhibitors) may be allowed; however, appropriate monitoring of prothrombin time/international normalized ratio (PT/INR) should be performed.

8. STUDY PROCEDURES AND EVALUATIONS

8.1. Definition of efficacy variables

- *Overall Response Rate (ORR):* Assessed by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. This will be considered as the percentage/proportion of patients with confirmed complete response (CR) or partial response (PR) as their overall best response throughout the study period.

- *Duration of response* (DoR): Time from first confirmed response (CR or PR) to the date of the documented PD as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.

- *Time to response* (TtR): Time from first dosing date to the date of the documented ORR as determined using RECIST 1.1 criteria.

- *Progression-Free Survival* (PFS): Time from first dosing date to the date of confirmed PD. A subject who has not died will be censored at the last known date alive. PFS rate will be assessed through the proportion of patients free of PD at the end of follow-up.

- *Clinical benefit (CB)*: Percentage/proportion of patients with complete response (CR) or partial response (PR) or maintained stable disease (SD) as their overall best response throughout the study period, assessed by imaging follow-up (CT scan/MRI), on week 9, week 18 and then, every 12 weeks.

- *Overall Survival* (OS): Time from first dosing date to the date of death and the proportion/percentage of patients alive at the end of follow-up. A subject who has not died will be censored at the last known date alive. Survival will be assessed by recording patient status at each visit according to ***Table 4***. Long term follow up to be performed every 6 months.

8.2. Safety and tolerability

Safety assessments: Safety parameters are AE, SAE, AESI, pregnancy, medication error, overdose. Additional safety information could be derived from ECG, lab test, pregnancy test, or vital sign exam.

The assessment of adverse events will include the type of event (including symptoms, physical exam findings and laboratory abnormalities), the incidence, severity, timing, seriousness, and relatedness regarding the treatment under study. Adverse events will be recorded and reported in the corresponding section of the case report form. The grade of adverse events will be coded according to the National Cancer Institute's Common Toxicity criteria (NCI-CTCAE v5.0 scoring system). The worst toxicity score will be recorded. In case of SAE and AESI the investigator should immediately fill in the dedicated SAE form and send it by as detailed in ***Section 9.2.***

- *Adverse events (AE) assessment:* type, frequency, outcome of adverse events.

- *Treatment-related AEs:* An event is assessed as related to study treatment when there is a reasonable possibility that study treatment caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between study

treatment and the event. This event is called a suspected adverse reaction. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

- *Serious adverse events (SAEs)* assessment: type, frequency, grade, outcome, relation with study treatment, all considering the total number and proportion based on the intention-to-treat and per protocol populations.

8.3. Study determinations

Table 4 details the study determinations to be performed and the corresponding timeline.

Table 4. Study determinations

Visit	SCR	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7 up to Cycle N	Safety Visit	PFS FU	EOS FU
Timeline	**≤ 28 D prior to inclusion**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**within 30d after EOT**	**Q12W**	**Q6 months**
Visit window		**+/- 3d**												**Q3W +/-3d**	**+/-3d**	**+/- 7d**	
Clinical Assessments																	
Informed consent	x																
Medical History (Medical and oncology specific)	x																
Physical Exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
ECOG	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Contraception check	x	x		x		x		x		x		x		x	x		
Vital signs (BP, PR)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Laboratory and biological sample studies																	
Archival tumor block	x																
Blood collection (biomarkers)	x							x						x (D1C7)		x at DP	
Faecal sample (biomarkers)	x							x								x at DP	
Coagulation	x	x		x		x		x		x		x	x	x	x		
Hematology*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Blood chemistry*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Thyroid function	x	x		x		x		x		x		x		x	x		
HBV/HCV test	x																
Pregnancy test (serum/urine)	x	x		x		x		x		x		x		x	x		
Urinalysis	x	x		x		x		x		x		x		x	x		
Cardiac monitoring																	
ECG	x	**If clinically indicated**													x		

FEVI	**x**	**If clinically indicated**												**x**		
Disease assessment																
Tumor evaluation	**x**		**On week 9 , week 18 (prior starting atezolizumab monotherapy and every 12 weeks +/-7 days thereafter until the of objective disease progression or death (whichever comes first)**													
Survival assessment																**x**
IMP follow-up																
Treatment dosing compliance		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**		
Chemotherapy administration		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**			
Atezolizumab administration		**x**		**x**		**x**		**x**		**x**		**x**		**x**		
Concomitant medications	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
New systemic cancer treatment															**x**	**x**
Safety assessment																
Adverse events	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**		

D: Day/s; Q3W: Every 3 weeks; Q12W: Every 12 weeks; EOT: End of treatment; PFS: Progression-free survival; EOS: End of study.

Informed consent: Informed consent of study procedures may be obtained prior to the screening. If laboratory or imaging procedures were performed for different reasons prior to signing consent, these can be used for screening purposes with the consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of inclusion.

Medical History: Should include information on prior systemic adjuvant or neoadjuvant therapy regimens, surgery and radiation therapy. Comorbidities: cardiovascular disease, previous cancer and diabetes, pulmonary disease, dementia, etc.

Physical exam: Includes an examination of major body systems and weight (height at screening only). Additional PE may be performed as clinically indicated. During the physical examination, a stethoscope will be used to carefully auscultate the lungs, additional respiratory functional tests should be performed as per local practise when suspecting pneumonitis (more information is provided in annex 1 of this protocol).

ECOG PS: ECOG may be recorded by telephone if the patient is not coming to site for other reasons.

Contraception check: Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his/her designee will instruct the patient to call immediately if one or both contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

Vital signs: To include blood pressure (BP) and pulse rate (PR). Body weight is to be recorded at each visit along with vital signs.

Laboratory Studies:** Complete blood count that includes total white blood cell count with leukocyte formula, Hb, and platelet count. The analytical studies may be performed up to 72 hours before the scheduled visits in order to have the results at the time of the patient's visit. ***During the first 6 cycles of treatment with split doses of gemcitabine plus cisplatin, complete blood count and biochemistry (liver, renal and electrolytes) on D1 and D8are mandatory for patient safety assurance and treatment continuation. Biochemistry tests include albumin, alkaline phosphatase, lactate dehydrogenase (LDH), calcium, magnesium, phosphorus, sodium, potassium, creatinine, creatine kinase, direct bilirubin, indirect bilirubin, total bilirubin, total protein, urea, uric acid, amylase, lipase, and glucose tests. Liver test panel functions include alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT) tests. Tests for pancreatic enzymes include lipase, protease (optional), amylase, and trypsinogen (optional) tests. If screening clinical chemistry and haematology assessments are performed within 3 days prior to day 1 (first infusion day), they do not need to be repeated at day 1.

Faecal samples: Specimens will be collected at baseline (before start of treatment), Cycle 4 Day 1 and after progression; the sample must be processed and retained in the local laboratory until Sponsor indications for shipment.

Thyroid Function: TSH and free T4.

HBV/HCV test: Serology including HIV, hepatitis B (HBsAg and anti-HBc), and hepatitis C virus (HCV).

Pregnancy test (serum/urine): For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of the study drug, and every 4 weeks thereafter. Pregnancy tests may occur on day 1, but the results must be available and reviewed by the treating physician or investigator prior to commencing an infusion.

Urinalysis: Protein, glucose, blood, Urine dipstick/other semiquantitative method, for urine protein: if ≥ 2+, collect 24-hour.

ECG: 12-lead ECG. Any clinically significant abnormalities detected require triplicate ECG results.

FEVI: MUGA Scan or ECHO, the technique used at screening will be consistently used throughout the study, in the following assessments.

Tumor assessments: CT scan or MRI is to be performed at baseline, on week 9, on week 18 and q12w ± 1w until the confirmation of objective disease progression or death (whichever comes first). The same imaging technique used to characterize each identified and reported lesion at screening will be employed in the following tumor assessments. This schedule must be followed regardless of any delays in dosing, in case of suspected pseudo-progression; treatment should be continued until progression of disease is confirmed from the imaging results. RECIST assessments will be performed on images from CT scans (preferred) or MRI, each preferably with IV contrast of the neck, chest, abdomen (including liver and adrenal glands), and pelvis. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of inclusion and, ideally, should be performed as close as possible to and prior to the start of treatment. CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response. Assessment of response will be performed using RECIST 1.1. If radiologic imaging shows disease progression, the confirmatory scans should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of PD (in the absence of clinically

significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessment at the next scheduled visit.

Treatment dosing compliance: Study drug compliance will be assessed by the Investigator and/or study personnel at each patient's visit, and it will be captured in the patient's records as part of source documentation at each patient's visit. Corresponding drug administration information will be reported also in the eCRF.

Chemotherapy dispensing/administration: Results for LTFs, electrolytes, and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or investigator prior to dosing. Specific details on haematological and renal function parameters for treatment interruption and resuming are detailed in the gemcitabine and cisplatin administration section.

Atezolizumab dispensing/administration: Every 3 weeks until PD or unacceptable toxicity. Continuation of atezolizumab treatment could be considered for patients who have been reported with PD on the week 9 radiological evaluation but, according to the PI's criteria, might be considered as with clinical benefit.

Adverse events: Adverse events should be documented and recorded at each visit using NCI-CTCAE v5.0. AEs (serious and non-serious) should be recorded in the eCRF and patient records, from the time the patient has taken at least 1 dose of study treatment through and including 90 calendar days after the last dose of IMP. If a patent begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. For SAEs, the active reporting period to Sponsor or it designated, begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in this study, through and including 90 calendar days after the last administration of the investigational products.

Concomitant medications: Concomitant medication will be recorded from 28 days prior to start of study treatment and up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (i.e., antiemetics treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (e.g. transfusions).

Biomarker study: Archival Tumor block at baseline and processed blood samples at baseline, day 1 of cycle 7 (D1), and at EOT/progression. Blood samples should be obtained in all patients at the time of EOT (even by toxicity without progressing) and samples are to be stored at site at -80 ºC and are to be sent at the end of study (1 dry ice shipment per site).

New systemic cancer treatment: Information on subsequent treatments should include the list of post-treatment therapies, drugs administered, and the date of initiation and discontinuation of each drug, and the corresponding disease progression date (if applicable). All the data will be recorded in the medical record and in the eCRF.

Survival assessment (EOS): After progression, the patient will be followed for survival until death, loss of follow-up, total patient consent withdrawal (refusing to any trial procedure), or end of study. Patient long term follow-up to determine status (alive, death, loss of follow up, etc.) may be performed by phone, if the patient is not coming to the clinic due to other reasons. The investigator must document in writing the results of the phone call in the patient records and in the eCRF.

8.4. Determinations in the selection phase (screening and baseline determinations)

Within 28 days prior to inclusion:

- Informed consent
- Medical History (Medical and oncology specific)
- Archival tumor block
- HBV/HCV test
- ECG
- FEVI
- Tumor assessment
- Thyroid function
- Urinalysis

Within 3 days prior to inclusion (not needed to be repeated if it is performed within 3 days to treatment initiation)

- Physical Exam
- ECOG
- Contraception check

- Vital signs (BP, PR)
- Coagulation
- Hematology
- Blood chemistry
- Pregnancy test (serum/urine)
- Blood collection (biomarkers)
- Faecal sample collection (biomarkers)
- Adverse events
- Concomitant medications

8.5. Determinations and procedures during the treatment period (up to cycle 6)

8.5.1. Day 1 (considering 3 week cycles)

- Physical Exam
- ECOG
- Contraception check
- Vital signs (BP, PR)
- Coagulation
- Hematology
- Blood chemistry
- Thyroid function
- Pregnancy test (serum/urine)
- Urinalysis
- Adverse events
- Concomitant medications
- Treatment dosing compliance
- Atezolizumab administration
- Split doses of gemcitabine and cisplatin administration

8.5.2. Day 8 (considering 3 week cycles)

- Physical Exam
- ECOG
- Vital signs
- Hematology
- Blood chemistry
- Adverse events
- Treatment dosing compliance
- Concomitant medication
- Split doses of gemcitabine and cisplatin administration

8.5.3. Other determinations during treatment

- **Tumor assessment:** On week 9, week 18 (prior starting atezolizumab monotherapy and every 12 weeks +/-7 days thereafter until the confirmation of objective disease progression or death (whichever comes first).
- **Safety determinations:** Hematology and Blood chemistry (including renal function assessment with urea and creatinine) should be evaluated weekly during the first 6 cycles of treatment as per recommendations for gemcitabine treatment.
- **When clinically indicated:** ECG, and FEVI.

8.5.4. Determinations and procedures on day 1 of cycle 7 (D1-C7) and subsequent cycles (D1-Cn)

- Physical Exam
- ECOG
- Contraception check
- Vital signs (BP, PR)
- Coagulation
- Hematology
- Blood chemistry
- Thyroid function
- Pregnancy test (serum/urine)
- Urinalysis
- Treatment compliance dosing
- Atezolizumab administration
- Concomitant medication
- Adverse event

When clinically indicated: *urinalysis, ECG, and FEVI.*

Additionally at D1-C7:

- Blood collection (biomarkers) only D1 C7.
- Tumor assessment: CT Scan or MRI prior to D1C7 (on week 18 from treatment starting).

When applicable

- ***Tumor assessment:*** *CT Scan or MRI is to be performed on week 9, week 18 and every 12 weeks until the confirmation of objective disease progression or death (whichever comes first).*
- ***When clinically indicated:*** *ECG, and FEVI.*

8.6. Determinations at safety visit

- Physical Exam
- ECOG
- Contraception check
- Vital signs (BP, PR)
- Coagulation
- Hematology
- Blood chemistry
- Thyroid function
- Pregnancy test (serum/urine)
- Urinalysis
- ECG
- FEVI
- Adverse events
- Concomitant medications

8.7. Follow-up determinations

8.7.1. Follow up after end of treatment (prior PD)

Every 12 weeks:

- **Tumor assessment:** CT Scan or MRI is to be performed on week 9, week 18 and every 12 weeks until the confirmation of objective disease progression or death (whichever comes first).
- New systemic cancer treatment.
- **By the time of disease progression,** Blood collection (biomarkers)

8.7.2. Follow up after end of treatment (after PD)

Every 6 months:

- New systemic cancer treatment
- Survival assessment

9. SAFETY EVALUATION

ICH GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

Any event involving adverse drug reactions (ADR), illnesses with onset during the study or

exacerbations of pre-existing illnesses should be recorded.

In addition, clinically significant changes in physical examination findings and abnormal objective test findings (e.g., x-ray, ECG) should also be recorded as AE. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- test result is associated with clinically significant symptoms, and/or
- test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
- test result leads to any of the outcomes included in the definition of a SAE, and/or test result is considered to be an AE by the investigator.

9.1. Definitions

The definitions from ICH GCP apply in this trial protocol.

9.1.1. Adverse event (AE)

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject which does not necessarily have a causal relationship with the study treatment.

Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

9.1.2. Atezolizumab Adverse Event of Special Interest

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 9.2 for reporting instructions).

Adverse events of special interest for this study are as follows:

- 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.
- Suspected transmission of an infectious agent by the study treatment, as defined below
- Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

9.1.3. Laboratory Abnormalities

All laboratory data required by this protocol and any other clinical investigations will be reviewed. Any abnormal value that leads to a change in subject management (eg, dose reduction or delay or requirement for additional medication or monitoring) or that is considered to be of clinical significance by the Investigator will be reported as an AE or SAE as appropriate, unless this value is consistent with the subject's present disease state or is consistent with values obtained prior to entry into the study.

9.1.4. Medication errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, the wrong patient at the wrong time, or at the wrong dosage strength.

Such medication errors occurring to a study participant are to be captured on the eCRF, and reported through the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.
Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AEs are captured on an AE CRF page.

The guidance on reporting of medication errors also applies to the reporting of overdose.

9.1.4.1. Atezolizumab overdose

The standard fixed dose of Atezolizumab is 1200 mg is equivalent to 15 mg/kg in a typical patient. No dose-limiting toxicities were observed at the 20 mg/kg dose level and the incidence and intensity of AEs reported have not been shown to be dependent on dose. A maximum tolerated dose has not been established.
Atezolizumab is supplied in vials containing the fixed 1200 mg dose of drug substance, which minimizes the chance of overdose. Because the dose per patient is not based on weight or body surface area, and no dose calculation is required, the risk of overdose due to medication errors is minimal.
The data available to date suggest that the potential for harm from overdose is very low.

9.1.4.2. Gemcitabine overdose

There is no known antidote for overdose of gemcitabine. Doses as high as 5700 mg/m2 have been administered by intravenous infusion over 30-minutes every 2 weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

9.1.4.3. Cisplatin overdose

An acute overdose of cisplatin may result in renal failure, liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, untreatable nausea and vomiting and/or neuritis. An overdose may be fatal.

There is no specific antidote in the event of an over dosage of cisplatin. Even if haemodialysis is initiated 4 hours after the overdose it has little effect on the elimination of cisplatin from the body following a strong and rapid fixation of cisplatin to proteins.

Treatment in the event of an overdose consists of general support measures.

9.1.5. Adverse reaction (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered.

9.1.6. Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that at any dose:

1. Results in death (is fatal),
2. Is life-threatening,
3. Requires or prolongs inpatient hospitalization,
4. Results in persistent or significant disability or incapacity,
5. Is a congenital anomaly or birth defect, or
6. Is medically significant.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE.

Medical and scientific judgement should be exercised in deciding whether urgent reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the above definition.

Any suspected transmission of an infectious agent through the medication is also considered a SAE.

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; 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 9.2 for reporting instructions).

9.1.7. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in the previous sections, and will be handled as SAEs in the safety database.

9.1.8. Life Threatening Event

It is any event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

9.1.9. Hospitalization / Prolongation of Hospitalization

Any event requiring hospitalization (or prolongation of hospitalization) that occurs or worsens during a patient's participation in a clinical study must be reported as a serious adverse event. Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the investigator or treating physician.

Hospitalizations that do not meet the criteria for serious adverse event reporting are:

1. Reasons described in protocol (e.g., drug administration, protocol-required investigations). Hospitalizations or prolonged hospitalization for a complication of therapy administration or procedures will be reported as a Serious Adverse Event.
2. Hospitalization or prolonged hospitalization for technical, practical or social reasons, in the absence of an adverse event.
3. Pre-planned hospitalizations (i.e., planned before study entry). Any surgery or procedure planned before study entry must be documented on the case report form.

9.1.10. Unexpected adverse event (not listed)

An unexpected AA, whose nature or severity does not correspond to the product information. The reference documents to establish the expectedness will be:

- Atezolizumab, last version of Investigator Brochure available for the Sponsor
- Gemcitabine, last version of the SmPC.
- Cisplatin, last version of the SmPC.

9.1.11. Adverse Event Associated With the Use of the Drug (Adverse Reaction)

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting

requirements, if applicable.

For combination treatments, causality assessment will be performed for each of the individual drugs included in the combination.

An adverse event is considered associated with the use of the drug (Adverse Reaction) if the attribution is possible, probable, or very likely by the definitions listed below.

9.1.12. Attribution Definitions

Not Related
An adverse event that is not related to the use of the drug.

Doubtful
An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible
An adverse event that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable
An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by de-challenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

9.1.3. Intensity (Severity) Criteria

The intensity of AEs will be classified using the Common Terminology Criteria for AEs of the National Cancer Institute, version 5.0 (NCI-CTCAE) and will be recorded in detail as instructed in the eCRF. If an AE occurs that is not listed in the NCI-CTCAE V5.0 classification system, the 5-point scale detailed below will be used instead:

- Mild: General malaise, without interruption of normal daily activity.
- Moderate: Sufficient general malaise to reduce or affect normal daily activity.
- Severe: Incapacity for work or the development of normal daily activity.
- Life threatening or disabling: Represents an immediate threat to life.
- Death: AE-related.

Grade

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 (v5.0), 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 9.2 for reporting instructions), per the definition of serious adverse event in Section 9.1.

9.1.14. Exposure during Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, within 5 months after the last dose of atezolizumab , or within 6 months after the last dose of atezolizumab, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).

Any pregnancy that occurs in a female partner of a male study participant should also be reported to the sponsor within 24 hours of becoming aware. Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if his partner becomes pregnant during the chemotherapy treatment period or within 6 months after the last dose of chemotherapy. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

In both cases, the investigator must immediately notify the Sponsor Pharmacovigilance Office by sending the Pregnancy form (see ISF).

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, study discontinuation must be reported following the before procedure described during at least 1 year after child-bearing.

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)

or abortion should be reported as a SAE.

9.1.15. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.
An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

9.1.16. Expedited reporting

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report all serious adverse events that are unlisted (unexpected) and be associated with the use of the study drug. The sponsor must report these events to investigators and competent authorities in accordance with current regulations.

9.2. Collection and reporting of Adverse Events information

The sponsor will collect AEs up to 30 days after administration of the last dose of study drug.

All adverse events must be recorded using medical terminology in the source document and the eCRF. Investigators must assess the severity (grade) of the event following NCI-CTCAE V 5.0 Criteria and assign a relationship to study therapy and pursue and obtain information adequate both to determine the outcome and to assess whether it meets the criteria for classification as a SAE requiring immediate notification. The investigator must provide any information as requested by the sponsor in addition to that on the eCRF.

Any serious adverse event which occurs from patient informed consent signature, during the clinical study or within 90 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported. Beyond this period of time, only those SAEs suspected to be related to the study drug will be reported.

All SAEs suspected to be related to study treatment should be followed after the treatment/study withdrawal until the event or its symptoms have resolved or stabilized at a grade acceptable to the Investigator, Chief investigator and/or Sponsor.

Site staff should notify the sponsor, all the pregnancies of female subjects and female partners of male subjects that occurred during the clinical trial within 24 hours from becoming aware. Site staff should also communicate the outcome of the pregnancy within 24 hours since the awareness.

The cause of death of a deceased patient in a clinical trial, whether the case of an expected event or associated with the investigational agent, is considered an SAE and therefore must be

communicated using the SAE form. The autopsy report should be sent to Sponsor identified only with the patient inclusion number.

[redacted]

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to [redacted]

All SAEs suspected to be related to study drug must be followed up after the time of therapy discontinuation until the event or its consequences resolve or stabilize at an acceptable level for the investigator, the Trial Chief Investigator and/or Sponsor.

Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

10. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the Sponsor.

This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

10.1. Sample size calculation

Fleming's phase II procedure (*Fleming TR, 1982*) will be used. The null hypothesis that the smallest response probability is 0.3 will be tested against a one-sided alternative. In the first stage, 46 patients will be accrued. An intermediate analysis will be performed once these first 46 patients reach 6 months after study treatment initiation. If there are 16 or fewer responses in these 46 patients, the study will be stopped. This intermediate analysis is established as a cut-off point to stop the study if the benefit for the patient in terms of objective response does not justify its continuation with sufficient clarity. If there is no preliminary evidence in the first 46 patients, which allows enough statistical power to reject the null hypothesis, the recruitment will stop as it is considered that the efficacy of the treatment is not sufficient to justify the inclusion of more patients. Otherwise, 20 additional patients will be accrued for a total of 66. The null hypothesis will be rejected if 25 or more responses are observed in 66 patients. This design yields a type I error rate of 0.05 and power of 0.9 when the true response rate is 0.5.

Variables	Descriptions
α	Probability of type I error: 0.05
β	Probability of type II error: 0.1
p_0	Response Probability of Poor Drug (P0) ---> 0.30
P1	Response Probability of Good Drug (P1) ---> 0.50
Nmax	Maximum number of patients to be recruited: 66
Numstage	Number of stages in Phase II clinical trial: 2
n_i	Number of patients to be recruited in stage i= 46
R1	Upper Limit For 1st Stage Rejection of Drug (r1)= 16
R	Upper Limit for 2nd Stage Rejection of Drug (r)= 25

10.2. Study endpoints

10.2.1. Primary endpoint

Overall Response Rate (ORR): Percentage/proportion of patients with confirmed complete response (CR) or partial response (PR) as their overall best response throughout the study period.

10.2.2. Secondary endpoints

Efficacy endpoints:

- ***Duration of response*** **(DoR):** Time from first confirmed response (CR or PR) to the date of the documented PD as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.
- ***Time to response*** **(TtR):** Time from first dosing date to the date of the documented ORR as determined using RECIST 1.1 criteria.
- ***Clinical benefit*****:** Percentage/proportion of patients with confirmed complete response (CR) or partial response (PR), or stable disease (SD) as their overall best response throughout the study period.
- ***Overall Survival*** **(OS)**
    - Time from first dosing date to the date of death. A subject who has not died will be censored at the last known date alive.
    - Proportion of patients alive at the end of the atezolizumab plus split dose of gemcitabine and cisplatin combination stage.
    - Proportion of patients alive at the end of follow-up.
- ***Progression-Free Survival*** **(PFS)**
    - Time from first dosing date to the date of confirmed PD. A subject who has not died will be censored at the last known date alive.
    - Proportion of patients free of PD at 6 months since start of treatment.
    - Proportion of patients free of PD at the end of follow-up.

Safety endpoints

- ***Adverse events*** **(AE)** assessment: Type, frequency, severity and outcome of adverse events .
- ***Treatment-related AEs:*** Type, frequency, severity and outcome.

Exploratory endpoints

- Biomarkers and/or genes expression and participant outcomes.

10.3. Efficacy assessment

10.3.1. Efficacy variables

Overall Response Rate (ORR) at 6 months from first dose: includes patients with confirmed persistent partial (PR) and complete response (CR) as best response according to RECIST v 1.1, at 6 months from adaptive the study treatment initiation.

Overall Response Rate (ORR) from first dose: includes patients with confirmed persistent partial (PR) and complete response (CR) as best response according to RECIST 1.1, at the end of their participation in the study.

Time to response: Time to response (TTR) is defined as the time from the start of study treatment to the first objective tumor response (tumor shrinkage of ≥30%) observed for patients who achieved a CR or PR.

Duration of response (DOR): DOR is calculated as the time from the date of first documented CR or PR, as per RECIST 1.1, to the first documented progression or death due to underlying cancer.

Overall Survival (OS): Median Overall Survival (mOS) is calculated as the time from the date of inclusion to date of death due to any cause.

Progression-free Survival (PFS): Median Progression free survival (mPFS) is defined as the time from the date of inclusion to the date of the first documented disease progression or death due to any cause, whichever occurs first. PFS will be determined based on tumour assessment (RECIST version 1.1 criteria). The local Investigator's assessments will be used for analyses. Patients who are alive and have not progressed at the last follow-up will be censored at the date of the last available image determination (CT scan or MRI). Patients with no additional image test other than that at baseline will be censored to the day after inclusion. Patients initiating new anticancer therapy (without progression to the study treatment) will be censored to the date of new anticancer therapy initiation.

Clinical Benefit (CB) Rate: Clinical Benefit Rate (CBR) is defined as the percentage of patients who achieved complete response, partial response and stable disease. Stable disease should be maintained for at least 6 months to be considered as a CBR event.

10.4. Safety assessment

The safety population (SP) consists of all enrolled subjects who received at least one dose of study treatment. Patients will be monitored for safety during all the stages of the study. All safety and tolerability assessments will be done at pre-dosing time, unless otherwise specified.

Safety parameters are AE, SAE, AESI, pregnancy, medication error, and overdose. Additional safety information could be derived from ECG, lab test, pregnancy test, or vital sign exam.

The assessment of adverse events will include the type of event (including symptoms, physical exam findings and laboratory abnormalities), the incidence, severity, timing, seriousness, and relatedness regarding the treatment under study. Adverse events will be recorded and reported in the corresponding section of the case report form. The grade of adverse events will be coded according to the National Cancer Institute’s Common Toxicity criteria (NCI-CTCAE v5.0 scoring system). The worst toxicity score will be recorded.

10.5. Definition of study populations

Data will be analysed in the following populations:

1. *Intent-To-Treat (ITT):* All patients that have been enrolled in the trial.
2. *Evaluable population per protocol (PP):* All patients fulfilling all eligibility criteria without any protocol deviation that makes the patient invalid for the primary endpoint evaluation.
3. *Safety population (SP):* All patients receiving at least one dose of the study treatments.

10.6. Data quality control

A Data Management Plan (DMP) will be elaborated for this trial in order to outline the data management procedures and the related responsibilities of trial staff. The DMP will clearly specify the data quality control tasks to be performed and the corresponding responsibility, timelines, etc., according to international guidelines in the subject and GCPs.

Following data entry of the investigator staff into the data capture system (eCRF), the data entered will be reconciled against the original case report form, review form/clinic notes/laboratory reports by CRA during monitoring visits, according to the monitoring plan. Any identified issues should be clarified with the Investigator staff. Any necessary corrections should be made in the corresponding field of the eCRF.

The monitoring plan will establish that source data verification (SDV) is expected for a subset of variables, according to study status, starting on the approval of this DMP and the SDV strategy agreed.

Remote QC activities will be outlined in the Monitoring Plan for relevant variables as eligibility, primary endpoints, safety endpoints and relevant secondary endpoints.

Performance of these checks is expected on all the patients included (this estimate may vary according to the quality of the data reported by the research team).

Any finding will be reflected in the monitoring report and will be conveniently managed with sites (including Principal Investigator) and informed to the Coordinating Investigator, as the representative of the Sponsor in this study, and when applicable, notified to competent authorities according to local regulations.

10.7. Statistical analysis

For each categorical variable, the results will be summarised by frequencies and percentages/proportions along with 95 % confidence intervals (95% CIs) when applicable.

For each continuous variable, the results will be summarised by descriptive statistics such as median, range, and range or by means, standard deviations, and (95% CIs). For time to event endpoints, Kaplan-Meier estimates at selected time points and corresponding curves will be presented. Time to event is derived relative to the first study treatment administration and will be expressed in weeks and/or months.

Vital signs, ECG parameters, clinical laboratory data (haematology, serum biochemistry, and urinalysis) will be presented in tabular form. Laboratory values will be expressed as absolute values and in grades (ordinal categorical variables), when feasible. In case of laboratory findings reported as adverse events, values will be presented and/or classified according to NCI CTCAE v 5.0.

All adverse events, including treatment-emergent AE (AEs starting after the administration of study treatment and up to study completion) will be summarised by system organ class and preferred term. Grading will be presented by type and in tables showing the frequency and percentage of the within-patient worst grades. In addition, grade ≥ 3 AEs will be summarised separately. Further analyses could be performed.

Analysis will be based on observed data, and missing data for drop-outs are not replaced by methods like LOCF (last option carried forward).

Full analysis details will be outlined in the statistical analysis plan (SAP).

11. LEGAL AND ETHICS CONSIDERATION

11.1. Ethical conduct of the study

The study will be conducted in accordance with the principles of the Helsinki Declaration Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 updated to its latest version Fortaleza, Brazil, October 2013. With the Good Clinical Practice (GCP) standards issued by the Working Party on Medicinal Product Efficacy of the European Economic Community (1990) (CPMP / ICH / 135/95).

And the laws and regulations in force in Spain:

- The Oviedo Convention of April 4, 1997 on human rights and biomedicine, ratified in the BOE in October 1999.
- The rules for the adequate protection of personal data, in accordance with Law 3/2018 Protection of Personal Data and guarantee of digital rights.
- The rights and obligations regarding information and clinical documentation, as provided in Law 41/2002, of November 14, basic regulation of patient autonomy.
- Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for Investigation with medicinal products and the Spanish Clinical Studies Registry.
- Law 14/2007, of July 3, on Biomedical Research.

11.2. Independent Ethical Committee (IEC) Review

Prior to the commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents to the Central IEC for its approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File.

The IEC will be asked to document the date of the meeting at which the favourable opinion or approval was given, with the members and voting members present. Written evidence of favourable opinion or approval that clearly identifies the trial, the clinical trial protocol and the version, the Subject Information and Informed Consent Form, should be provided.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC, before implementation of substantial changes. Relevant safety information will be submitted to the IEC during the course of the trial, in accordance with national regulations and requirements.

Initial IEC positive vote, and all materials approved by the IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

11.3. Authorities

The study protocol and/or related documents will be submitted to regulatory authorities before commencement of the clinical trial, as national authorities in the country where the trial is taking place.

11.4. Informed consent

The patient should sign an informed consent that will include the information for the clinical trial and associated translational research.

The clinician will have to explain the nature, objectives and possible consequences of the clinical trial in a manner that is understandable by the patient. The patient must give his/her consent before being admitted into the study and before biological samples are taken.

The study subject will provide his/her consent, signing by duplicate the appropriate model. For this purpose, each model must carry the signature of investigator and patient. The investigator will retain one copy of the original of each patient signed consent form.

The investigator will not start any investigation related with the study until the written consent has been obtained.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by the Ethics Committee.

11.5. Confidentiality

In order to guarantee the confidentiality of the clinical trial data according to the provisions of The rules for the adequate protection of personal data, in accordance with Law 3/2018 Protection of Personal Data and guarantee of digital rights, only the personnel designated by the Sponsor will have access to the patient data for monitoring/auditing purposes, Investigators and his/her staff, the Ethic Committee and the pertinent Competent Authorities.

The investigator should facilitate access to the source documents and data for monitoring and auditing purposes.
The content of the case report forms (CRF), as well as the documents generated during the study will be protected from non-permitted uses by persons not involved in the investigation, and will therefore be considered strictly confidential and not revealed to third parties, except those specified in the previous paragraphs.

11.6. Insurance Policy

The insurance or indemnity in accordance with pertinent regulatory requirements will be provided. All patients in this study are insured through the corresponding insurance policy that satisfies the conditions stipulated by the RD 1090/2015 in Spain.

11.7. End of study definition

The end of study is defined as the Last Patient Last Visit (LPLV) and will be considered at 24 months after last patient first visit (LPFV), Sponsor will ask survival status of all patients at the final clinical trial database closing, in order to maximise the median follow up of patients for overall survival data.

11.8. Early study termination

The clinical trial may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavourable risk benefit judgment for any IMP. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, poor enrolment, or the discontinuation of clinical development of

the IMP or withdrawal of the IMP from the market for safety reasons.

Health Authorities and Independent Ethics Committees (IECs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

In case of early termination of the study, all the study material (study drugs, etc.) must be returned to the Sponsor.

12. STUDY PROCEDURES

12.1. Responsibilities according to Good Clinical Practice

Responsibilities of the principal investigator of each participating center includes what is detailed in section 4 of the Guideline for good clinical practice E6 (R2).

12.2. Instructions for e-CRF completion

The data will be recorded using the Electronic Data Capture software property of MFAR S.L. The MFAR e-CRF environment will be used for data collection in this study. [redacted] Access to data is secure and restricted for authorised users. Each user requires a username and password for exclusively personal use, as per good clinical practice.

All the EDC users are uniquely identified by name, all the access to the software is made through a secure, encrypted connection and all the activities are logged and audited.

All the EDC forms are designed according to the eCRF defined by the study protocol, and are validated according to the DVP (Data Validation Plan). There will be eCRFs for different visits, and whether these are mandatory (m) and non-mandatory eCRFs (such as laboratory testing and the corresponding validation of variables, rules and extraction).

Data on Adverse Event (AE), Adverse Reactions (AR), Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected SARs (SUSARs) will be undertaken by Sites in the eCRF and are transferred to the study database along with the rest of variables.

Electronic Case Report Form (eCRF) includes the CTCAE version 5.0 terms as a pulldown list in order to categorise the events, additionally when the variable “SAE” is marked as “yes”, an automatic email is sent to the MFAR Staff in order to be aware of the paper based SAE form is expected to be received, for regulatory reporting purposes. As data cleaning procedure, SAE received in paper based form are conciliate with the adverse events data collected in the eCRF and is ensured that all the events reported by means of SAE form are also collected in the eCRF, that is the final destination of any adverse event (whether be AE, AR, SAE, SAR or SUSAR).

12.3. Drug supply

AUREA is an Investigator Initiated Study, Atezolizumab will be supplied by the Sponsor through Roche, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. The treatment for patients not progressing at 24 months will be according to PI criteria, following his/her local normal practise. If as per Treating Physician criteria, the best option for the patient would be to continue with Atezolizumab, the administration may continue but following Site’s supply channels (other than those provided by Sponsor), after managing local administrative approvals

Gemcitabine and Cisplatin will be provided by the sites as per standard care criteria.

12.3.1. Packaging and labelling

Packaging and labeling of study treatment will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines.

12.4. Final report and Publications

As stated in article 42 of RD 1090/2015 of clinical trials, the Sponsor is obliged to publish both positive and negative results of the authorized clinical trials in scientific journals and with mention to the Ethical Committee of Clinical Research that approved the study.

The clinical publication will be carried out by the Coordinating Investigator in collaboration and Principal Investigators. Coordinating Investigator and Principal Investigators who contributed with at least 3% of the patients will be the authors. The order of authors will strictly depend on the number of patients included by the Investigators.
The anonymity of the source subjects of the data and biological samples will be maintained at all times.

The results or conclusions of the study will be communicated primarily in scientific publications before being released to the non-health public.

No efficacy study outcome will be reported prematurely or sensationalistically.

Participating investigators should not publish any patient data that is directly related to the study objectives until the trial report is published.

The trial will be registered in the Spanish Registry of Clinical Studies (REEC) and www.clinicaltrials.gov.

12.5. Monitoring

The study will be monitored through local visits, telephone calls and periodic inspection of CRFs. During the study, according to monitoring plan, a monitor from MFAR Clinical Research or a representative will have regular contact with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to MFAR Clinical Research.
- Confirm that AEs and SAEs have been properly documented on eCRFs, all SAEs have been forwarded to MFAR Clinical Research, and all the SAEs that met criteria for reporting have been forwarded to the IEC

The monitor will be available between visits if the investigator(s) or other staff members need information or advice.

12.6. Clinical Study Report

According to local regulation, the summary of results of the trial will be sent to the AEMPS and the CEIm no later than one year after the date of the end of the trial globally. The summary of results will follow the European format required for EudraCT.

12.7. Protocol Amendments

Supplements and changes to the protocol can be performed exclusively by the Sponsor, who must submit them to the Ethics Committee and the local Regulatory Authority protocol amendments.

Relevant safety information will be submitted to the IEC during the course of the trial, in accordance with national regulations and requirements.

Initial IEC positive vote, and all materials approved by the IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

12.8. Data Handling

The data will be recorded using the Electronic Data Capture software property of MFAR S.L., which is developed and maintained with strict observance of the regulatory standards for Clinical EDC systems, with special observance of the guidelines specified at:

- CPMP/ICH/135/95. ICH E6. Note for Guidance on Good Clinical Practice.
- Good Clinical Data Management Practice, Version 4, Society for Clinical Data Management (SCDM), October 2005.
- EMEA. Reflection on expectations for electronic source documents used in clinical trials. London, 17 October 2007.
- Directive 9 Guidance for Industry. Part 11, Electronic Records; Electronic Signatures – Scope and Application (August 2003).
- FDA. Guidance for Industry. Computerised Systems Used in Clinical Investigations (May 2007).
- FDA. Guidance for Industry. Part 11, Electronic Records; Electronic Signatures – Scope and Application (August 2003)
- Organic Law 3/2018, of December 5, Protection of Personal Data and guarantee of digital rights

The EDC database is hosted at a data server located at the Data Centre maintained by Claranet SAU located at "[redacted]". The physical access to the Data Centre is restricted to authorised Claranet personnel, and logical access to the database is restricted to named MFAR personnel.

All the EDC users are uniquely identified by name, all the access to the software is made through a secure, encrypted connection and all the activities are logged and audited.

All the EDC forms are designed according to the eCRF defined by the study protocol, and are validated according to the DVP (Data Validation Plan).

12.9. Documentation

The Investigator/Institution should maintain trial documents according to ICH Topic E6

Section 8, and as required by pertinent regulatory requirements. According to RD 1090/2015 on Clinical trial, the archive period for all essential documents is 25 years.

Essential documents should be stored according to ICH GCP guidelines for a longer period of time, if required by pertinent regulations. The original patient data (clinical record) must be kept archived for the time stipulated by the study centre regulations.

All original subject files (medical records) must be stored at the site (hospital, research institution, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer (In Spain 25 years). In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

12.10. Audits and inspections

Authorised representatives of Sponsor, a regulatory authority, an Independent Ethics Committee may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonisation, and any applicable regulatory requirements. The investigator should contact the Sponsor through MFAR immediately if contacted by a regulatory agency about an inspection.

13. TRANSLATIONAL SUBSTUDIES

A key objective of the biomarker analyses that will be performed in this study is to investigate candidate biomarkers that may have predictive value in identifying those patients who may benefit from treatment with the combination of atezolizumab 1 and split dose GC. In addition, analyses of blood biomarkers obtained before, during and after treatment will provide an opportunity to investigate pharmacodynamic effects. Samples collected at the End of Treatment/Withdrawal visit enable investigation of potential mechanisms of resistance to the drug combination.

The following biological samples are required:

- Tumor sample, archive tumor sample in order to evaluate changes in signaling molecules in response to study treatment in tumour tissue.
- Processed blood samples obtained before treatment, at D1C7 of treatment, and at the end of treatment/progression, in order to evaluate changes in signaling molecules in response to study treatment in blood.
- Faecal samples for microbiome analyses.

13.1. Archived Tumor Biospecimens

Somatic alterations in tumours including proteomics, transcriptomics and metabolics will be analyzed. No germinal line determinations will be performed.

Tumor biological specimens from archived tissue samples will be used to analyze candidate DNA, RNA, or protein markers, or relevant signature of markers for their ability to identify those patients who are most likely to benefit from treatment with the study drugs.

Tumor tissue biomarker analyses, including determination of PD-L1 status, will be performed retrospectively in a central laboratory. PD-L1 status will be assessed using a validated PD-L1 IHC test kit manufactured under GMP specifications, in conjunction with a pre-specified scoring algorithm and cutoff defining PD-L1 positive versus negative status that will be established prior to initiation of scoring of PD-L1.

Additional tumor tissue biomarkers that may be analyzed include, but may not necessarily be limited to, gene expression profiles and/or quantitation of tumor-infiltrating CD8+ T lymphocytes by IHC and/or tissue FoxP3, PD-1, or PD-L2.

13.2. Peripheral Blood

Specimens will be processed and retained in local laboratories until Sponsor indications for shipments. It will include whole blood, serum and plasma samples that will be retained in the central laboratory for exploratory assessments.

Samples may be used to identify or characterize cells, DNA, RNA, or protein markers known or suspected to be of relevance to the mechanisms of action, or the development of resistance to study treatment. These include biomarkers that may aid in the identification of those patients who might preferentially benefit from treatment with IMP 1 in combination with IMP 2, which may include but are not limited to biomarkers related to anti-tumor immune response or target modulation, such as (not necessarily be limited to) soluble IL-8 or IFNγ.

Information regarding sample collection, management and shipments are provided in the translational research manual.

13.3. Faecal samples

Specimens will be processed and retained in local laboratories until Sponsor indications for shipments. It will include a total of 3 samples: basal faecal sample collected prior treatment initiation, faecal sample at Cycle 4 Day 1 and after progression. Information regarding sample collection, management and shipments are provided in the translational research manual.

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APPENDICES

Appendix 1. Management of Atezolizumab-specific Adverse Events

A) Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	● **Continue atezolizumab and monitor closely.** ● **Re-evaluate on serial imaging.** ● **Consider patient referral to pulmonary specialist.** ● **For Grade 1 pneumonitis, consider withholding atezolizumab.**
Pulmonary event, Grade 2	● **Withhold atezolizumab for up to 12 weeks after event onset.** [a] ● **Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone or equivalent.** ● **If event resolves to Grade 1 or better, resume atezolizumab.** [b] ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.** [c] ● **For recurrent events or events with no improvement after 48–72 hours of corticosteroids, treat as a Grade 3 or 4 event.**
Pulmonary event, Grade 3	● **Permanently discontinue atezolizumab and contact Medical Monitor.** [c] ● **Bronchoscopy or BAL is recommended.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone.** ● **If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.** ● **If event resolves to Grade 1 or better, taper corticosteroids over 1 month.**

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate).Medical Monitor is available to advise as needed.

B) Management Guidelines for Hepatic Events

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

C) Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	● **Continue atezolizumab.** ● **Initiate symptomatic treatment.** ● **Endoscopy is recommended if symptoms persist for 7 days.** ● **Monitor closely.**
Diarrhea or colitis, Grade 2	● **Withhold atezolizumab for up to 12 weeks after event onset.** [a] ● **Initiate symptomatic treatment.** ● **Patient referral to GI specialist is recommended.** ● **For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.** ● **If event resolves to Grade 1 or better, resume atezolizumab.** [b] ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.** [c]
Diarrhea or colitis, Grade 3	● **Withhold atezolizumab for up to 12 weeks after event onset.** [a] ● **Refer patient to GI specialist for evaluation and confirmatory biopsy.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If event resolves to Grade 1 or better, resume atezolizumab.** [b] ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.** [c]
Diarrhea or colitis, Grade 4	● **Permanently discontinue atezolizumab and contact Medical Monitor.** [c] ● **Refer patient to GI specialist for evaluation and confirmation biopsy.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If 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] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab

should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

D) Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	● **Continue atezolizumab.** ● **Initiate treatment with thyroid replacement hormone.** ● **Monitor TSH closely.**
Symptomatic hypothyroidism	● **Withhold atezolizumab.** ● **Initiate treatment with thyroid replacement hormone.** ● **Monitor TSH closely.** ● **Consider patient referral to endocrinologist.** ● **Resume atezolizumab when symptoms are controlled and thyroid function is improving.**
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** ● **Continue atezolizumab.** ● **Monitor TSH every 4 weeks.** ● **Consider patient referral to endocrinologist.** **TSH < 0.1 mU/L:** ● **Follow guidelines for symptomatic hyperthyroidism.** ● **Consider patient referral to endocrinologist.**
Symptomatic hyperthyroidism	● **Withhold atezolizumab.** ● **Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.** ● **Consider patient referral to endocrinologist.** ● **Resume atezolizumab when symptoms are controlled and thyroid function is improving.** ● **Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism.**
Symptomatic adrenal insufficiency, Grade 2 - 4	● **Withhold atezolizumab for up to 12 weeks after event onset.** [a] ● **Refer patient to endocrinologist.** ● **Perform appropriate imaging.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab.** [b] ● **If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.** [c]
Hyperglycemia, Grade 1 or 2	● **Continue atezolizumab.** ● **Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines.** ● **Monitor for glucose control.**
Hyperglycemia, Grade 3 or 4	● **Withhold atezolizumab.** ● **Initiate treatment with insulin.** ● **Evaluate for diabetic ketoacidosis and manage as per institutional guidelines.** ● **Monitor for glucose control.** ● **Resume atezolizumab when symptoms resolve and glucose**

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

IV= intravenous;

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

E) Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	● **Continue atezolizumab.** ● **Patient referral to ophthalmologist is strongly recommended.** ● **Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.** ● **If symptoms persist, treat as a Grade 2 event.**
Ocular event, Grade 2	● **Withhold atezolizumab for up to 12 weeks after event onset.a** ● **Patient referral to ophthalmologist is strongly recommended.** ● **Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.** ● **If event resolves to Grade 1 or better, resume atezolizumab.b** ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]**
Ocular event, Grade 3 or 4	● **Permanently discontinue atezolizumab and contact Medical Monitor. c Refer patient to ophthalmologist.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.** ● **If event resolves to Grade 1 or better, taper corticosteroids over 1 month.**

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

F) Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 2, 3 or 4	**Permanently discontinue 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 corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** **If 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] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

G) Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] **Fever [b] with or without constitutional symptoms**	● **Immediately interrupt infusion.** ● **Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.** ● **If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate.** ● **If symptoms recur, discontinue infusion of this dose.** ● **Administer symptomatic treatment, c including maintenance of IV fluids for hydration.** ● **In case of rapid decline or prolonged CRS (2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2.** ● **For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.**
Grade 2 [a] **Fever [b] with hypotension not requiring vasopressors** **<u>and/or</u>** **Hypoxia requiring low-flow oxygen d by nasal cannula or blow-by**	● **Immediately interrupt infusion.** ● **Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.** ● **If symptoms recur, discontinue infusion of this dose.** ● **Administer symptomatic treatment. [c]** ● **For hypotension, administer IV fluid bolus as needed.** ● **Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.** ● **Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS.** ● **Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).** ● **Consider anti-cytokine therapy. [e]** ● **Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor.** ● **If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS.** ● **If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.**
Grade 3 [a] **Fever [b] with hypotension requiring a vasopressor (with**	● **Permanently discontinue atezolizumab and contact Medical Monitor. [f]** ● **Administer symptomatic treatment. [c]** ● **For hypotension, administer IV fluid bolus and vasopressor as needed.**

or without vasopressin) **<u>and/or</u>** **Hypoxia requiring high-flow oxygen d by nasal cannula, face mask, non-rebreather mask, or venturi mask**	● **Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.** ● **Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS.** ● **Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).** ● **Consider anti-cytokine therapy. [e]** ● **Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.**
Grade 4 [a] **Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin)** **<u>and/or</u>** **Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)**	● **Permanently discontinue atezolizumab and contact Medical Monitor. [f]** ● **Administer symptomatic treatment. [c]** ● **Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice.** ● **Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS.** ● **Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).** ● **Consider anti-cytokine therapy. [e] For patients who are refractory to anti-cytokine therapy, experimental treatments [g] may be considered at the discretion of the investigator and in consultation with the Medical Monitor.** ● **Hospitalize patient until complete resolution of symptoms.**

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI National Cancer Institute.
Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
[b] Fever is defined as temperature 38C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
[c] Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
[d] Low flow is defined as oxygen delivered at 6 L/min, and high flow is defined as oxygen delivered at 6 L/min.
[e] There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors/ICI (*Rotz et al. 2017*; *Adashek and Feldman 2019*), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
[f] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit-risk ratio.
[g] Refer to *Riegler et al. (2019)* for information on experimental treatments for CRS.

H) Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5 - 2.0 ULN:** ● **Continue atezolizumab.** ● **Monitor amylase and lipase weekly.** ● **For prolonged elevation (e.g., > 3 weeks), consider treatment** ● **with corticosteroids equivalent to 10 mg/day oral prednisone.** **Asymptomatic with amylase and/or lipase > 2.0 - 5.0 x ULN:** ● **Treat as a Grade 3 event.**
Amylase and/or lipase elevation, Grade 3 or 4	● **Withhold atezolizumab for up to 12 weeks after event onset.[a]** ● **Refer patient to GI specialist.** ● **Monitor amylase and lipase every other day.** ● **If no improvement, consider treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.** ● **If event resolves to Grade 1 or better, resume atezolizumab. [b]** ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]** ● **For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]**
Immune-mediated pancreatitis, Grade 2 or 3	● **Withhold atezolizumab for up to 12 weeks after event onset.[a]** ● **Refer patient to GI specialist.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If event resolves to Grade 1 or better, resume atezolizumab. [b]** ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]** ● **For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]**
Immune-mediated pancreatitis, Grade 4	● **Permanently discontinue atezolizumab and contact Medical Monitor. [c]** ● **Refer patient to GI specialist.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If 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] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

I) Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	● **Continue atezolizumab.** ● **Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).**
Dermatologic event, Grade 2	● **Continue atezolizumab.** ● **Consider patient referral to dermatologist for evaluation and, if indicated, biops.** ● **Initiate treatment with topical corticosteroids.** ● **Consider treatment with higher-potency topical corticosteroids if event does not improve.** ● **If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.**
Dermatologic event, Grade 3	● **Withhold atezolizumab for up to 12 weeks after event onset.[a]** ● **Refer patient to dermatologist for evaluation and, if indicated, biopsy.** ● **Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours.** ● **If event resolves to Grade 1 or better, resume atezolizumab. [b]** ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]**
Dermatologic event, Grade 4	● **Permanently discontinue atezolizumab and contact Medical Monitor. [c]**
Stevens-Johnson syndrome or toxic epidermal necrolysis, (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** ● **Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.** ● **Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy.** ● **Follow the applicable treatment and management guidelines above.** ● **If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.**

a Atezolizumab may be withheld for a longer period of time (i.e., 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

b If corticosteroids have been initiated, they must be tapered over 1 month to the equivalent of 10 mg/day oral prednisone before atezolizumab can be resumed.

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed..

- For suspected SCARs the patients should be referred to a dermatologist for further diagnosis and management
- Atezolizumab should be withheld for patients with suspected SJS or TEN
- Atezolizumab should be permanently withdrawn for any grade confirmed SJS or TEN
- Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

J) Management Guidelines for Neurologic Disorders

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

K) Management Guidelines for Immune-Mediated Meningoencephalitis

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

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

L) Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	● **Continue atezolizumab.** ● **Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.**
Renal event, Grade 2	● **Withhold atezolizumab for up to 12 weeks after event onset.** [a] ● **Refer patient to renal specialist.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.** ● **If event resolves to Grade 1 or better, resume atezolizumab.** [b] ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.** [c]
Renal event, Grade 3 or 4	● **Permanently discontinue atezolizumab and contact Medical Monitor.** ● **Refer patient to renal specialist and consider renal biopsy.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.** ● **If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.**

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

M) Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	● **Continue atezolizumab.** ● **Refer patient to rheumatologist or neurologist.** ● **Initiate treatment as per institutional guidelines.**
Immune-mediated myositis, Grade 2	● **Withhold atezolizumab for up to 12 weeks after event onset a and contact Medical Monitor.** ● **Refer patient to rheumatologist or neurologist.** ● **Initiate treatment as per institutional guidelines.** ● **Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.** ● **If event resolves to Grade 1 or better, resume atezolizumab. [b]** ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]**
Immune-mediated myositis, Grade 3	● **Withhold atezolizumab for up to 12 weeks after event onset a and contact Medical Monitor.** ● **Refer patient to rheumatologist or neurologist.** ● **Initiate treatment as per institutional guidelines.** ● **Respiratory support may be required in more severe cases.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, resume atezolizumab. b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]** ● **For recurrent events, treat as a Grade 4 event.**
Immune-mediated myositis, Grade 4 (CTCAE v5.0 guidelines only)	● **Permanently discontinue atezolizumab and contact Medical Monitor. [c]** ● **Refer patient to rheumatologist or neurologist.** ● **Initiate treatment as per institutional guidelines.** ● **Respiratory support may be required in more severe cases. Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 12 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] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the assessment of benefit-risk by the investigator and in alignment with the protocol requirement for duration of treatment and documented by the investigator. Medical Monitor is available to advise as needed.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to rechallenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). Medical Monitor is available to advise as needed.

Clinical Trial Protocol

Protocol Number:	SOGUG-2020-IEC(VEJ)-1
Title:	Phase II, multicenter, non-randomized, single-arm, open-label trial of atezolizumab in combination of split-doses of gemcitabine plus cisplatin in patients with locally advanced or metastatic urothelial carcinoma
Short title:	Study of atezolizumab combined with split-dose gemcitabine plus cisplatin in urothelial carcinoma
Acronym:	AUREA
Nº EudraCT:	2020-001326-65
Sponsor:	Spanish Oncology Genitourinary Group (SOGUG) [redacted]
Coordinating: Investigator:	Guillermo de Velasco, M.D., PhD. [redacted]

VERSION 1.1 - 6.NOV.2020

Confidentiality Statement

The information contained in this document is the property of the sponsor and therefore is provided confidentially for review by you, your investigative team, the Investigational Ethics Committee, and the competent authorities. This information must not be revealed to any other party without previous authorization in writing by the sponsor, except as needed to obtain the informed consent of the subjects who may be given the medicinal product.

SPONSOR'S PROTOCOL SIGNATURE PAGE

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonization Good Clinical Practice, and all applicable Health Authority requirements and national laws.

[redacted]

SOGUG Chairman	Signature	Signature date (DD-mm-YYYY)

Dr. Guillermo de Velasco

Coordinating Investigator	Signature	Signature date (DD-mm-YYYY)

PRINCIPAL INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

I have read this protocol and agree to conduct this clinical trial in accordance with all the provisions of the Protocol, any approved protocol amendments, International Conference on Harmonization Good Clinical Practice, Helsinki Declaration and all applicable Health Authority requirements and national laws

Site: _____

Name: _____

Date:_____

Principal Investigator Signature:_____

INDEX

1. SUMMARY

1.1. Type of application
Clinical trial with approved medications with a potential better regimen.

1.2. Study Title
Phase II, multicenter, non-randomized, single-arm, open-label trial of atezolizumab in combination of split-doses of gemcitabine plus cisplatin in patients with locally advanced or metastatic urothelial carcinoma

1.3. Protocol Number and Version
SOGUG-2020-IEC(VEJ)-1 - VERSION 1.1 6.NOV.2020

1.4. Nº EudraCT
2020-001326-65

1.5. Sponsor Data
Spanish Oncology Genitourinary Group (SOGUG)
[redacted]

1.6. Coordinating Investigator
Guillermo de Velasco, M.D., PhD.
[redacted]

1.7. Principal Investigators
The list of sites and the corresponding Principal Investigators is provided in the attached document.

1.8. Study Sites
It is expected the participation of 12 Sites in Spain.

1.9. Monitoring Organization
MFAR Clinical Research
[redacted]

1.10. Disease under study
Locally advanced and metastatic urothelial carcinoma (mUC)

1.11. Study Phase
Phase II clinical trial; Investigator Initiated Study (IIS)

1.12. Study Treatments

All study treatments are intended for administration as described below (regarding maximum treatment duration as per protocol), until PD, unacceptable toxicity, investigator's decision or patient's consent withdrawal (whichever occurs first).

- **Atezolizumab** at a fixed dose of 1200 mg/m^2 by intravenous (IV) infusion on D1 of each cycle up to disease progression, unacceptable toxicity or absence of clinical benefit. AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation.

- **Gemcitabine** 1000 mg/m^2 IV on D1 and 1000 mg/m^2 IV on D8 of each 21-day cycle *plus* **Cisplatin** 70 mg/m^2 by IV on split-dose schedule of 35 mg/m^2 on day 1 (D1) and 35 mg/m^2 on day 8 (D8) <u>for up to 6 cycles.</u>

1.13. Objectives

Primary Objective:

To evaluate the preliminary efficacy of atezolizumab plus split-dose gemcitabine and cisplatin (GC) for the first-line setting, in patients with histologically confirmed advanced (locally advanced and metastatic) urothelial cancer in terms of overall response rate (ORR) assessed by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Secondary Objectives

Efficacy:

- To evaluate the *duration of response (DoR)* associated with the study treatment, understood as the time from first confirmed response (CR or PR) to the date of the documented progressive disease as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.
- To determine the *overall survival (OS)* of patients with locally-advanced or mUC treated with the intended treatment regimen, understood as the time from first dosing date to the date of death. A subject who has not died will be censored at the lastat last known date alive.
- To evaluate the *time to response (TtR)* associated with the study treatment, understood as the time from the first dose of the study treatment to theand confirmed response (CR or PR) based on RECIST 1.1 criteria.
- To evaluate the *clinical benefit rate (CBR)*, defined as the percentage of patients who have achieved complete response, partial response and stable disease. Stable disease should be maintained for at least 6 months to be considered as CBR event.
- To determine the *progression-free survival (PFS)* of patients with locally-advanced or mUC treated with the intended treatment regimen, defined as the time from first dosing date until disease progression or death from any cause. Patients who have not progressed and start a new line of treatment will be censored.

Safety:

- To evaluate *safety* of the intended treatment regimen based on the frequency and severity of adverse events assessed by NCI CTCAE v5.0.

Exploratory objectives

- To explore potential correlation of efficacy with relevant potential prognostic factors/stratification factors

- To evaluate the relationship between the expression of PD-L1 and microbiome with ORR and PFS during experimental treatment.

1.14. Endpoints

Primary endpoint:

- *Overall Response Rate (ORR)*

Secondary endpoints

- *Duration of response* (DoR)
- *Overall Survival* (OS)
- *Time to response* (TtR)
- *Clinical benefit* (CB)
- *Progression-Free Survival* (PFS)

Safety endpoints

- *Adverse events* (AE)
- *Treatment-related AEs* (TRAEs)

Exploratory endpoints

- Biomarkers expression

1.15. Sample Size

A minimum of 66 patients will be included in the trial.

1.16. Eligibility and withdrawal criteria

Inclusion criteria

1. Male or female subjects ≥ 18 years old.
2. Written informed consent approved by the Independent Ethics Committee (IEC), prior to the performance of any trial activities.
3. Patients with histologically documented, locally advanced (T4B, any N; or any T, N2-3) or metastatic urothelial carcinoma (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).*
4. Patients should not be eligible (unfit) for full dose of cisplatin, in the investigator's judgement, based on:
   a. Age older than 70 years.
   b. ECOG Performance status (PS) 2 or Karnofsky PS of 60 - 70% (only 15 patients will be included with ECOG 2).
   c. Measured creatinine clearance (ClCr) > 30 and < 60 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for the determination of creatinine clearance:

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

   d. Any other reason the physician considers but should specify in the CRF and discussed with the PI.

5. At least one measurable lesion through radiographic tumor evaluation (CT scan or magnetic resonance imaging/MRI) as defined by RECIST version 1.1, that has not been previously irradiated within 4 weeks prior to the study enrolment.

6. Patients with an archival or *de novo* tumor biopsy (representative formalin-fixed paraffin-embedded/FFPE paraffin block obtained within 6 months prior to inclusion) with an associated pathology report, for testing of PD-L1 expression prior to study enrollment. Samples in unstained slides could be acceptable (at least 15 slides).

7. Patients with adequate normal organ and marrow function as defined below:

   a. Haemoglobin ≥ 9.0 g/dL.
   b. Absolute neutrophil count (ANC) ≥ 1500 per mm^3.
   c. Platelet count ≥ 100,000 per mm^3.
   d. Serum bilirubin ≤ 1.5 X institutional upper limit of normal (ULN) unless liver metastases are present, in which case it must be ≤ 2X ULN. This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology); however, they will be allowed only in consultation with their physician.
   e. Serum transaminases (ALT, AST and GGT) ≤ 2.5X institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 3X ULN.

8. No major active bleeding.

9. Female subjects of childbearing potential (not surgically sterile or at least 2 years postmenopausal) must provide a negative urine pregnancy test at screening, and use a medically accepted double barrier method of contraception (i.e. condom with spermicide + IUD or cervical caps). In addition, they must agree to continue the use of this double barrier method for the duration of the study and for 6 months after participation in the study.

10. Males should agree to abstain from sexual intercourse with a female partner or agree to use a double barrier method of contraception (i.e. condom with spermicide, in addition to having their female partner use some contraceptive measures such as oral contraceptive drugs, intrauterine device (IUD) hormonal contraception, or cervical caps), for the duration of the study and for 6 months after participation in the study

11. Willingness and ability of patients to comply with the protocol for the duration of the study including undergoing treatment as well as availability for scheduled visits and examinations including follow up.

Exclusion criteria

1. Prior treatment with any immune checkpoint inhibitor therapy (e.g., CTLA4, PD-1, or PD-L1 targeting agent).*

   **Note*: Prior adjuvant or neoadjuvant treatment with targeted therapy/checkpoint inhibitors is allowed, as long as the last dose was administered at least 12 months prior to the patient inclusion in this trial.

2. Presence of active second malignancy and/or prior malignancy in the last 2 years is allowed except for the following:
   a. adequately treated basal cell or squamous cell skin cancer,
   b. adequately treated Stage I or II cancer from which the patient is currently in complete remission per investigators' clinical judgment.
3. Patient receiving radiation therapy within 4 weeks before inclusion.
4. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
5. Active or prior documented inflammatory bowel disease (e.g.., Crohn's disease and ulcerative colitis).
6. History of allogeneic organ transplant.
7. Subjects having a diagnosis of immunodeficiency or are receiving systemic steroid therapy or any other form of immunosuppressive therapy within 28 days prior to the first dose of trial treatment.
8. Current or prior use of immunosuppressive medication within 7 days prior to enrolment, except the following:
   a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);
      i. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;
      ii. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
9. The subject has uncontrolled, significant intercurrent or recent illness (within 6 months prior to inclusion) including, but not limited to, the following conditions:
   a. Cardiovascular disorders:
      i. Class 3 or 4 congestive heart failure as defined by the New York Heart Association, unstable angina pectoris, and serious cardiac arrhythmias.
      ii. Uncontrolled hypertension defined as sustained blood press > 150 mm hg systolic or > 100 mm hg diastolic despite optimal antihypertensive treatment.
      iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction, other ischemic event, or thromboembolic event (e.g., deep venous thrombosis [DVT] and pulmonary embolism) within 6 months before inclusion. Subjects with a more recent diagnosis of DVT are allowed if stable, asymptomatic, and treated with LMWH for at least 6 weeks before study treatment.

b. Gastrointestinal disorders (e.g., malabsorption syndrome or gastric outlet obstruction) including those associated with a high risk of perforation or fistula formulation:
    i. Tumours invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.
    ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before inclusion. Note: complete healing of an intra-abdominal abscess must be confirmed prior to start of the treatment.

c. Clinically significant hematemesis or hemoptysis of > 0.5 teaspoon (> 2.5 ml) of red blood or history of other significant bleeding within 3 months before treatment.

d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation.

e. Lesions invading major pulmonary blood vessels.

f. Other clinically significant disorders such as:
    i. Active infection requiring systemic treatment, infection with human immunodeficiency virus or acquired immunodeficiency syndrome-related illness, or chronic hepatitis B or C infection.
    ii. Serious non-healing wound/ulcer/bone fracture.
    iii. Malabsorption syndrome.
    iv. Moderate to severe hepatic impairment (child-pugh B or C).
    v. Requirement for hemodialysis or peritoneal dialysis.
    vi. Uncontrolled diabetes mellitus.

10. Major surgery (e.g., GI surgery and removal or biopsy of brain metastasis) within 8 weeks before inclusion. Complete wound healing from major surgery must have occurred 4 weeks before study treatment and from minor surgery (e.g., simple excision, tooth extraction) at least 10 days before study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

11. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

12. Any test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or chronic infection.

13. Women who are pregnant or are breastfeeding.

14. Male patients must be surgically sterile or must agree to use effective contraception during the period of therapy.

15. Any of the following within 6 months prior to study entry: myocardial infarction, uncontrolled angina, uncontrolled hypertension, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack.

16. Previously identified allergy or hypersensitivity to components of the study treatment formulations.

1.17. Planned trial period

- Enrolment/recruitment period: 12 months
- First patient first visit (FPFV): TBD
- Last patient last visit (LPLV): FPFV + 24 months
- Treatment period: Up to 24 months of LPFV
- Follow-up period: 24 months
- Planned end of study date: FPFV + up to 36 months

GLOSSARY OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ADR	**Adverse drug reaction**
AE	**Adverse event**
aUC	**Advanced urothelial cancer**
BMI	**Body Mass Index**
BP	**Blood Pressure**
CIs	**Confidence intervals**
CK	**Creatine kinase (CK), also known as creatine phosphokinase (CPK) or phosphocreatine kinase**
CB	**Clinical benefit**
CR	**Complete Response**
CRA	**Clinical Research Associate**
CTCAE	**Common Terminology Criteria for Adverse Events**
CT Scan	**Computed Tomography Scan**
DMP	**Data Management Plan**
CYP	**Cytochromes P450 enzymes**
DoR	**Duration of response**
DVP	**Data Validation Plan**
ECHO	**Echocardiogram**
ECG	**Electrocardiogram**
ECOG	**Eastern Cooperative Oncology Group**
eCRF	**Electronic Case Report Form**
EDC	**Electronic Data Capture**
ECG	**Electrocardiogram**
EMA	**European Medicines Agency**
ESMO	**European Society of Medical Oncology**
FBE	**Full blood examination**
FDA	**US Food and Drug Administration**
FFPE	**Formalin-fixed paraffin-embedded**

FPFV	**First patient first visit**
FU	**Follow-up**
GC	**Gemcitabine plus cisplatin**
GCP	**Good Clinical Practice**
G-CSF	**Granulocyte colony-stimulating factor**
GH	**Growth hormone**
Hb	**Haemoglobin**
IB	**Investigator Brochure**
ICF	**Informed Consent Form**
ICH	**International Conference on Harmonization**
ICI	**Immune Checkpoint Inhibitors**
IEC	**Independent Ethics Committee**
IgG1	**Immunoglobulin G1**
IIS	**Investigator Initiated Study**
IMP	**Investigational Medicinal Product**
ISF	**Investigator Site File**
ITT	**Intention To Treat**
IUD	**Intrauterine device**
LPLV	**Last visit Last patient**
MedDRA	**Medical Dictionary for Regulatory Activities**
MRI	**Magnetic Resonance Imaging**
mUC	**Metastatic urothelial cancer**
MUGA	**Multigated Acquisition Scan**
MVAC	**Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin**
NCI	**National Cancer Institute (USA)**
ORR	**Overall response rate**
OS	**Overall Survival**
PD	**Progression disease**
PE	**Physical Examination**
PFS	**Progression Free Survival**
PI	**Principal Investigator**

PP	**Per Protocol**
PR	**Partial Response**
PS	**Performance Status**
QD	**Quaque die, every day “once daily”**
QxW	**Every X weeks**
RECIST	**Response Evaluation Criteria In Solid Tumours**
REEC	**Registro Español de Estudios Clínicos (Spanish Registry of Clinical Studies)**
Rx	**Radiography**
SAE	**Serious adverse event**
SAP	**Statistical Analysis Plan**
SAR	**Serious adverse reaction**
SC	**Subcutaneous**
SD	**Stable disease**
SDV	**Source Data Verification**
SmPC	**Summary of Product Characteristics**
SP	**Safety Population**
SUSAR	**Suspected unexpected serious adverse reaction**
PD-1	**Programmed death-1**
PD-L1	**Programmed death ligand-1**
TR	**Translational Research**
UC	**Urothelial cancer**
ULN	**Upper Limit of Normality**
VS	**Vital Signs**
WBC	**White Blood Count**
wGC	**weekly Gemcitabine plus cisplatin**
WHO	**World Health Organization**

2. GENERAL INFORMATION

2.1. Study Identification

Short title: Study of atezolizumab and split-dose cisplatin/gemcitabine and in urothelial carcinoma

Protocol number: SOGUG-2020-IEC (VEJ-1)

EudraCT No.: 2020-001326-65

2.2. Monitoring Organization

MFAR Clinical Research
[redacted]

2.3. Sponsor information

Spanish Oncology Genitourinary Group (SOGUG)
[redacted]

2.4. Coordinating investigator

Guillermo de Velasco M.D., PhD.
[redacted]

2.5. Investigators and study centres

It is expected the participation of 12 Sites in Spain. The list of Sites and the corresponding Principal Investigators is provided in a separated document.

3. INVESTIGATIONAL MEDICINAL PRODUCT (IMP) DESCRIPTION

3.1. Study medication

Atezolizumab:

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01XC

Presentation: 60 mg/mL glass vials of 20-mL, nominal atezolizumab amount per vial, 1200 mg. Commercial medication labeled for clinical trial.

Pharmaceutical form: Concentrate for solution for infusion. Clear, colourless to slightly yellowish liquid.

Supply: Roche Pharma will supply atezolizumab to the Sponsor that will supply this product to the sites pharmacy.

Gemcitabine

Pharmacotherapeutic group: Antineoplastic agents - Alkylating agents - Antimetabolites - Pyrimidine analogues, ATC code: L01BC05

Presentation:; Glass vial: *200 mg/5.3 mL *or* 200 mg/2 mL; 1000 mg/10 mL or 1000 mg/26.3mL; 1500 mg/15 mL and *2000 mg/52.6 mL *or* 2000 mg/20 mL. Commercial medication not-labeled for clinical trial.

Pharmaceutical form: *Concentrate for solution for infusion according to different commercial presentations authorized in Spain.

Supply: By participating sites under standard treatment criteria

Cisplatin

Pharmacotherapeutic group: Antineoplastic agents - Other antineoplastic agents, ATC code: L01XA01

Presentation: 1 mg/mL glass vials of 10-mL, 50-mL and 100-mL. Commercial medication not-labeled for clinical trial.

Pharmaceutical form: Concentrate for solution for infusion.

Supply: By participating sites under standard treatment criteria.

4. RATIONALE AND OBJECTIVES

4.1. Rationale

4.1.1. Current state of the art

Cisplatin-based chemotherapy (70 mg/m^2) has been the standard of care for first-line treatment for surgically unresectable and metastatic patients fit enough to tolerate cisplatin for more than 30 years (*Saxman SB, et al. 1997; Von der Maase, et al. 2000; Bellmunt J, et al. 2016*). However, a standard dose schedule is not feasible for a significant number of patients (about 50%). Age-related physiological changes and comorbidities are common in the uro-oncology field and, as expected, affect treatment choices and outcomes. Renal function impairment, cardiovascular disease, neuropathy, hearing loss are commonly reported in patients with bladder cancer (*Bellmunt J, et al. 2016*; *Katz H, et al. 2017*); but its toxicity (*van Leenders GJLH, 2019*).

According to the most recent update on cumulative evidence and as summarized in the most recent ESMO Bladder Cancer Treatment Recommendations published on 16 December 2019, a number of cisplatin-containing regimens are acceptable although gemcitabine and cisplatin [I, A] is the most widely accepted (*Von der Maase, et al. 2000*). Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) [I, B], MVAC with granulocyte colony-stimulating factor (G-CSF) [I, B], and gemcitabine, cisplatin and paclitaxel [I, C] are alternatives which have established themselves as options over time (*Loehrer PJ, et al. 1992; Sternberg CN, et al 2006; Bellmunt J, et al. 2012; Grande E, et al. 2019*). Although these specific regimens may lack proven advantage or non-inferiority compared with gemcitabine and cisplatin, they can be considered as options in selected patients.

4.1.2. Split-Dose Cisplatin

For those patients with mUC cisplatin-ineligible or who have progressed on a platinum-based regimen treatment options are limited (*Koshkin VS, et al. 2018*) and are usually palliated with carboplatin-based regimen, single-agent taxane or gemcitabine, or split-dose cisplatin-based regimens may be employed. In fact, some studies have presented data on up to 50% of patients eligible for cisplatin might be treated with carboplatin-based chemotherapy based on physician criteria (ie. IMvigor 130; *Grande E, et al. 2019*).

The difficult-to-treat concept of this disease entails the undoubtedly high age of most of around 80% of patients with UC (*Gore JL, et al. 2010*).

Administration of cisplatin 35 mg/m2 on day 1 + 8 or 1 + 2 (i.e., split schedule) is a commonly used alternative. Several studies have reported that split dose GC has comparable response rates in metastatic disease to other platinum containing regimens (*Morales-Barrera R, et al. 2012*), but has a favourable toxicity profile and considerably less time burden on day care facilities (*Sellers LE, et al. 2016*). These led us to consider that split dose GC should be a feasible alternative to the longer more toxic regimens, particularly in metastatic disease.

4.1.3. PD-L1 and the role of atezolizumab in mUC

Expression of programmed death ligand-1 (PD-L1) is prevalent among many human tumors (*Dong et al. 2002*), and its overexpression is associated with poor prognosis for patients with certain cancers (*Thompson et al. 2006; Hamanishi et al. 2007; Okazaki T and Honjo T, 2007;*

Hino et al. 2010, Mu et al. 2011). Therefore, interruption of the PD-L1/PD 1 pathway represents an attractive strategy to reinvigorate tumor-specific T cell immunity.

Since May 2016, five different agents targeting the PD-1/PD-L1 pathway (atezolizumab, pembrolizumab, nivolumab, avelumab, durvalumab) have received FDA approval for the treatment of aUC in the platinum-refractory setting, while pembrolizumab and atezolizumab are FDA-approved for cisplatin-ineligible patients in the first-line setting (*Koshkin VS 2018*). For platinum or chemotherapy-ineligible patients with mUC, immune checkpoint inhibitors (ICI) such as inhibitors of programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) are approved regardless of PD-L1 expression, including pembrolizumab and atezolizumab (*Einstein and Sonpavde, 2019*).

Atezolizumab is a humanized immunoglobulin (IgG1) monoclonal antibody that is produced in Chinese hamster ovary (CHO) cells. Atezolizumab targets programmed death-ligand 1 (PD-L1) on tumor-infiltrating immune cells (ICs) or tumor cells (TCs) and prevents interaction with the programmed death-1 (PD-1) receptor and B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells and other immune cells. The PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T cell response through increased T cell priming, expansion, and/or effector function. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc effector function. By eliminating Fc-effector function and antibody-dependent cell-mediated cytotoxicity, antibody-mediated clearance of activated effector T cells is also eliminated.

Atezolizumab has demonstrated efficacy and a tolerable safety profile in a range of cancers, including locally advanced or mUC (*Herbst RS, et al. 2014; Powles T, et al. 2014, Fehrenbacher L et al. 2016; McDermott DF, et al. 2016; Rosenberg JE, et al. 2016*). Cumulative data on efficacy at the time of this study design (March 2020) suggest that atezolizumab as a single-agent for first-line in patients with mUC entails clinical benefit in terms of objective responses, durable responses, and OS.

Clinical data from the first-line cisplatin-ineligible IMvigor210 cohort—the first report of an anti–PD-L1/PD-1 checkpoint inhibitor in this setting— atezolizumab conferred significant clinical benefit (*Rosenberg JE, et al. 2016*), leading to accelerated regulatory approval, and several biomarkers associated with response were identified. Furthermore, encouraging durable response rates, survival and tolerability (*Balar AV, et al. 2017*) have been also reported.

Interim results (2018) from the ongoing IMvigor 130 trial (atezolizumab *vs* atezolizumab plus platinum-based chemotherapy in locally advanced/mUC not previously treated) has shown a reduction on survival for those patients treated with atezolizumab alone when compared to those who received platinum-based chemotherapy (carbo- or cis- at physician discretion), not previously treated and with tumors showing a low-PD-L1 expression (<5% of immune cells with positive staining) (*EMA Tecentriq Assessment Report*).

4.2. Hypothesis

The results of trials combining checkpoint inhibitors or platinum-based chemotherapy plus PD-1/PD-L1 inhibitors are eagerly awaited. The combination of split cisplatin with

atezolizumab is a feasible treatment that may provide better outcomes than carboplatin/based combinations.

In the IMvigor130, 52% of patients considered cisplatin eligible at the entry of the study were treated with carboplatin. Subanalysis presented at ESMO 2019 (*Grande E, et al. 2019*) has also shown a longer median OS are achieved with cisplatin-based chemotherapy combined with atezolizumab (21.7 months) when compared to the carboplatin-based chemotherapy plus atezolizumab (14.2 months), with similar findings when it comes to PFS 8.8 months with cisplatin/gemcitabine/atezolizumab vs 7.1 months carboplatin/gemcitabine/atezolizumab.

A reasonable strategy may be the use of split cisplatin with atezolizumab to increase the number of patients receiving cisplatin.

4.3. Rationale for dose selection

As per Atezolizumab Investigator's Brochure (IB) at the time of this study design (*version 15, July 2019*), the standard fixed dose of 1200 mg, equivalent to 15mg/kg in a typical patient. No dose-limiting toxicities were observed at the 20 mg/kg dose level and the incidence and intensity of AEs reported have not been shown to be dependent on dose. A maximum tolerated dose has not been established. Atezolizumab is supplied in vials containing the fixed 1200 mg dose of drug substance, which minimizes the chance of overdose. Because the dose per patient is not based on weight or body surface area, and no dose calculation is required, the risk of overdose due to medication errors is minimal. The data available to date suggest that the potential for harm from overdose is very low.

Weekly gemcitabine with GC every 3-4 weeks is considered conventional first-line chemotherapy for aUC. Weekly split-dose cisplatin with wGC might be less toxic and have similar activity. Considering the probable lower nephrotoxicity of fractionated cisplatin, prospective evaluation of wGC might be warranted across cisplatin-eligible and -ineligible patients to develop a single chemotherapy template for the development of combinations with biological agents in a broad population of patients (*Maughan BL, et al. 2013*).

In conclusion, the proposed scientific rationale and the preliminary benefit-risk profile of the study treatments observed in previous trials support the further investigation of the combination in the patient population and dosification regimen chosen for this study.

4.4. Study Objectives

4.4.1. Primary Objectives

To evaluate the preliminary efficacy of atezolizumab plus split-dose gemcitabine and cisplatin (GC) for the first-line setting, in patients with histologically confirmed advanced (locally advanced and metastatic) urothelial cancer in terms of overall response rate (ORR) assessed by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

4.4.2. Secondary Objectives

Efficacy:

- To evaluate the *duration of response (DoR)* associated with the study treatment,

understood as the time from first confirmed response (CR or PR) to the date of the documented progressive disease as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.

- To determine the *overall survival (OS)* of patients with locally-advanced or mUC treated with the intended treatment regimen, understood as the time from first dosing date to the date of death. A subject who has not died will be censored at the last known date alive.
- To evaluate the *time to response (TtR)* associated with the study treatment, understood as the time from the first dose of the study treatment to the and confirmed response (CR or PR) based on RECIST 1.1 criteria.
- To evaluate the *clinical benefit rate (CBR)*, defined as the percentage of patients who have achieved complete response, partial response and stable disease. Stable disease should be maintained for at least 6 months to be considered as a CBR event.
- To determine the *progression-free survival (PFS)* of patients with locally-advanced or mUC treated with the intended treatment regimen, defined as the time from first dosing date until disease progression or death from any cause. Patients who have not progressed and start a new line of treatment will be censored.

Safety:

- To evaluate *safety* of the intended treatment regimen based on the frequency and severity of adverse events assessed by NCI CTCAE v5.0.

4.4.3. Exploratory objectives

- To explore potential correlation of efficacy with relevant potential prognostic factors/stratification factors
- To evaluate the relationship between the expression of PD-L1 and microbiome with ORR and PFS during experimental treatment.

5. STUDY DESIGN

5.1. Study design

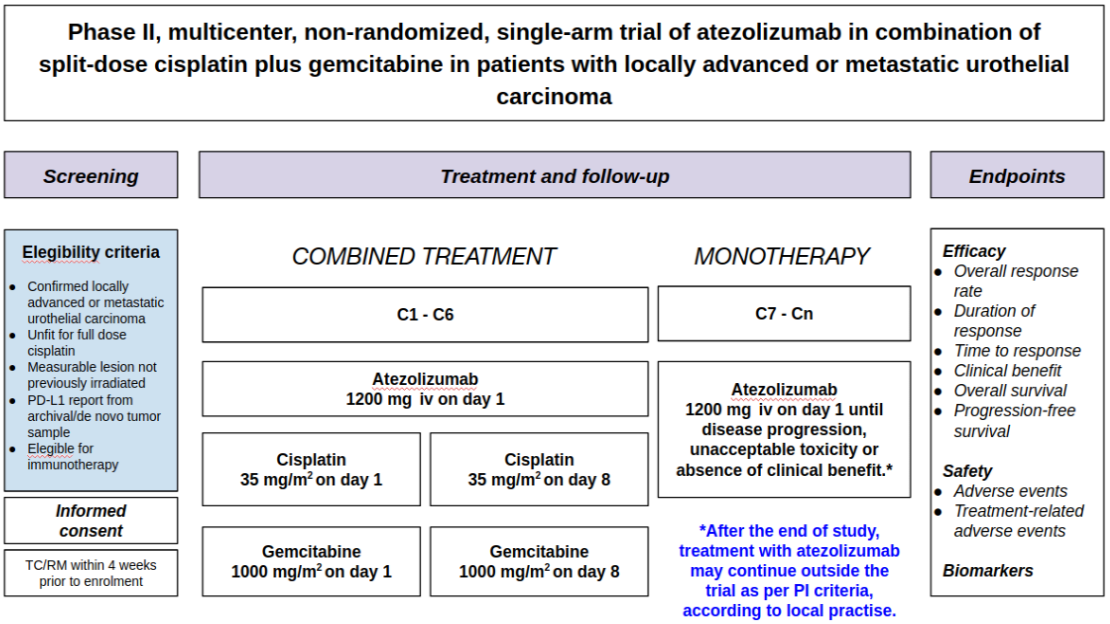
The AUREA study is a multicenter, open labelled, single arm, Phase II clinical trial of of atezolizumab in combination of split-dose cisplatin plus gemcitabine in patients with locally advanced or metastatic urothelial carcinoma (additional details on the eligibility criteria of the study are found in section 6 of this protocol).

The design includes screening phase, combined treatment initial phase, monotherapy treatment phase, follow-up phase and translational research with biopsies, blood samples and faecal samples.

The dose scheme includes the initial dose of atezolizumab (1200 mg) intravenously administered every 21 days (one cycle) up to disease progression, unacceptable toxicity or absence of clinical benefit. Dose adjustment or dose reductions of atezolizumab are not expected. Additional information on the treatment, modifications, and dose delays is available in section 7 of this protocol. AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation.

Study treatment will begin as soon as possible after signing the informed consent (as per ***section 5.2*** of this protocol) and inclusion will be completed as per ***section 5.3*** of this protocol.

Figure 1. Study design



Phase II, multicenter, non-randomized, single-arm trial of atezolizumab in combination of split-dose cisplatin plus gemcitabine in patients with locally advanced or metastatic urothelial carcinoma
Screening
Treatment and follow-up
Endpoints
Elegibility criteria
Confirmed locally advanced or metastatic urothelial carcinoma
Unfit for full dose cisplatin
Measurable lesion not previously irradiated
PD-L1 report from archival/de novo tumor sample
Elegible for immunotherapy
Informed consent
TC/RM within 4 weeks prior to enrolment
COMBINED TREATMENT
MONOTHERAPY
C1 - C6
C7 - Cn
Atezolizumab 1200 mg/m² iv on day 1
Atezolizumab 1200 mg/m² iv on day 1 until disease progression, unacceptable toxicity or absence of clinical benefit.*
Cisplatin 35 mg/m² on day 1
Cisplatin 35 mg/m² on day 8
Gemcitabine 1000 mg/m² on day 1
Gemcitabine 1000 mg/m² on day 8
*After the end of study, treatment with atezolizumab may continue outside the trial as per PI criteria, according to local practise.
Efficacy
Overall response rate
Duration of response
Time to response
Clinical benefit
Overall survival
Progression-free survival
Safety
Adverse events
Treatment-related adverse events
Biomarkers

5.2. Patient selection

Once all regulatory and sponsor requirements are completed confirming that the study is fully active in the corresponding site, informed consents can be offered to potential patients, and patient selection can start in this site.

5.3. Screening period and screening failure

Informed consent will be obtained prior to the start of the specified screening window. Procedures conducted as part of the subject's routine clinical management (e.g.., blood count determinations and imaging studies) prior to signing of ICF may be used for screening or for defining baseline data, provided these procedures are conducted as specified in the protocol.

Other procedures (such as the faecal sample collection) must be developed once the patient has provided the signed consent for participation.

Once ICFs are signed, a trial screening number will be assigned to each patient after

registering at Electronic Data Capture (EDC) platform. Each site will receive access to the EDC platform to register each screened case because as per GCP guidelines, it is mandatory to register every patient who signs a consent form.

Furthermore, within the Investigator Site File (ISF), a Patient Identification List will be included in order to identify patients according to local normal practice. This document will allow for immediate and unequivocal identification of patients participating in this clinical trial.

This document will always be stored under Investigator staff custody at the site. The screening number will identify patients throughout the screening period while procedures needed to confirm the subjects' suitability for the trial protocol, such as clinical laboratory tests, imaging, and others are performed.

Screening determinations should be performed as per indications specified in ***Table 4*** include ICF signature, eligibility assessments, tumour characteristics, ECG, clinical evaluation (AE, PE, ECOG, VS, BMI, and symptom control), laboratory determinations (FBE, Biochemistry, electrolytes, liver panel TF), Pancreatic enzymes, serology, urinalysis, pregnancy test, concomitant medication, biological samples (tumour sample, biomarkers), CT Scan / MRI. Availability of archival tumor blocks should be verified. Additional information about screening procedures can be found in ***Section 8.4*** of this protocol.

5.4. Patient registration/enrollment

After confirming that a patient fulfils all eligibility criteria of the study (***Section 6***, *study population*), site staff will initiate the electronic case report form (eCRF) registration procedure. Once registration has been completed, the site staff will receive the "Inclusion confirmation communication", and study treatment can be initiated as per ***Section 7*** *(treatment description*).

5.5. Treatment description, doses and schedules

During treatment, patients should be visited at baseline for administration of the study treatment (Day 1 of each cycle) as follows: Atezolizumab 1200 mg, gemcitabine 1000 mg/m^2 and cisplatin 35 mg/m^2. A second visit on day 8 (D8) should be compiled in order to administer the second dose of gemcitabine 1000 mg/m^2 and cisplatin 35 mg/m^2 cisplatin.

Atezolizumab will be administered first as a IV infusion according to what is detailed in section 7.4 of this protocol, followed by the cisplatin infusion and then the gemcitabine infusion. The GC infusion will start at least 30 minutes after completion of the atezolizumab infusion. At the investigator's discretion, atezolizumab may be administered over a longer infusion time (60 minutes) if the participant developed a prior infusion reaction.

This regimen will be repeated every three weeks (q3w) for up to 6 cycles. Once cycle 6 is done, Atezolizumab 1200 mg/m^2 will be administered as monotherapy every 3 weeks until disease progression, discontinuation due to unacceptable toxicity, withdrawal of consent or absence of clinical benefit. AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative

regulation.

All chemotherapy agents' preparation, premedication, administration, monitoring, and management of complications are to follow local prescription guidelines and regulations. The dose of chemotherapy may be capped per local standards.
All participants will be monitored continuously for adverse events (AEs) while on study treatment. Treatment modifications (eg, dose delay, reduction, retreatment, or discontinuation) will be based on specific laboratory and adverse event criteria, as described in ***Section 7.45.2*** and ***Section 7.55.3***.

Table 1. AUREA's trial treatment schedule

Drug	Drug	Frequency	Administration	Treatment period	Use
Atezolizumab	**1200 mg**	**Q3W**	**IV infusion**	**Day 1 of each cycle**	**Experimental**
Gemcitabine	**1000 mg/m^2/day**	**Q3W**	**IV infusion**	**Day 1 and Day 8 of each cycle up to 6 cycles**	**Experimental**
Cisplatin	**35 mg/m^2/day**	**Q3W**	**IV infusion**	**Day 1 and Day 8 of each cycle up to 6 cycles**	**Experimental**

5.6. Duration of study, recruitment, treatment and follow-up

- Enrolment/recruitment period: 12 months
- First patient first visit (FPFV): TBD
- Last patient last visit (LPLV): FPFV + 24 months
- Treatment period: Up to 24 months from LPFV
- Follow-up period: 24 months
- Planned end of study date: FPFV + up to 36 months

5.7. Determinations during the study

Determination during the study will be performed as per ***Table 4*** and ***Section 8.3*** of this protocol.

5.7.1. Screening phase

The baseline assessments and procedures should be performed within 28 days before inclusion, and when applicable, as close as possible to the start of study treatment.

5.7.2. Treatment phase

Before each treatment administration chemotherapy/atezolizumab administration laboratory, medical consulting and other determinations will be performed according to ***Table 4*** and ***Section 8.5*** to ensure that treatment can be safely administered.

A CT Scan or MRI will be performed at baseline, on week 9, week 18 and then every 12 weeks (q12w) ± 1w until objective disease progression as per PI's criteria or death (whichever comes first). Blood samples for biomarkers studies should be collected before administration

of cycles 4 and 7 and at the time of PD (end of treatment if applicable).

For patients with progression reported as per RECIST criteria at week 9, continuity of treatment with atezolizumab should be evaluated by the PI of each site as per clinical benefit criteria.

5.7.3. Safety visit (after the end of treatment by any reason)

Safety follow-up visits will be scheduled up to 30 days after the last dose of study treatment (end of treatment).

5.7.4. Follow up until progression

After the end of the combined treatment with atezolizumab and split dose of gemcitabine and cisplatin, if the patient has finished treatment without progression and does not start a new treatment line, will be visited every 12 weeks. At the time of progression blood samples should be collected for biomarkers studies.

5.7.5. Follow up after progression

Overall, after progression, patients will continue the long-term follow up every 6 months until death or end of study. Sponsor will ask the survival status of all patients at the final clinical trial database closing, in order to maximise the median follow up of patients for overall survival data.

In cases where atezolizumab treatment has been maintained because of clinical benefit, follow up will comply with the “Follow up until progression” conditions, with visits every 12 weeks along with radiological evaluation/assessment of the disease.

5.8. End of study (EoS)

The end of study is defined as the Last Patient Last Visit (LPLV) and will be considered at 24 months after last patient first visit (LPFV), Sponsor will ask survival status of all patients at the final clinical trial database closing, in order to maximise the median follow up of patients for overall survival data.

5.9. Outcome assessments

5.9.1. Response evaluation according RECIST 1.1

All patients will have their best response according to RECIST criteria 1.1 from the start of study treatment until the end of treatment classified as outlined below:

- Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later.
- Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Tumour markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.
- Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.
- Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment, for example where the tumour burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

5.9.2. Safety assessments

Safety parameters are AE, SAE, AESI, pregnancy, medication error, overdose. Additional safety information could be derived from ECG, lab test, pregnancy test, or vital sign exam. The assessment of adverse events will include the type of event (including symptoms, physical exam findings and laboratory abnormalities), the incidence, severity, timing, seriousness, and relatedness regarding the treatment under study. Adverse events will be recorded and reported in the corresponding section of the case report form. The grade of adverse events will be coded according to the National Cancer Institute's Common Toxicity criteria (NCI-CTCAE v5.0 scoring system). The worst toxicity score will be recorded. In case of SAE and AESI the investigator should immediately fill in the dedicated SAE form and send it by as detailed in ***Section 9.2***

6. STUDY POPULATION

6.1. Inclusion criteria

1. Male or female subjects ≥ 18 years old.

2. Written informed consent approved by the Independent Ethics Committee (IEC), prior to the performance of any trial activities.

3. Patients with histologically documented, locally advanced (T4B, any N; or any T, N2-3) or metastatic urothelial carcinoma (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).*

4. Patients should not be eligible (unfit) for full dose of cisplatin, in the investigator's judgement, based on:
   a. Age older than 70 years
   a. ECOG Performance status (PS) 2 or Karnofsky PS of 60 - 70% (only 15 patients will be included with ECOG 2)
   b. Measured creatinine clearance (ClCr) > 30 and < 60 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for the determination of creatinine clearance:

      Males:

      $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

      Females:

      $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

   c. Any other reason the physician considers but should specify in the CRF and discussed with the PI.
5. At least one measurable lesion through radiographic tumor evaluation (CT scan or magnetic resonance imaging) as defined by RECIST version 1.1, that has not been previously irradiated within 4 weeks prior to the study enrolment.

6. Patients with an archival or *de novo* tumor biopsy (representative formalin-fixed paraffin-embedded/FFPE paraffin block obtained within 6 months prior to inclusion) with an associated pathology report, for testing of PD-L1 expression prior to study enrollment. Samples in unstained slides could be acceptable (at least 15 slides).

7. Patients with adequate normal organ and marrow function as defined below:
   a. Haemoglobin (Hb) ≥ 9.0 g/dL.
   b. Absolute neutrophil count (ANC) ≥ 1500 per mm^3.
   c. Platelet count ≥ 100,000 per mm^3.
   d. Serum bilirubin ≤ 1.5 X institutional upper limit of normal (ULN) unless liver metastases are present, in which case it must be ≤ 2X ULN. This will not

apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology); however, they will be allowed only in consultation with their physician.

e. Serum transaminases (ALT, AST and GGT) ≤ 2.5X institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 3X ULN.

8. No major active bleeding.

9. Female subjects of childbearing potential (not surgically sterile or at least 2 years postmenopausal) must provide a negative urine pregnancy test at screening, and use a medically accepted double barrier method of contraception (i.e. condom with spermicide + IUD or cervical caps). In addition, they must agree to continue the use of this double barrier method for the duration of the study and for 6 months after participation in the study.

10. Males should agree to abstain from sexual intercourse with a female partner or agree to use a double barrier method of contraception (i.e. condom with spermicide, in addition to having their female partner use some contraceptive measures such as oral contraceptive drugs, intrauterine device (IUD) hormonal contraception, or cervical caps), for the duration of the study and for 6 months after participation in the study

11. Willingness and ability of patients to comply with the protocol for the duration of the study including undergoing treatment as well as availability for scheduled visits and examinations including follow up.

6.2. Exclusion criteria

1. Prior treatment with any immune checkpoint inhibitor therapy (e.g., CTLA4, PD-1, or PD-L1 targeting agent).*

   **Note*: Prior adjuvant or neoadjuvant treatment with targeted therapy/checkpoint inhibitors is allowed, as long as the last dose was administered at least 12 months prior to the patient inclusion in this trial.

2. Presence of active second malignancy and/or prior malignancy in the last 2 years is allowed except for the following:
   a. adequately treated basal cell or squamous cell skin cancer,
   b. adequately treated Stage I or II cancer from which the patient is currently in complete remission per investigators' clinical judgment.

3. Patient receiving radiation therapy within 4 weeks before inclusion.

4. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

5. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis).

6. History of allogeneic organ transplant.

7. Subjects having a diagnosis of immunodeficiency or are receiving systemic steroid therapy or any other form of immunosuppressive therapy within 28 days prior to the first dose of trial treatment.

8. Current or prior use of immunosuppressive medication within 7 days prior to enrolment, except the following:
    a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);
        i. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;
        ii. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
9. The subject has uncontrolled, significant intercurrent or recent illness (within 6 months prior to inclusion) including, but not limited to, the following conditions:

    a. Cardiovascular disorders:
        i. Class 3 or 4 congestive heart failure as defined by the New York Heart Association, unstable angina pectoris, and serious cardiac arrhythmias.
        ii. Uncontrolled hypertension defined as sustained blood press > 150 mm hg systolic or > 100 mm hg diastolic despite optimal antihypertensive treatment.
        iii. Stroke (including transient ischemic attack [TIA]), myocardial infarction, other ischemic event, or thromboembolic event (e.g., deep venous thrombosis [DVT] and pulmonary embolism) within 6 months before inclusion. Subjects with a more recent diagnosis of DVT are allowed if stable, asymptomatic, and treated with LMWH for at least 6 weeks before study treatment.

    b. Gastrointestinal disorders (e.g., malabsorption syndrome or gastric outlet obstruction) including those associated with a high risk of perforation or fistula formulation:
        i. Tumours invading the GI tract, active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic or biliary duct, or gastric outlet obstruction.
        ii. Abdominal fistula, GI perforation, bowel obstruction, or intra-abdominal abscess within 6 months before inclusion. Note: complete healing of an intra-abdominal abscess must be confirmed prior to start of the treatment.

    c. Clinically significant hematemesis or hemoptysis of > 0.5 teaspoon (> 2.5 ml) of red blood or history of other significant bleeding within 3 months before treatment.

    d. Cavitating pulmonary lesion(s) or known endobronchial disease manifestation.

    e. Lesions invading major pulmonary blood vessels.

f. Other clinically significant disorders such as:
    i. Active infection requiring systemic treatment, infection with human immunodeficiency virus or acquired immunodeficiency syndrome-related illness, or chronic hepatitis B or C infection.
    ii. Serious non-healing wound/ulcer/bone fracture.
    iii. Malabsorption syndrome.
    iv. Moderate to severe hepatic impairment (child-pugh B or C).
    v. Requirement for hemodialysis or peritoneal dialysis.
    vi. Uncontrolled diabetes mellitus.

10. Major surgery (e.g., GI surgery and removal or biopsy of brain metastasis) within 8 weeks before inclusion. Complete wound healing from major surgery must have occurred 4 weeks before study treatment and from minor surgery (e.g., simple excision, tooth extraction) at least 10 days before study treatment. Subjects with clinically relevant ongoing complications from prior surgery are not eligible.

11. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

12. Any test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or chronic infection.

13. Women who are pregnant or are breastfeeding.

14. Male patients must be surgically sterile or must agree to use effective contraception during the period of therapy.

15. Any of the following within 6 months prior to study entry: myocardial infarction, uncontrolled angina, uncontrolled hypertension, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack.

16. Previously identified allergy or hypersensitivity to components of the study treatment formulations.

6.3. Criteria for withdrawal from the treatment and study

6.3.1. Permanent Interruption of study treatments

Any reason for discontinuing investigational products must be clearly recorded on the electronic case report forms (eCRF).

Patients will receive the product under investigation as per schedule described in section 5.5 of this protocol or until any of the following occurs:

- *Objective disease progression*. However, patients with disease progression at week 9 who are continuing to derive clinical benefit from the study treatment will be eligible to continue with single-agent atezolizumab, provided that the treating physician has determined that the benefit/risk for doing so is favorable;
- *Global deterioration of health status requiring discontinuation*;

- Unacceptable toxicity. If the unacceptable toxicity is attributed to one of the two study treatments, the investigator (in discussion with the sponsor) may continue treatment with the other study treatment;
- Investigator's decision;
- Pregnancy;
- Protocol violation, only when non-compliance might significantly impact in patients safety and/or trial results validity, as per case by case Sponsor assessment/criteria;
- Lost to follow-up;
- Patient refused further treatment (follow-up permitted by patient);
- Study terminated by sponsor;
- Death.

For all participants, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration' in the source data and in the eCRF.

A temporary interruption in study medication due to an AE is not considered to be permanent discontinuation from investigational product.

Tumor assessments for participants, who discontinue study treatment without radiographic progression, should continue as per protocol until radiographic progression is determined.

Chemotherapy dose reduction is allowed in study. Any participant with two prior dose reductions to one agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent. A participant who is discontinued from the chemotherapy treatment will remain on the study and receive atezolizumab.

If a participant meets criteria for discontinuation and the investigator is unable to determine whether the event is related to atezolizumab or chemotherapy, the participant should discontinue all treatments.

The assessment for discontinuation of atezolizumab should be made separately from the assessment made for discontinuation of chemotherapy. If criteria for discontinuation for atezolizumab are met before the first 6 atezolizumab + split-doses of gemcitabine and cisplatin chemotherapy cycles have been completed, the split-dose GC chemotherapy may continue until 6 cycles have been completed.

6.3.2. Withdrawal from the study

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw at any time.

The investigator may also, at his/her discretion, withdraw the subject from participating in this study at any time, or the sponsor may discontinue the study.

Reasons for early withdrawal from the study should be documented in the eCRF as:

- Study closed/terminated by sponsor;
- Lost to follow-up;
- Investigator's decision;
- Subject withdrew consent (refused further follow-up);
- Major protocol non-compliance. Protocol violation, only when non-compliance might significantly impact in patients safety and/or trial results validity, as per case by case Sponsor assessment/criteria;

- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstances, every effort should be made to document patient outcomes, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Date of withdrawal from the study, with reason for withdrawal, will be recorded on the eCRF. In the case of death, a death certificate should be obtained if possible, with the cause of death evaluated and documented.

Note: Patients withdrawn the trial for any reason, cannot enter again.

7. TREATMENT DESCRIPTION

For the purpose of this study, the investigational products as defined by (ICH E6 1.33) are atezolizumab, cisplatin and gemcitabine.

7.1. Study medication

7.1.1. Atezolizumab

Atezolizumab will be supplied as 60 mg/mL glass vials of 20-mL, nominal atezolizumab amount per vial, 1200 mg.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines.

The information on the study treatment will be in accordance with approved submission documents.

AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation.

7.1.2. Gemcitabine and Cisplatin

Gemcitabine and cisplatin will be supplied as per site clinical standards.

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines, under commercial presentation and each site availability.

The information on the study treatment will be in accordance with approved submission documents.

7.2. Treatment accountability and compliance

According to local legislation, the investigator will record in the medical history that the patient is taking the medication as prescribed for each new cycle in the study.

7.2.1. Atezolizumab accountability and compliance

Atezolizumab will be dosed at the investigational site, compliance will be assessed by reviewing the consistency of information in the IWRS, the eCRF, patient records, nurse sheets, and in the pharmacy source documentation.

7.2.2. Gemcitabine and Cisplatin accountability and compliance

Compliance of the split-dose GC chemotherapy will be assessed by reviewing the consistency of information in the eCRF, patient records, nurse sheets, and in the pharmacy source documentation.

7.3. Preparation and Dispensing

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

Investigational products should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

7.3.1. Atezolizumab preparation and dispensing

Atezolizumab will be dosed at the investigational site. Atezolizumab must not be used for any purpose other than the trial. The administration of trial investigational products to patients who have not been enrolled into the trial is not covered by the trial insurance.

7.3.2. Gemcitabine plus cisplatin preparation and dispensing

The GC treatment will be administered in quantities appropriate for the study visit schedule and according to local practice. A qualified staff member will record all the study treatment using the local practise. Procedures described in each institution's pharmacy or hospital standard operating procedure manual should be followed when handling hazardous drugs.

7.4. Investigational Medical Products Administration

7.4.1. Atezolizumab administration

Atezolizumab will be administered after all procedures/assessments have been completed as described in the Schedule of Activities (***Table 4***), as a 1-hour IV infusion once every 3 weeks until disease progression, unacceptable toxicity or absence of clinical benefitbenefitt. AUREA is an Investigator Initiated Study, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. For those patients in which the PI considers that the best option for the patient is continuing atezolizumab for more than 24 months, available commercial Site supplies should be used, after managed local administrative regulation.

The infusions must not be administered as an intravenous push or bolus. The initial dose of atezolizumab must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Atezolizumab will be administered in IV infusion bags containing 0.9% sodium chloride (NaCl) and infusion lines equipped with 0.2 or 0.22 m in-line filters. The IV bag may be constructed of polyvinyl chloride, polyolefin, polyethylene, or polypropylene. The IV infusion line may be constructed of polyvinyl chloride, polyethylene, polybutadiene, or polyurethane and the 0.2 or 0.22 m in-line filter may be constructed of polyethersulfone or polysulfone. The use of administration supplies composed of materials other than those listed should be avoided if possible. Atezolizumab can be diluted to concentrations between 3.2 mg/mL and 16.8 mg/mL in IV bags containing 0.9% NaCl. Atezolizumab must be prepared/diluted under appropriate aseptic conditions as it does not contain antimicrobial preservatives.

The prepared solution for infusion should be used immediately to limit microbial growth in case of potential accidental contamination. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user. For flat or fixed dosing (1200 mg for

this clinical trial) in IV infusion bags, the dose solution may be stored at 2°C–8°C (36°F – 46°F) for 24 hours or at ambient temperature ≤ 25°C (77°F) for 8 hours. This time includes storage and time for administration for infusion.. Do not shake or freeze infusion bags containing the dose solution.

Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the Dosage and Administration Instruction contained in the Summary of Product Characteristics, and when applicable, the corresponding Pharmacy Guidelines.

Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. See more information in ***Appendix 1***.

7.4.1.1. Intrapatient Atezolizumab Dose Reduction

The dose amount required to prepare the atezolizumab infusion solution will be based on the corresponding flat dose of 1200 mg established in this protocol. Overall, Atezolizumab dose reduction for toxicity management is not permitted. Toxicity management (dose delay or discontinuation) in case of immune-mediated events is described in ***Appendix 1***.

7.4.2. Gemcitabine and cisplatin administration

The infusions must not be administered as an intravenous push or bolus. The estimated total infusion time for this treatment takes up to two hours for Day 1 and Day 8 of each 21-days cycle. Typically, IV hydration is given both before and after cisplatin and can add up to two hours on administration days. Infusion times may vary depending on physician preference or patient tolerability.

7.4.2.1. Gemcitabine administration

Gemcitabine will be administered after all procedures/assessments have been completed as described in the Schedule of Activities (***Table 4***), as a 30-minutes IV infusion on days 1 and 8 once every 3 weeks for a maximum of 6 cycles.

Gemcitabine is tolerated well during infusion and may be administered ambulant. If extravasation occurs, generally the infusion must be stopped immediately and started again in another blood vessel. The patient should be monitored carefully after the administration. Treatment omitted will not be reinstated within a cycle. Treatment will start on day 1 of the next cycle once the absolute granulocyte count reaches at least 1,500 ($x10^6$/l) and the platelet count reaches 100,000 ($x10^6$/l).

7.4.2.2. Cisplatin administration

Cisplatin should be administered by intravenous infusion over a period of 6 to 8 hours on days 1 and 8 once every 3 weeks for a maximum of 6 cycles. Adequate hydration must be maintained from 2 to 12 hours prior to administration until minimum 6 hours after the

administration of cisplatin. Hydration is necessary to cause sufficient diuresis during and after treatment with cisplatin. It is realised by intravenous infusion of one of the following solutions specified on the SmPC.

7.4.2.3. Intrapatient Gemcitabine and Cisplatin Dose Reduction

According to the current version of Gemcitabine Summary of Product Characteristics (*Gemcitabine SmPC*) at the time of this study design (March 2020), dose modifications are considered in case of ***haematological toxicity*** as described below. For the matter of this study, information on dose modification recommendations for gemcitabine given in monotherapy or in combination with cisplatin for bladder cancer are described.

Dose modifications due to haematological toxicity: Initiation of a cycle
For all indications, the patient must be monitored before each dose for platelet and granulocyte counts. Patients should have an absolute granulocyte count of at least 1,500 (x 10^6 /l) and platelet account of 100,000 (x 10^6 /l) prior to the initiation of a cycle.

Dose modifications due to haematological toxicity: Within a cycle
Dose modifications of gemcitabine within a cycle should be performed according to ***Table 2***:

Table 2. Dose modification of gemcitabine within a cycle for bladder cancer, NSCLC and pancreatic cancer, given in monotherapy or in combination with cisplatin

Absolute granulocyte count (x 10^6/l)		**Platelet count (x 10^6/l)**	**Percentage of standard dose of Gemcitabine (%)**
> 1,000	**and**	**> 100,000**	**100**
500 - 1,000	**or**	**50,000-100,000**	**75**
<500	**or**	**< 50,000**	**Omit dose***

*Treatment omitted will not be reinstated within a cycle before the absolute granulocyte count reaches at least 500 (x106 /l) and the platelet count reaches 50,000 (x10^6 /l).

Dose modifications due to haematological toxicity: Subsequent cycles for all indications
The gemcitabine dose should be reduced to 75% of the original cycle initiation dose, in the case of the following hematologic toxicities (***Table 3***):

Table 3. Dose modification of gemcitabine in subsequent cycles for all indications

	Count (x 10^6/l)	**Time**	**Percentage of standard dose of Gemcitabine (%)**
Absolute granulocyte	**< 500**	**> 5 days**	**75**
	< 100	**> 3 days**	**75**
Platelet count	**< 25,000**	**Not applicable**	**75**
Febrile neutropenia	**-**	**-**	**75**
Cycle delay > 1 week to toxicity	**-**	**-**	**75**

Patients will be monitored closely for toxicity; Gemcitabine may be adjusted by dosing

interruption with or without dose reduction as indicated in ***Table 2*** and ***Table 3.***

Management of patients requiring more than 2 dose reductions of any of the IMPs (one dose level decrease at a time) should be discussed with the Coordinating Investigator.

Patients who have undergone dose reduction may also undergo dose re-escalation back to the previous dose level at the discretion of the Investigator in the absence of Grade ≥2 non-hematologic treatment-related toxicity for at least 28 days.

7.5. Special Precautions for Investigational Medical Products

7.5.1. Special Precautions for Atezolizumab

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Pneumonitis secondary to PD1/PDL1 inhibitor drugs is a rare but potentially serious side effect, patients should be monitored for signs and symptoms of pneumonitis during physical examination (PE), and causes other than immune-mediated pneumonitis should be ruled out in the case of findings during PE.

7.5.1.1. Hepatic impairment

No dedicated studies of atezolizumab have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of atezolizumab between patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin 1.0 to 1.5 ULN and any AST, n=71) and normal hepatic function (bilirubin and AST ≤ ULN, n=401). No data are available in patients with either moderate (bilirubin > 1.5 to 3.0 x ULN and any AST) or severe (bilirubin > 3.0 ULN and any AST) hepatic impairment. Hepatic impairment was defined by the National Cancer Institute criteria of hepatic dysfunction. More information available in the current version of Atezolizumab Investigator's Brochure.

7.5.1.2. Renal impairment

No dedicated studies of atezolizumab have been conducted in patients with renal impairment. More information available in the current version of Atezolizumab Investigator's Brochure.

7.5.1.3. Reproductive and Developmental Toxicity

Reproductive and developmental toxicity studies with atezolizumab have not been conducted. The PD-L1/ programmed death 1 (PD-1) signaling pathway is well established as essential in maternal/fetal tolerance and embryo-fetal survival during gestation (*Guleria et al. 2005; Habicht et al. 2007; D'Addio et al. 2011*). Administration of atezolizumab is expected to have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality.

7.5.1.4. Immune-mediated adverse reactions

Most immune-mediated adverse reactions that occur during treatment with atezolizumab are reversible with the interruptions of atezolizumab and initiation of corticosteroids and/or

supportive care. Immune-mediated adverse reactions affecting more than one body system have been observed; these may occur after the last dose of atezolizumab.

For suspected immune-mediated adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical studies in patients whose immune-mediated adverse reactions could not be controlled with systemic corticosteroid use, the administration of other systemic immunosuppressants may be considered.

Atezolizumab must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones. Specific guidelines for the management of atezolizumab-specific adverse events is available in ***Appendix 1***.

1) Pulmonary events

Pneumonitis secondary to PD1/PDL1 inhibitor drugs is a rare but potentially serious side effect, patients should be monitored for signs and symptoms of pneumonitis during physical examination (PE), and causes other than immune-mediated pneumonitis should be ruled out in the case of findings during PE.

Cases of pulmonary events, including dyspnea, cough, fatigue and pulmonary infiltrates, have been observed in clinical trials with atezolizumab. Patients should be monitored for pulmonary signs and symptoms.

Treatment with atezolizumab should be withheld for Grade 2 pulmonary event , and corticosteroids equivalent 1 to 2 mg/kg/day oral prednisone should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 pulmonary events.

2) Hepatic events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in ***Appendix 1***.

3) Gastrointestinal events

Immune-mediated colitis has been associated with the administration of atezolizumab. All events of diarrhea or colitis should be thoroughly evaluated for other common etiologies. For events of significant duration or or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis. More information provided in ***Appendix 1***.

4) Endocrine events

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected.

Thyroid-stimulating hormone (TSH) and free triiodothyronine (T3) and thyroxine (T4) levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, GH, 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. More information provided in ***Appendix 1***.

5) Ocular events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). More information provided in ***Appendix 1***.

6) Immune-Mediated Myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab and should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type Natriuretic Peptide]) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope.

Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of 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 ***Appendix 1***.

7) Infusion-Related Reactions and Cytokine-Release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated infusion-related reactions, due to IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end -organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (*Rotz et al. 2017*; *Adashek and Feldman 2019*), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs during Cycle 1 and CRS are provided in ***Appendix 1***.

8) 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 ***Appendix 1***.

9) Dermatologic events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in ***Appendix 1***.

10) Neurologic Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in ***Appendix 1***.

11) Immune-Mediated Meningoencephalitis

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness.

Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or

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

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in ***Appendix 1***

12) Renal events

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in ***Appendix 1***.

13) Immune-Mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase/CK increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

14) Severe Cutaneous Adverse Reactions (SCAR)

SCARs are a heterogeneous group of immunologically mediated drug eruptions. Although rare, these events are potentially fatal, and mainly constituted by erythema multiforme, acute generalised exanthematous pustulosis, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS). As per epidemiology data, the incidence of SJS and TEN ranges from 0.8 to 5.3 and 1.2 to 6 per million person-years respectively.

A cumulative analysis of the company safety database across the TECENTRIQ (atezolizumab) program identified at total of 99 cases of SCARs, of which 36 were confirmed by histopathology or specialist diagnosis, in patients who have received TECENTRIQ (atezolizumab). Approximately 23,654 clinical trial patients and 106,316 patients in post-marketing settings have been exposed to TECENTRIQ (atezolizumab) as of 17 May 2020. The incidence rates of SCAR, regardless of severity, from pooled atezolizumab monotherapy (N=3178) and combination therapy (N=4371) company sponsored clinical studies were 0.7% and 0.6% respectively. One fatal case of TEN was reported in a 77 year old female patient who received atezolizumab monotherapy.

Patients with signs and symptoms of SCAR should be treated according to the guidelines in ***Appendix 1***.

7.5.2. Special Precautions for Gemcitabine

Prolongation of the infusion time and increased dosing frequency have been shown to increase toxicity. Further information on particular risk for toxicity (including haematological toxicity, hepatic insufficiency, concomitant radiotherapy, live vaccinations, cardiovascular risk, pulmonary effects, renal, fertility or sodium control are displayed in the Gemcitabine SmPC.

7.5.3. Special Precautions for Cisplatin

This agent should only be administered under the direction of oncologists in specialist units under conditions permitting adequate monitoring and surveillance. Supportive equipment should be available to control anaphylactic reactions.

Cisplatin reacts with metallic aluminium to form a black precipitate of platinum. All aluminium containing IV sets, needles, catheters and syringes should be avoided. The solution for infusion should not be mixed with other drugs or additives.

Appropriate monitoring and management of the treatment and its complications are only possible if adequate diagnosis and exact treatment conditions are available.

Further information on particular risks including nephrotoxicity, neuropathies, ototoxicity, allergic reactions, hepatic function and haematological formula, carcinogenic potential, injection site reactions are displayed in the Cisplatin SmPC.

7.6. Investigational Product Storage

The investigational products should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational products are only dispensed to study participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The investigator, or an approved representative (eg, pharmacist), will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Storage conditions stated in the SRSD (ie, IB) will be superseded by the storage conditions stated on the label. Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery.

The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken must be documented and reported to the sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used

until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct patients on the proper storage requirements for take-home investigational products.

7.6.1. Atezolizumab storage

Atezolizumab must be refrigerated at 2°C - 8°C (36°F - 46°F) upon receipt until use. Atezolizumab and the diluent vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab Drug Product or the diluent; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial. Vial contents should not be frozen or shaken and should be protected from light by keeping the vial in the outer carton. This information is also available in the pharmacy manual.

7.6.2. Gemcitabine and cisplatin storage

Gemcitabine and cisplatin must be stored and controlled as specified in the product label.

7.7. Investigational Product Accountability

The delegated investigation site staff must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All bottles of study drug must be returned to the investigator by the patient at the end of each cycle and at the end of the trial, tThe sponsor will provide instructions as to the disposition of any unused investigational product if the investigative site is unable to destroy at site per local procedures.

7.8. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product Atezolizumab (e.g., at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor, and all destruction must be adequately documented.

7.9. Concomitant Treatments

Medications or vaccinations specifically prohibited in the Exclusion Criteria are also not allowed during the active treatment period, except for the administration of inactivated

influenza vaccine.

If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from study therapy or medication/vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication/vaccination schedule requires the mutual agreement of the investigator, the sponsor, and the patient.

Concomitant treatment considered necessary for the patient's wellbeing may be given at the discretion of the treating physician. All concomitant treatments, blood products, as well as non-drug interventions received by patients from screening until the end of study visit will be recorded on the CRF.

Concomitant medications and treatments, including herbal supplements, will be recorded from 28 days prior to the start of study treatment and up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (e.g., antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (e.g., transfusions).

Concurrent anticancer therapy with agents other than atezolizumab and GC are not allowed. Medications intended solely for supportive care (i.e., antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

7.9.1. Inhibitors and Inducers of CYP Enzymes

Because antibodies are cleared principally by catabolism (i.e., cleavage to small peptides and amino acids), atezolizumab is not expected to show pharmacokinetic interactions with other drugs, and is therefore not expected to interact with other drugs through protein binding, effects on cytochrome P450 activity, renal excretion or competition for common drug transporter proteins. No formal pharmacokinetic drug interaction studies have thus been undertaken with atezolizumab.

7.9.2. Concomitant Surgery

No specific information on the effect of Atezolizumab on wound healing are reported in the current version of IB nor SmPC.

7.9.3. Concomitant Radiotherapy

Toxicity of concurrent administration of gemcitabine (simultaneous or ≤ 7 days apart) depends on many different factors, including the dose of gemcitabine, the frequency of gemcitabine administration, radiation dose, radiotherapy planning technique, tissue to radiate and the theoretical irradiation volume. For the matter of this study, radiotherapy within 4 weeks prior to inclusion is considered an exclusion criteria.

For non-concurrent gemcitabine administration (administered> 7 days apart), data analysis does not indicate an increased toxicity when gemcitabine is administered at least 7 days before or after radiotherapy, except for late skin toxicity. The data that can be started administration of gemcitabine when the acute effects of radiation therapy have resolved or at least one week after radiation therapy. Radiation injury has been detected in irradiated tissues (e.g. esophagitis, colitis, and pneumonitis) in association with both concurrent and non-concurrent

use of gemcitabine. Further information can be obtained in the current version of Gemcitabine SmPC.

7.9.4. Other Prohibited Concomitant Medications and Therapies

Clarifications about Steroid Use: Data indicate that corticosteroids have an adverse effect on T-cell function and that they inhibit and damage lymphocytes (*Schleimer RP, et al. 1984; Khan MM, 2008*).

Furthermore, as with all immunotherapies intended to augment cell-mediated immunity, there is a risk that concomitant immunosuppressants such as steroids will counteract the intended benefit of the proposed study treatment. However, studies with anti-CTLA4 compounds indicate that short-term use of steroids may be employed without compromising clinical outcomes (*Weber JS, et al. 2012*).

Therefore, the use of steroids during this trial is restricted as follows:

- *Therapeutic use:* for the treatment of infusion-related reactions and short-term treatment of irAEs, steroids are permitted according to the modalities indicated in ***Appendix 1***.
- *Physiologic use:* steroid replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.
- *Prophylactic use*, e.g., for the prevention of acute infusion-related reactions, is prohibited, ***except*** prior to CT or MRI.

7.10. Rescue Medications and Supportive Care

7.10.1. Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- *Diarrhea:* All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

- *Nausea/Vomiting*: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

- *Anti-infectives:* Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice. Prophylactic administration should be considered for the cases outlined in ***Appendix 1***.

- *Anti-inflammatory or narcotic analgesics* may be offered as needed. Acetaminophen/paracetamol to a maximum total daily dose of 2 g is permitted. Daily intake over 2 g is prohibited.

- Patients who need to be on anticoagulant therapy during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be

administered, coumadin or other coumarin derivatives or other anticoagulants (including direct Xa inhibitors) may be allowed; however, appropriate monitoring of prothrombin time/international normalized ratio (PT/INR) should be performed.

8. STUDY PROCEDURES AND EVALUATIONS

8.1. Definition of efficacy variables

- *Overall Response Rate (ORR):* Assessed by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. This will be considered as the percentage/proportion of patients with confirmed complete response (CR) or partial response (PR) as their overall best response throughout the study period.

- *Duration of response* (DoR): Time from first confirmed response (CR or PR) to the date of the documented PD as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.

- *Time to response* (TtR): Time from first dosing date to the date of the documented ORR as determined using RECIST 1.1 criteria.

- *Progression-Free Survival* (PFS): Time from first dosing date to the date of confirmed PD. A subject who has not died will be censored at the last known date alive. PFS rate will be assessed through the proportion of patients free of PD at the end of follow-up.

- *Clinical benefit (CB)*: Percentage/proportion of patients with complete response (CR) or partial response (PR) or maintained stable disease (SD) as their overall best response throughout the study period, assessed by imaging follow-up (CT scan/MRI), on week 9, week 18 and then, every 12 weeks.

- *Overall Survival* (OS): Time from first dosing date to the date of death and the proportion/percentage of patients alive at the end of follow-up. A subject who has not died will be censored at the last known date alive. Survival will be assessed by recording patient status at each visit according to ***Table 4***. Long term follow up to be performed every 6 months.

8.2. Safety and tolerability

Safety assessments: Safety parameters are AE, SAE, AESI, pregnancy, medication error, overdose. Additional safety information could be derived from ECG, lab test, pregnancy test, or vital sign exam.

The assessment of adverse events will include the type of event (including symptoms, physical exam findings and laboratory abnormalities), the incidence, severity, timing, seriousness, and relatedness regarding the treatment under study. Adverse events will be recorded and reported in the corresponding section of the case report form. The grade of adverse events will be coded according to the National Cancer Institute's Common Toxicity criteria (NCI-CTCAE v5.0 scoring system). The worst toxicity score will be recorded. In case of SAE and AESI the investigator should immediately fill in the dedicated SAE form and send it by as detailed in ***Section 9.2.***

- *Adverse events (AE) assessment:* type, frequency, outcome of adverse events.

- *Treatment-related AEs:* An event is assessed as related to study treatment when there is a reasonable possibility that study treatment caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between study

treatment and the event. This event is called a suspected adverse reaction. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

- *Serious adverse events (SAEs)* assessment: type, frequency, grade, outcome, relation with study treatment, all considering the total number and proportion based on the intention-to-treat and per protocol populations.

8.3. Study determinations

Table 4 details the study determinations to be performed and the corresponding timeline.

Table 4. Study determinations

Visit	**SCR**	**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**Cycle 7 up to Cycle N**	**Safety Visit**	**PFS FU**	**EOS FU**
Timeline	**≤ 28 D prior to inclusion**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**within 30d after EOT**	**Q12W**	**Q6 months**
Visit window		**+/- 3d**												**Q3W +/-3d**	**+/-3d**	**+/- 7d**	
Clinical Assessments																	
Informed consent	x																
Medical History (Medical and oncology specific)	x																
Physical Exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
ECOG	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Contraception check	x	x		x		x		x		x		x		x	x		
Vital signs (BP, PR)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Laboratory and biological sample studies																	
Archival tumor block	x																
Blood collection (biomarkers)	x							x						x (D1C7)		x at DP	
Faecal sample (biomarkers)	x							x								x at DP	
Coagulation	x	x		x		x		x		x		x	x	x	x		
Hematology*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Blood chemistry*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Thyroid function	x	x		x		x		x		x		x		x	x		
HBV/HCV test	x																
Pregnancy test (serum/urine)	x	x		x		x		x		x		x		x	x		
Urinalysis	x	x		x		x		x		x		x		x	x		
Cardiac monitoring																	
ECG	x	**If clinically indicated**													x		

FEVI	**x**	**If clinically indicated**												**x**		
Disease assessment																
Tumor evaluation	**x**		**On week 9 , week 18 (prior starting atezolizumab monotherapy and every 12 weeks +/-7 days thereafter until the of objective disease progression or death (whichever comes first)**													
Survival assessment																**x**
IMP follow-up																
Treatment dosing compliance		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**		
Chemotherapy administration		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**			
Atezolizumab administration		**x**		**x**		**x**		**x**		**x**		**x**		**x**		
Concomitant medications	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
New systemic cancer treatment															**x**	**x**
Safety assessment																
Adverse events	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**		

D: Day/s; Q3W: Every 3 weeks; Q12W: Every 12 weeks; EOT: End of treatment; PFS: Progression-free survival; EOS: End of study.

Informed consent: Informed consent of study procedures may be obtained prior to the screening. If laboratory or imaging procedures were performed for different reasons prior to signing consent, these can be used for screening purposes with the consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of inclusion.

Medical History: Should include information on prior systemic adjuvant or neoadjuvant therapy regimens, surgery and radiation therapy. Comorbidities: cardiovascular disease, previous cancer and diabetes, pulmonary disease, dementia, etc.

Physical exam: Includes an examination of major body systems and weight (height at screening only). Additional PE may be performed as clinically indicated. During the physical examination, a stethoscope will be used to carefully auscultate the lungs, additional respiratory functional tests should be performed as per local practise when suspecting pneumonitis (more information is provided in annex 1 of this protocol).

ECOG PS: ECOG may be recorded by telephone if the patient is not coming to site for other reasons.

Contraception check: Male patients who are able to father children and female patients who are of childbearing potential will need to affirm that they meet the criteria for correct use of 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the patient the need to use 2 highly effective contraception methods consistently and correctly and document such conversation in the patient's chart. In addition, the investigator or his/her designee will instruct the patient to call immediately if one or both contraception methods are discontinued, or if pregnancy is known or suspected in the patient or the patient's partner.

Vital signs: To include blood pressure (BP) and pulse rate (PR). Body weight is to be recorded at each visit along with vital signs.

Laboratory Studies:** Complete blood count that includes total white blood cell count with leukocyte formula, Hb, and platelet count. The analytical studies may be performed up to 72 hours before the scheduled visits in order to have the results at the time of the patient's visit. ***During the first 6 cycles of treatment with split doses of gemcitabine plus cisplatin, complete blood count and biochemistry (liver, renal and electrolytes) on D1 and D8 are mandatory for patient safety assurance and treatment continuation. Biochemistry tests include albumin, alkaline phosphatase, lactate dehydrogenase (LDH), calcium, magnesium, phosphorus, sodium, potassium, creatinine, creatine kinase, direct bilirubin, indirect bilirubin, total bilirubin, total protein, urea, uric acid, amylase, lipase, and glucose tests. Liver test panel functions include alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT) tests. Tests for pancreatic enzymes include lipase, protease, amylase, and trypsinogen tests. If screening clinical chemistry and haematology assessments are performed within 3 days prior to day 1 (first infusion day), they do not need to be repeated at day 1.

Faecal samples: Specimens will be collected at baseline (before start of treatment), Cycle 4 Day 1 and after

progression; the sample must be processed and retained in the local laboratory until Sponsor indications for shipment.

Thyroid Function: TSH and free T4.

HBV/HCV test: Serology including HIV, hepatitis B (HBsAg and anti-HBc), and hepatitis C virus (HCV).

Pregnancy test (serum/urine): For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of the study drug, and every 4 weeks thereafter. Pregnancy tests may occur on day 1, but the results must be available and reviewed by the treating physician or investigator prior to commencing an infusion.

Urinalysis: Protein, glucose, blood, Urine dipstick/other semiquantitative method, for urine protein: if ≥ 2+, collect 24-hour.

ECG: 12-lead ECG. Any clinically significant abnormalities detected require triplicate ECG results.

FEVI: MUGA Scan or ECHO, the technique used at screening will be consistently used throughout the study, in the following assessments.

Tumor assessments: CT scan or MRI is to be performed at baseline, on week 9, on week 18 and q12w ± 1w until the confirmation of objective disease progression or death (whichever comes first). The same imaging technique used to characterize each identified and reported lesion at screening will be employed in the following tumor assessments. This schedule must be followed regardless of any delays in dosing, in case of suspected pseudo-progression; treatment should be continued until progression of disease is confirmed from the imaging results. RECIST assessments will be performed on images from CT scans (preferred) or MRI, each preferably with IV contrast of the neck, chest, abdomen (including liver and adrenal glands), and pelvis. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of inclusion and, ideally, should be performed as close as possible to and prior to the start of treatment. CR and PR must be confirmed with repeated imaging performed at least 4 weeks after initial documentation of response. Assessment of response will be performed using RECIST 1.1. If radiologic imaging shows disease progression, the confirmatory scans should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessment at the next scheduled visit.

Treatment dosing compliance: Study drug compliance will be assessed by the Investigator and/or study personnel at each patient's visit, and it will be captured in the patient's records as part of source documentation at each patient's visit. Corresponding drug administration information will be reported also in the eCRF.

Chemotherapy dispensing/administration: Results for LTFs, electrolytes, and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or investigator prior to dosing. Specific details on haematological and renal function parameters for treatment interruption and resuming are detailed in the gemcitabine and cisplatin administration section.

Atezolizumab dispensing/administration: Every 3 weeks until PD or unacceptable toxicity. Continuation of atezolizumab treatment could be considered for patients who have been reported with PD on the week 9 radiological evaluation but, according to the PI's criteria, might be considered as with clinical benefit.

Adverse events: Adverse events should be documented and recorded at each visit using NCI-CTCAE v5.0. AEs (serious and non-serious) should be recorded in the eCRF and patient records, from the time the patient has taken at least 1 dose of study treatment through and including 90 calendar days after the last dose of IMP. If a patent begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. For SAEs, the active reporting period to Sponsor or it designated, begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in this study, through and including 90 calendar days after the last administration of the investigational products.

Concomitant medications: Concomitant medication will be recorded from 28 days prior to start of study treatment and up to 90 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (i.e., antiemetics treatment and prophylaxis), the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (e.g. transfusions).

Biomarker study: Archival Tumor block at baseline and processed blood samples at baseline, day 1 of cycle 4 and 7 (D1), and at EOT/progression. Blood samples should be obtained in all patients at the time of EOT (even by toxicity without progressing) and samples are to be stored at site at -80 ºC and are to be sent at the end of study (1 dry ice shipment per site).

New systemic cancer treatment: Information on subsequent treatments should include the list of post-treatment therapies, drugs administered, and the date of initiation and discontinuation of each drug, and the corresponding disease progression date (if applicable). All the data will be recorded in the medical record and in the eCRF.

Survival assessment (EOS): After progression, the patient will be followed for survival until death, loss of follow-up, total patient consent withdrawal (refusing to any trial procedure), or end of study. Patient long term follow-up to determine status (alive, death, loss of follow up, etc.) may be performed by phone, if the patient is not coming to the clinic due to other reasons. The investigator must document in writing the results of the phone call in

the patient records and in the eCRF.

8.4. Determinations in the selection phase (screening and baseline determinations)

Within 28 days prior to inclusion:

- Informed consent
- Medical History (Medical and oncology specific)
- Archival tumor block
- HBV/HCV test
- ECG
- FEVI
- Tumor assessment
- Thyroid function
- Urinalysis

Within 3 days prior to inclusion (not needed to be repeated if it is performed within 3 days to treatment initiation)

- Physical Exam
- ECOG
- Contraception check
- Vital signs (BP, PR)
- Coagulation
- Hematology
- Blood chemistry
- Pregnancy test (serum/urine)
- Blood collection (biomarkers)
- Faecal sample collection (biomarkers)
- Adverse events
- Concomitant medications

8.5. Determinations and procedures during the treatment period (up to cycle 6)

8.5.1. Day 1 (considering 3 week cycles)

- Physical Exam
- ECOG
- Contraception check
- Vital signs (BP, PR)
- Coagulation
- Hematology
- Blood chemistry
- Thyroid function
- Pregnancy test (serum/urine)
- Urinalysis
- Adverse events
- Concomitant medications
- Treatment dosing compliance
- Atezolizumab administration

- Split doses of gemcitabine and cisplatin administration
- Blood collection (biomarkers) only D1 C4.
- Faecal sample collection (biomarkers) only D1 C4.

8.5.2. Day 8 (considering 3 week cycles)

- Physical Exam
- ECOG
- Vital signs
- Hematology
- Blood chemistry
- Adverse events
- Treatment dosing compliance
- Concomitant medication
- Split doses of gemcitabine and cisplatin administration

8.5.3. Other determinations during treatment

- **Tumor assessment:** On week 9, week 18 (prior starting atezolizumab monotherapy and every 12 weeks +/-7 days thereafter until the confirmation of objective disease progression or death (whichever comes first).
- **Safety determinations:** Hematology and Blood chemistry (including renal function assessment with urea and creatinine) should be evaluated weekly during the first 6 cycles of treatment as per recommendations for gemcitabine treatment.
- **When clinically indicated:** ECG, and FEVI.

8.5.4. Determinations and procedures on day 1 of cycle 7 (D1-C7) and subsequent cycles (D1-Cn)

- Physical Exam
- ECOG
- Contraception check
- Vital signs (BP, PR)
- Coagulation
- Hematology
- Blood chemistry
- Thyroid function
- Pregnancy test (serum/urine)
- Urinalysis
- Treatment compliance dosing
- Atezolizumab administration
- Concomitant medication
- Adverse event

When clinically indicated: *urinalysis, ECG, and FEVI.*

Additionally at D1-C7:

- Blood collection (biomarkers) only D1 C7.
- Tumor assessment: CT Scan or MRI prior to D1C7 (on week 18 from treatment starting).

When applicable

- ***Tumor assessment:*** *CT Scan or MRI is to be performed on week 9, week 18 and every*

12 weeks until the confirmation of objective disease progression or death (whichever comes first).

- ***When clinically indicated:*** *ECG, and FEVI.*

8.6. Determinations at safety visit

- Physical Exam
- ECOG
- Contraception check
- Vital signs (BP, PR)
- Coagulation
- Hematology
- Blood chemistry
- Thyroid function
- Pregnancy test (serum/urine)
- Urinalysis
- ECG
- FEVI
- Adverse events
- Concomitant medications

8.7. Follow-up determinations

8.7.1. Follow up after end of treatment (prior PD)

Every 12 weeks:

- **Tumor assessment:** CT Scan or MRI is to be performed on week 9, week 18 and every 12 weeks until the confirmation of objective disease progression or death (whichever comes first).
- New systemic cancer treatment.
- **By the time of disease progression,** Blood collection (biomarkers), Faecal sample collection.

8.7.2. Follow up after end of treatment (after PD)

Every 6 months:

- New systemic cancer treatment
- Survival assessment

9. SAFETY EVALUATION

ICH GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

Any event involving adverse drug reactions (ADR), illnesses with onset during the study or exacerbations of pre-existing illnesses should be recorded.

In addition, clinically significant changes in physical examination findings and abnormal objective test findings (e.g., x-ray, ECG) should also be recorded as AE. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- test result is associated with clinically significant symptoms, and/or
- test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
- test result leads to any of the outcomes included in the definition of a SAE, and/or test result is considered to be an AE by the investigator.

9.1. Definitions

The definitions from ICH GCP apply in this trial protocol.

9.1.1. Adverse event (AE)

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject which does not necessarily have a causal relationship with the study treatment.

Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

9.1.2. Atezolizumab Adverse Event of Special Interest

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 9.2 for reporting instructions).

Adverse events of special interest for this study are as follows:

- 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.
- Suspected transmission of an infectious agent by the study treatment, as defined below
- Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

9.1.3. Laboratory Abnormalities

All laboratory data required by this protocol and any other clinical investigations will be reviewed. Any abnormal value that leads to a change in subject management (eg, dose reduction or delay or requirement for additional medication or monitoring) or that is considered to be of clinical significance by the Investigator will be reported as an AE or SAE as appropriate, unless this value is consistent with the subject's present disease state or is consistent with values obtained prior to entry into the study.

9.1.4. Medication errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, the wrong patient at the wrong time, or at the wrong dosage strength.

Such medication errors occurring to a study participant are to be captured on the eCRF, and reported through the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.
Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AEs are captured on an AE CRF page.
The guidance on reporting of medication errors also applies to the reporting of overdose.

9.1.4.1. Atezolizumab overdose

The standard fixed dose of Atezolizumab is 1200 mg is equivalent to 15 mg/kg in a typical patient. No dose-limiting toxicities were observed at the 20 mg/kg dose level and the incidence and intensity of AEs reported have not been shown to be dependent on dose. A maximum tolerated dose has not been established.
Atezolizumab is supplied in vials containing the fixed 1200 mg dose of drug substance, which minimizes the chance of overdose. Because the dose per patient is not based on weight or body surface area, and no dose calculation is required, the risk of overdose due to medication errors is minimal.
The data available to date suggest that the potential for harm from overdose is very low.

9.1.4.2. Gemcitabine overdose

There is no known antidote for overdose of gemcitabine. Doses as high as 5700 mg/m2 have been administered by intravenous infusion over 30-minutes every 2 weeks with clinically acceptable toxicity. In the event of suspected overdose, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

9.1.4.3. Cisplatin overdose

An acute overdose of cisplatin may result in renal failure, liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, untreatable nausea and vomiting and/or neuritis. An overdose may be fatal.

There is no specific antidote in the event of an over dosage of cisplatin. Even if haemodialysis is initiated 4 hours after the overdose it has little effect on the elimination of cisplatin from the body following a strong and rapid fixation of cisplatin to proteins.

Treatment in the event of an overdose consists of general support measures.

9.1.5. Adverse reaction (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered.

9.1.6. Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that at any dose:

1. Results in death (is fatal),
2. Is life-threatening,
3. Requires or prolongs inpatient hospitalization,
4. Results in persistent or significant disability or incapacity,
5. Is a congenital anomaly or birth defect, or
6. Is medically significant.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting

period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE.

Medical and scientific judgement should be exercised in deciding whether urgent reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the above definition.

Any suspected transmission of an infectious agent through the medication is also considered a SAE.

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; 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 9.2 for reporting instructions).

9.1.7. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in the previous sections, and will be handled as SAEs in the safety database.

9.1.8. Life Threatening Event

It is any event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

9.1.9. Hospitalization / Prolongation of Hospitalization

Any event requiring hospitalization (or prolongation of hospitalization) that occurs or worsens during a patient's participation in a clinical study must be reported as a serious adverse event. Prolongation of hospitalization is defined as any extension of an inpatient hospitalization beyond the stay anticipated/required for the initial admission, as determined by the investigator or treating physician.

Hospitalizations that do not meet the criteria for serious adverse event reporting are:

1. Reasons described in protocol (e.g., drug administration, protocol-required investigations). Hospitalizations or prolonged hospitalization for a complication of therapy administration or procedures will be reported as a Serious Adverse Event.
2. Hospitalization or prolonged hospitalization for technical, practical or social reasons, in the absence of an adverse event.
3. Pre-planned hospitalizations (i.e., planned before study entry). Any surgery or procedure planned before study entry must be documented on the case report form.

9.1.10. Unexpected adverse event (not listed)

An unexpected AA, whose nature or severity does not correspond to the product information. The reference documents to establish the expectedness will be:

- Atezolizumab, last version of Investigator Brochure available for the Sponsor
- Gemcitabine, last version of the SmPC.
- Cisplatin, last version of the SmPC.

9.1.11. Adverse Event Associated With the Use of the Drug (Adverse Reaction)

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting

requirements, if applicable.

For combination treatments, causality assessment will be performed for each of the individual drugs included in the combination.

An adverse event is considered associated with the use of the drug (Adverse Reaction) if the attribution is possible, probable, or very likely by the definitions listed below.

9.1.12. Attribution Definitions

Not Related
An adverse event that is not related to the use of the drug.

Doubtful
An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible
An adverse event that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable
An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by de-challenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

9.1.3. Intensity (Severity) Criteria

The intensity of AEs will be classified using the Common Terminology Criteria for AEs of the National Cancer Institute, version 5.0 (NCI-CTCAE) and will be recorded in detail as instructed in the eCRF. If an AE occurs that is not listed in the NCI-CTCAE V5.0 classification system, the 5-point scale detailed below will be used instead:

- Mild: General malaise, without interruption of normal daily activity.
- Moderate: Sufficient general malaise to reduce or affect normal daily activity.
- Severe: Incapacity for work or the development of normal daily activity.
- Life threatening or disabling: Represents an immediate threat to life.
- Death: AE-related.

Grade

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 (v5.0), 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 9.2 for reporting instructions), per the definition of serious adverse event in Section 9.1.

9.1.14. Exposure during Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, within 5 months after the last dose of atezolizumab , or within 6 months after the last dose of atezolizumab, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).

Any pregnancy that occurs in a female partner of a male study participant should also be reported to the sponsor within 24 hours of becoming aware. Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if his partner becomes pregnant during the chemotherapy treatment period or within 6 months after the last dose of chemotherapy. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

In both cases, the investigator must immediately notify the Sponsor Pharmacovigilance Office by sending the Pregnancy form (see ISF).

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, study discontinuation must be reported following the before procedure described during at least 1 year after child-bearing.

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) or abortion should be reported as a SAE.

9.1.15. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.
An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

9.1.16. Expedited reporting

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report all serious adverse events that are unlisted (unexpected) and be associated with the use of the study drug. The sponsor must report these events to investigators and competent authorities in accordance with current regulations.

9.2. Collection and reporting of Adverse Events information

The sponsor will collect AEs up to 30 days after administration of the last dose of study drug.

All adverse events must be recorded using medical terminology in the source document and the eCRF. Investigators must assess the severity (grade) of the event following NCI-CTCAE V 5.0 Criteria and assign a relationship to study therapy and pursue and obtain information adequate both to determine the outcome and to assess whether it meets the criteria for

classification as a SAE requiring immediate notification. The investigator must provide any information as requested by the sponsor in addition to that on the eCRF.

Any serious adverse event which occurs from patient informed consent signature, during the clinical study or within 90 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported. Beyond this period of time, only those SAEs suspected to be related to the study drug will be reported.

All SAEs suspected to be related to study treatment should be followed after the treatment/study withdrawal until the event or its symptoms have resolved or stabilized at a grade acceptable to the Investigator, Chief investigator and/or Sponsor.

Site staff should notify the sponsor, all the pregnancies of female subjects and female partners of male subjects that occurred during the clinical trial within 24 hours from becoming aware. Site staff should also communicate the outcome of the pregnancy within 24 hours since the awareness.

The cause of death of a deceased patient in a clinical trial, whether the case of an expected event or associated with the investigational agent, is considered an SAE and therefore must be communicated using the SAE form. The autopsy report should be sent to Sponsor identified only with the patient inclusion number.

[redacted]

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to [redacted] within 24 hours.

All SAEs suspected to be related to study drug must be followed up after the time of therapy discontinuation until the event or its consequences resolve or stabilize at an acceptable level for the investigator, the Trial Chief Investigator and/or Sponsor.

Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

10. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the Sponsor.

This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

10.1. Sample size calculation

Fleming's phase II procedure (*Fleming TR, 1982*) will be used. The null hypothesis that the smallest response probability is 0.3 will be tested against a one-sided alternative. In the first stage, 46 patients will be accrued. An intermediate analysis will be performed once these first 46 patients reach 6 months after study treatment initiation. If there are 16 or fewer responses in these 46 patients, the study will be stopped. This intermediate analysis is established as a cut-off point to stop the study if the benefit for the patient in terms of objective response does not justify its continuation with sufficient clarity. If there is no preliminary evidence in the first 46 patients, which allows enough statistical power to reject the null hypothesis, the recruitment will stop as it is considered that the efficacy of the treatment is not sufficient to justify the inclusion of more patients. Otherwise, 20 additional patients will be accrued for a total of 66. The null hypothesis will be rejected if 25 or more responses are observed in 66 patients. This design yields a type I error rate of 0.05 and power of 0.9 when the true response rate is 0.5.

Variables	Descriptions
α	**Probability of type I error: 0.05**
β	**Probability of type II error: 0.1**
p_0	**Response Probability of Poor Drug (P0) ---> 0.30**
P1	**Response Probability of Good Drug (P1) ---> 0.50**
Nmax	**Maximum number of patients to be recruited: 66**
Numstage	**Number of stages in Phase II clinical trial: 2**
n_i	**Number of patients to be recruited in stage i= 46**
R1	**Upper Limit For 1st Stage Rejection of Drug (r1)= 16**
R	**Upper Limit for 2nd Stage Rejection of Drug (r)= 25**

10.2. Study endpoints

10.2.1. Primary endpoint

Overall Response Rate (ORR): Percentage/proportion of patients with confirmed complete response (CR) or partial response (PR) as their overall best response throughout the study period.

10.2.2. Secondary endpoints

Efficacy endpoints:

- ***Duration of response*** **(DoR):** Time from first confirmed response (CR or PR) to the date of the documented PD as determined using RECIST 1.1 criteria or death due to any cause, whichever occurs first.
- ***Time to response*** **(TtR):** Time from first dosing date to the date of the documented ORR as determined using RECIST 1.1 criteria.

- ***Clinical benefit*:** Percentage/proportion of patients with confirmed complete response (CR) or partial response (PR), or stable disease (SD) as their overall best response throughout the study period.
- ***Overall Survival* (OS)**
    - Time from first dosing date to the date of death. A subject who has not died will be censored at the last known date alive.
    - Proportion of patients alive at the end of the atezolizumab plus split dose of gemcitabine and cisplatin combination stage.
    - Proportion of patients alive at the end of follow-up.
- ***Progression-Free Survival* (PFS)**
    - Time from first dosing date to the date of confirmed PD. A subject who has not died will be censored at the last known date alive.
    - Proportion of patients free of PD at 6 months since start of treatment.
    - Proportion of patients free of PD at the end of follow-up.

Safety endpoints

- ***Adverse events* (AE)** assessment: Type, frequency, severity and outcome of adverse events .
- ***Treatment-related AEs:*** Type, frequency, severity and outcome.

Exploratory endpoints

- Biomarkers and/or genes expression and participant outcomes.

10.3. Efficacy assessment

10.3.1. Efficacy variables

Overall Response Rate (ORR) at 6 months from first dose: includes patients with confirmed persistent partial (PR) and complete response (CR) as best response according to RECIST v 1.1, at 6 months from adaptive the study treatment initiation.

Overall Response Rate (ORR) from first dose: includes patients with confirmed persistent partial (PR) and complete response (CR) as best response according to RECIST 1.1, at the end of their participation in the study.

Time to response: Time to response (TTR) is defined as the time from the start of study treatment to the first objective tumor response (tumor shrinkage of ≥30%) observed for patients who achieved a CR or PR.

Duration of response (DOR): DOR is calculated as the time from the date of first documented CR or PR, as per RECIST 1.1, to the first documented progression or death due to underlying cancer.

Overall Survival (OS): Median Overall Survival (mOS) is calculated as the time from the date of inclusion to date of death due to any cause.

Progression-free Survival (PFS): Median Progression free survival (mPFS) is defined as the time from the date of inclusion to the date of the first documented disease progression or death due to any cause, whichever occurs first. PFS will be determined based on tumour assessment (RECIST version 1.1 criteria). The local Investigator's assessments will be used for analyses. Patients who are alive and have not progressed at the last follow-up will be censored at the

date of the last available image determination (CT scan or MRI). Patients with no additional image test other than that at baseline will be censored to the day after inclusion. Patients initiating new anticancer therapy (without progression to the study treatment) will be censored to the date of new anticancer therapy initiation.

Clinical Benefit (CB) Rate: Clinical Benefit Rate (CBR) is defined as the percentage of patients who achieved complete response, partial response and stable disease. Stable disease should be maintained for at least 6 months to be considered as a CBR event.

10.4. Safety assessment

The safety population (SP) consists of all enrolled subjects who received at least one dose of study treatment. Patients will be monitored for safety during all the stages of the study. All safety and tolerability assessments will be done at pre-dosing time, unless otherwise specified.

Safety parameters are AE, SAE, AESI, pregnancy, medication error, and overdose. Additional safety information could be derived from ECG, lab test, pregnancy test, or vital sign exam.

The assessment of adverse events will include the type of event (including symptoms, physical exam findings and laboratory abnormalities), the incidence, severity, timing, seriousness, and relatedness regarding the treatment under study. Adverse events will be recorded and reported in the corresponding section of the case report form. The grade of adverse events will be coded according to the National Cancer Institute's Common Toxicity criteria (NCI-CTCAE v5.0 scoring system). The worst toxicity score will be recorded.

10.5. Definition of study populations

Data will be analysed in the following populations:

1. *Intent-To-Treat (ITT):* All patients that have been enrolled in the trial.
2. *Evaluable population per protocol (PP):* All patients fulfilling all eligibility criteria without any protocol deviation that makes the patient invalid for the primary endpoint evaluation.
3. *Safety population (SP):* All patients receiving at least one dose of the study treatments.

10.6. Data quality control

A Data Management Plan (DMP) will be elaborated for this trial in order to outline the data management procedures and the related responsibilities of trial staff. The DMP will clearly specify the data quality control tasks to be performed and the corresponding responsibility, timelines, etc., according to international guidelines in the subject and GCPs.

Following data entry of the investigator staff into the data capture system (eCRF), the data entered will be reconciled against the original case report form, review form/clinic notes/laboratory reports by CRA during monitoring visits, according to the monitoring plan. Any identified issues should be clarified with the Investigator staff. Any necessary corrections should be made in the corresponding field of the eCRF.

The monitoring plan will establish that source data verification (SDV) is expected for a subset of variables, according to study status, starting on the approval of this DMP and the SDV strategy agreed.

Remote QC activities will be outlined in the Monitoring Plan for relevant variables as

eligibility, primary endpoints, safety endpoints and relevant secondary endpoints.

Performance of these checks is expected on all the patients included (this estimate may vary according to the quality of the data reported by the research team).

Any finding will be reflected in the monitoring report and will be conveniently managed with sites (including Principal Investigator) and informed to the Coordinating Investigator, as the representative of the Sponsor in this study, and when applicable, notified to competent authorities according to local regulations.

10.7. Statistical analysis

For each categorical variable, the results will be summarised by frequencies and percentages/proportions along with 95 % confidence intervals (95% CIs) when applicable.

For each continuous variable, the results will be summarised by descriptive statistics such as median, range, and range or by means, standard deviations, and (95% CIs). For time to event endpoints, Kaplan-Meier estimates at selected time points and corresponding curves will be presented. Time to event is derived relative to the first study treatment administration and will be expressed in weeks and/or months.

Vital signs, ECG parameters, clinical laboratory data (haematology, serum biochemistry, and urinalysis) will be presented in tabular form. Laboratory values will be expressed as absolute values and in grades (ordinal categorical variables), when feasible. In case of laboratory findings reported as adverse events, values will be presented and/or classified according to NCI CTCAE v 5.0.

All adverse events, including treatment-emergent AE (AEs starting after the administration of study treatment and up to study completion) will be summarised by system organ class and preferred term. Grading will be presented by type and in tables showing the frequency and percentage of the within-patient worst grades. In addition, grade ≥ 3 AEs will be summarised separately. Further analyses could be performed.

Analysis will be based on observed data, and missing data for drop-outs are not replaced by methods like LOCF (last option carried forward).

Full analysis details will be outlined in the statistical analysis plan (SAP).

11. LEGAL AND ETHICS CONSIDERATION

11.1. Ethical conduct of the study

The study will be conducted in accordance with the principles of the Helsinki Declaration Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 updated to its latest version Fortaleza, Brazil, October 2013. With the Good Clinical Practice (GCP) standards issued by the Working Party on Medicinal Product Efficacy of the European Economic Community (1990) (CPMP / ICH / 135/95).

And the laws and regulations in force in Spain:

- The Oviedo Convention of April 4, 1997 on human rights and biomedicine, ratified in the BOE in October 1999.
- The rules for the adequate protection of personal data, in accordance with Law 3/2018 Protection of Personal Data and guarantee of digital rights.
- The rights and obligations regarding information and clinical documentation, as provided in Law 41/2002, of November 14, basic regulation of patient autonomy.
- Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for Investigation with medicinal products and the Spanish Clinical Studies Registry.
- Law 14/2007, of July 3, on Biomedical Research.

11.2. Independent Ethical Committee (IEC) Review

Prior to the commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents to the Central IEC for its approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File.

The IEC will be asked to document the date of the meeting at which the favourable opinion or approval was given, with the members and voting members present. Written evidence of favourable opinion or approval that clearly identifies the trial, the clinical trial protocol and the version, the Subject Information and Informed Consent Form, should be provided.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC, before implementation of substantial changes. Relevant safety information will be submitted to the IEC during the course of the trial, in accordance with national regulations and requirements.

Initial IEC positive vote, and all materials approved by the IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

11.3. Authorities

The study protocol and/or related documents will be submitted to regulatory authorities before commencement of the clinical trial, as national authorities in the country where the trial is taking place.

11.4. Informed consent

The patient should sign an informed consent that will include the information for the clinical trial and associated translational research.

The clinician will have to explain the nature, objectives and possible consequences of the clinical trial in a manner that is understandable by the patient. The patient must give his/her consent before being admitted into the study and before biological samples are taken.

The study subject will provide his/her consent, signing by duplicate the appropriate model. For this purpose, each model must carry the signature of investigator and patient. The investigator will retain one copy of the original of each patient signed consent form.

The investigator will not start any investigation related with the study until the written consent has been obtained.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by the Ethics Committee.

11.5. Confidentiality

In order to guarantee the confidentiality of the clinical trial data according to the provisions of The rules for the adequate protection of personal data, in accordance with Law 3/2018 Protection of Personal Data and guarantee of digital rights, only the personnel designated by the Sponsor will have access to the patient data for monitoring/auditing purposes, Investigators and his/her staff, the Ethic Committee and the pertinent Competent Authorities.

The investigator should facilitate access to the source documents and data for monitoring and auditing purposes.
The content of the case report forms (CRF), as well as the documents generated during the study will be protected from non-permitted uses by persons not involved in the investigation, and will therefore be considered strictly confidential and not revealed to third parties, except those specified in the previous paragraphs.

11.6. Insurance Policy

The insurance or indemnity in accordance with pertinent regulatory requirements will be provided. All patients in this study are insured through the corresponding insurance policy that satisfies the conditions stipulated by the RD 1090/2015 in Spain.

11.7. End of study definition

The end of study is defined as the Last Patient Last Visit (LPLV) and will be considered at 24 months after last patient first visit (LPFV), Sponsor will ask survival status of all patients at the final clinical trial database closing, in order to maximise the median follow up of patients for overall survival data.

11.8. Early study termination

The clinical trial may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavourable risk benefit judgment for any IMP. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, poor enrolment, or the discontinuation of clinical development of

the IMP or withdrawal of the IMP from the market for safety reasons.

Health Authorities and Independent Ethics Committees (IECs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

In case of early termination of the study, all the study material (study drugs, etc.) must be returned to the Sponsor.

12. STUDY PROCEDURES

12.1. Responsibilities according to Good Clinical Practice

Responsibilities of the principal investigator of each participating center includes what is detailed in section 4 of the Guideline for good clinical practice E6 (R2).

12.2. Instructions for e-CRF completion

The data will be recorded using the Electronic Data Capture software property of MFAR S.L. The MFAR e-CRF environment will be used for data collection in this study. [redacted]. Access to data is secure and restricted for authorised users. Each user requires a username and password for exclusively personal use, as per good clinical practice.

All the EDC users are uniquely identified by name, all the access to the software is made through a secure, encrypted connection and all the activities are logged and audited.

All the EDC forms are designed according to the eCRF defined by the study protocol, and are validated according to the DVP (Data Validation Plan). There will be eCRFs for different visits, and whether these are mandatory (m) and non-mandatory eCRFs (such as laboratory testing and the corresponding validation of variables, rules and extraction).

Data on Adverse Event (AE), Adverse Reactions (AR), Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected SARs (SUSARs) will be undertaken by Sites in the eCRF and are transferred to the study database along with the rest of variables.

Electronic Case Report Form (eCRF) includes the CTCAE version 5.0 terms as a pulldown list in order to categorise the events, additionally when the variable “SAE” is marked as “yes”, an automatic email is sent to the MFAR Staff in order to be aware of the paper based SAE form is expected to be received, for regulatory reporting purposes. As data cleaning procedure, SAE received in paper based form are conciliate with the adverse events data collected in the eCRF and is ensured that all the events reported by means of SAE form are also collected in the eCRF, that is the final destination of any adverse event (whether be AE, AR, SAE, SAR or SUSAR).

12.3. Drug supply

AUREA is an Investigator Initiated Study, Atezolizumab will be supplied by the Sponsor through Roche, the Sponsor will supply Atezolizumab for up to 24 months of treatment for each patient. The treatment for patients not progressing at 24 months will be according to PI criteria, following his/her local normal practise. If as per Treating Physician criteria, the best option for the patient would be to continue with Atezolizumab, the administration may continue but following Site’s supply channels (other than those provided by Sponsor), after managing local administrative approvals

Gemcitabine and Cisplatin will be provided by the sites as per standard care criteria.

12.3.1. Packaging and labelling

Packaging and labeling of study treatment will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines.

12.4. Final report and Publications

As stated in article 42 of RD 1090/2015 of clinical trials, the Sponsor is obliged to publish both positive and negative results of the authorized clinical trials in scientific journals and with mention to the Ethical Committee of Clinical Research that approved the study.

The clinical publication will be carried out by the Coordinating Investigator in collaboration and Principal Investigators. Coordinating Investigator and Principal Investigators who contributed with at least 3% of the patients will be the authors. The order of authors will strictly depend on the number of patients included by the Investigators.
The anonymity of the source subjects of the data and biological samples will be maintained at all times.

The results or conclusions of the study will be communicated primarily in scientific publications before being released to the non-health public.

No efficacy study outcome will be reported prematurely or sensationalistically.

Participating investigators should not publish any patient data that is directly related to the study objectives until the trial report is published.

The trial will be registered in the Spanish Registry of Clinical Studies (REEC) and www.clinicaltrials.gov.

12.5. Monitoring

The study will be monitored through local visits, telephone calls and periodic inspection of CRFs. During the study, according to monitoring plan, a monitor from MFAR Clinical Research or a representative will have regular contact with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to MFAR Clinical Research.
- Confirm that AEs and SAEs have been properly documented on eCRFs, all SAEs have been forwarded to MFAR Clinical Research, and all the SAEs that met criteria for reporting have been forwarded to the IEC

The monitor will be available between visits if the investigator(s) or other staff members need information or advice.

12.6. Clinical Study Report

According to local regulation, the summary of results of the trial will be sent to the AEMPS and the CEIm no later than one year after the date of the end of the trial globally. The summary of results will follow the European format required for EudraCT.

12.7. Protocol Amendments

Supplements and changes to the protocol can be performed exclusively by the Sponsor, who must submit them to the Ethics Committee and the local Regulatory Authority protocol amendments.

Relevant safety information will be submitted to the IEC during the course of the trial, in accordance with national regulations and requirements.

Initial IEC positive vote, and all materials approved by the IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

12.8. Data Handling

The data will be recorded using the Electronic Data Capture software property of MFAR S.L., which is developed and maintained with strict observance of the regulatory standards for Clinical EDC systems, with special observance of the guidelines specified at:

- CPMP/ICH/135/95. ICH E6. Note for Guidance on Good Clinical Practice.
- Good Clinical Data Management Practice, Version 4, Society for Clinical Data Management (SCDM), October 2005.
- EMEA. Reflection on expectations for electronic source documents used in clinical trials. London, 17 October 2007.
- Directive 9 Guidance for Industry. Part 11, Electronic Records; Electronic Signatures – Scope and Application (August 2003).
- FDA. Guidance for Industry. Computerised Systems Used in Clinical Investigations (May 2007).
- FDA. Guidance for Industry. Part 11, Electronic Records; Electronic Signatures – Scope and Application (August 2003)
- Organic Law 3/2018, of December 5, Protection of Personal Data and guarantee of digital rights

The EDC database is hosted at a data server located at the Data Centre maintained by Claranet SAU located at "[redacted]". The physical access to the Data Centre is restricted to authorised Claranet personnel, and logical access to the database is restricted to named MFAR personnel.

All the EDC users are uniquely identified by name, all the access to the software is made through a secure, encrypted connection and all the activities are logged and audited.

All the EDC forms are designed according to the eCRF defined by the study protocol, and are validated according to the DVP (Data Validation Plan).

12.9. Documentation

The Investigator/Institution should maintain trial documents according to ICH Topic E6 ***Section 8***, and as required by pertinent regulatory requirements. According to RD 1090/2015 on Clinical trial, the archive period for all essential documents is 25 years.

Essential documents should be stored according to ICH GCP guidelines for a longer period of time, if required by pertinent regulations. The original patient data (clinical record) must be kept archived for the time stipulated by the study centre regulations.

All original subject files (medical records) must be stored at the site (hospital, research institution, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer (In Spain 25 years). In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

12.10. Audits and inspections

Authorised representatives of Sponsor, a regulatory authority, an Independent Ethics Committee may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonisation, and any applicable regulatory requirements. The investigator should contact the Sponsor through MFAR immediately if contacted by a regulatory agency about an inspection.

13. TRANSLATIONAL SUBSTUDIES

A key objective of the biomarker analyses that will be performed in this study is to investigate candidate biomarkers that may have predictive value in identifying those patients who may benefit from treatment with the combination of atezolizumab 1 and split dose GC. In addition, analyses of blood biomarkers obtained before, during and after treatment will provide an opportunity to investigate pharmacodynamic effects. Samples collected at the End of Treatment/Withdrawal visit enable investigation of potential mechanisms of resistance to the drug combination.

The following biological samples are required:

- Tumor sample, archive tumor sample in order to evaluate changes in signaling molecules in response to study treatment in tumour tissue.
- Processed blood samples obtained before treatment, at D1 of cycles 41 and C7 of treatment, and at the end of treatment/progression, in order to evaluate changes in signaling molecules in response to study treatment in blood.
- Faecal samples for microbiome analyses, before treatment, at D1 of cycle 4 of treatment, and at the end of treatment/progression..

13.1. Archived Tumor Biospecimens

Somatic alterations in tumours including proteomics, transcriptomics and metabolics will be analyzed. No germinal line determinations will be performed.

Tumor biological specimens from archived tissue samples will be used to analyze candidate DNA, RNA, or protein markers, or relevant signature of markers for their ability to identify those patients who are most likely to benefit from treatment with the study drugs.

Tumor tissue biomarker analyses, including determination of PD-L1 status, will be performed retrospectively in a central laboratory. PD-L1 status will be assessed using a validated PD-L1 IHC test kit manufactured under GMP specifications, in conjunction with a pre-specified scoring algorithm and cutoff defining PD-L1 positive versus negative status that will be established prior to initiation of scoring of PD-L1.

Additional tumor tissue biomarkers that may be analyzed include, but may not necessarily be limited to, gene expression profiles and/or quantitation of tumor-infiltrating CD8+ T lymphocytes by IHC and/or tissue FoxP3, PD-1, or PD-L2.

13.2. Peripheral Blood

Specimens will be processed and retained in local laboratories until Sponsor indications for shipments. It will include whole blood, serum and plasma samples that will be retained in the central laboratory for exploratory assessments.

Samples may be used to identify or characterize cells, DNA, RNA, or protein markers known or suspected to be of relevance to the mechanisms of action, or the development of resistance to study treatment. These include biomarkers that may aid in the identification of those patients who might preferentially benefit from treatment with split doses of gemcitabine-cisplatinIMP 1 in combination with atezolizumabIMP 2, which may include but are not limited to biomarkers related to anti-tumor immune response or target modulation, such as (not necessarily be limited to) soluble IL-8 or IFNγ.

Information regarding sample collection, management and shipments are provided in the translational research manual.

13.3. Faecal samples

Specimens will be processed and retained in local laboratories until Sponsor indications for shipments. It will include a total of 3 samples: basal faecal sample collected prior treatment initiation, faecal sample at Cycle 4 Day 1 and after progression. Information regarding sample collection, management and shipments are provided in the translational research manual.

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APPENDICES

Appendix 1. Management of Atezolizumab-specific Adverse Events

A) Management Guidelines for Pulmonary Events, Including Pneumonitis

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

BAL = bronchoscopic alveolar lavage. CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.
Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.
[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of 10 mg/day oral prednisone before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

B) Management Guidelines for Hepatic Events

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

CTCAE Common Terminology Criteria for Adverse Events; LFT liver function tests; NCI National Cancer Institute.
Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0, except where indicated.
[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.
[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after

approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor

C) Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	● **Continue atezolizumab.** ● **Initiate symptomatic treatment.** ● **Endoscopy is recommended if symptoms persist for 7 days.** ● **Monitor closely.**
Diarrhea or colitis, Grade 2	● **Withhold atezolizumab for up to 12 weeks after event onset.** [a] ● **Initiate symptomatic treatment.** ● **Patient referral to GI specialist is recommended.** ● **For recurrent events or events that persist > 5 days, initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.** ● **If event resolves to Grade 1 or better, resume atezolizumab.** [b] ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.** [c]
Diarrhea or colitis, Grade 3	● **Withhold atezolizumab for up to 12 weeks after event onset.** [a] ● **Refer patient to GI specialist for evaluation and confirmatory biopsy.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If event resolves to Grade 1 or better, resume atezolizumab.** [b] ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.** [c]
Diarrhea or colitis, Grade 4	● **Permanently discontinue atezolizumab and contact Medical Monitor.** [c] ● **Refer patient to GI specialist for evaluation and confirmation biopsy.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If 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.**

CTCAE Common Terminology Criteria for Adverse Events; GI = gastrointestinal*; NCI National Cancer Institute.*

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0, except where indicated.

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

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

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

D) Management Guidelines for Hepatic Events

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

CTCAE Common Terminology Criteria for Adverse Events; LFT liver function tests; NCI National Cancer Institute.
Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0, except where indicated.
[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.
[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor

E) Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	● **Continue atezolizumab.** ● **Initiate treatment with thyroid replacement hormone.** ● **Monitor TSH weekly.**
Symptomatic hypothyroidism	● **Withhold 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 atezolizumab.** ● **Monitor TSH every 4 weeks.** **TSH < 0.1 mU/L:** ● **Follow guidelines for symptomatic hyperthyroidism.**
Symptomatic hyperthyroidism	● **Withhold atezolizumab.** ● **Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.** ● **Consider patient referral to endocrinologist.** ● **Resume atezolizumab when symptoms are controlled and thyroid function is improving.** ● **Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism.**
Symptomatic adrenal insufficiency, Grade 2 - 4	● **Withhold atezolizumab for up to 12 weeks after event onset.** [a] ● **Refer patient to endocrinologist.** ● **Perform appropriate imaging.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab.** [b] ● **If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.** [c]
Hyperglycemia, Grade 1 or 2	● **Continue atezolizumab.** ● **Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines.** ● **Monitor for glucose control.**
Hyperglycemia, Grade 3 or 4	● **Withhold atezolizumab.** ● **Initiate treatment with insulin.** ● **Monitor for glucose control.** ● **Resume atezolizumab when symptoms resolve and glucose levels are stable.**

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

IV= intravenous; CTCAE Common Terminology Criteria for Adverse Events; MRI magnetic resonance imaging; TSH thyroid-stimulating hormone; NCI National Cancer Institute.

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

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

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

F) Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	● **Continue atezolizumab.** ● **Patient referral to ophthalmologist is strongly recommended.** ● **Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.** ● **If symptoms persist, treat as a Grade 2 event.**
Ocular event, Grade 2	● **Withhold atezolizumab for up to 12 weeks after event onset.a** ● **Patient referral to ophthalmologist is strongly recommended.** ● **Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.** ● **If event resolves to Grade 1 or better, resume atezolizumab.b** ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]**
Ocular event, Grade 3 or 4	● **Permanently discontinue atezolizumab and contact Medical Monitor. c Refer patient to ophthalmologist.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.** ● **If event resolves to Grade 1 or better, taper corticosteroids over 1 month.**

CTCAE Common Terminology Criteria for Adverse Events; MRI magnetic resonance imaging; TSH thyroid-stimulating hormone; NCI National Cancer Institute.

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

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

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

G) Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 2	**Withhold 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 corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** **If event resolves to Grade 1 or better, resume atezolizumab. [b]** **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]**
	Permanently discontinue 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 corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** **If 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.**

CTCAE Common Terminology Criteria for Adverse Events; ECMO extracorporeal membrane oxygenation; NCI National Cancer Institute; VAD ventricular assist device.

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

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

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

H) Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] **Fever** [b] **with or without constitutional symptoms**	**Immediately interrupt infusion.** **Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.** **If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate.** **If symptoms recur, discontinue infusion of this dose.** **Administer symptomatic treatment, c including maintenance of IV fluids for hydration.** **In case of rapid decline or prolonged CRS (2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2.** **For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.**
Grade 2 [a] **Fever** [b] **with hypotension not requiring vasopressors** **<u>and/or</u>** **Hypoxia requiring low-flow oxygen d by nasal cannula or blow-by**	**Immediately interrupt infusion.** **Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset.** **If symptoms recur, discontinue infusion of this dose.** **Administer symptomatic treatment.** [c] **For hypotension, administer IV fluid bolus as needed.** **Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.** **Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS.** **Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).** **Consider anti-cytokine therapy.** [e] **Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor.** **If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered.** **For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS.** **If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.**
Grade 3 [a] **Fever** [b] **with hypotension requiring a vasopressor (with**	**Permanently discontinue atezolizumab and contact Medical Monitor.** [f] **Administer symptomatic treatment.** [c] **For hypotension, administer IV fluid bolus and vasopressor as needed.**

or without vasopressin) **<u>and/or</u>** **Hypoxia requiring high-flow oxygen d by nasal cannula, face mask, non-rebreather mask, or venturi mask**	**Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice.** **Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS.** **Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).** **Consider anti-cytokine therapy. [e]** **Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.**
Grade 4 [a] **Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin)** **<u>and/or</u>** **Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)**	**Permanently discontinue atezolizumab and contact Medical Monitor. [f]** **Administer symptomatic treatment. [c]** **Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice.** **Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS.** **Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).** **Consider anti-cytokine therapy. [e] For patients who are refractory to anti-cytokine therapy, experimental treatments [g] may be considered at the discretion of the investigator and in consultation with the Medical Monitor.** **Hospitalize patient until complete resolution of symptoms.**

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI National Cancer Institute.
Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.
[b] Fever is defined as temperature 38C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.
[c] Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.
[d] Low flow is defined as oxygen delivered at 6 L/min, and high flow is defined as oxygen delivered at 6 L/min.
[e] There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors/ICI (*Rotz et al. 2017*; *Adashek and Feldman 2019*), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
[f] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after consulting the Medical Monitor and considering the benefit-risk ratio.
[g] Refer to *Riegler et al. (2019)* for information on experimental treatments for CRS.

I) Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5 - 2.0 ULN:** ● **Continue atezolizumab.** ● **Monitor amylase and lipase weekly.** ● **For prolonged elevation (e.g., > 3 weeks), consider treatment** ● **with corticosteroids equivalent to 10 mg/day oral prednisone.** **Asymptomatic with amylase and/or lipase > 2.0 - 5.0 x ULN:** ● **Treat as a Grade 3 event.**
Amylase and/or lipase elevation, Grade 3 or 4	● **Withhold atezolizumab for up to 12 weeks after event onset.[a]** ● **Refer patient to GI specialist.** ● **Monitor amylase and lipase every other day.** ● **If no improvement, consider treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.** ● **If event resolves to Grade 1 or better, resume atezolizumab. [b]** ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]** ● **For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]**
Immune-mediated pancreatitis, Grade 2 or 3	● **Withhold atezolizumab for up to 12 weeks after event onset.[a]** ● **Refer patient to GI specialist.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If event resolves to Grade 1 or better, resume atezolizumab. [b]** ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]** ● **For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]**
Immune-mediated pancreatitis, Grade 4	● **Permanently discontinue atezolizumab and contact Medical Monitor. [c]** ● **Refer patient to GI specialist.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If 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.**

CTCAE Common Terminology Criteria for Adverse Events; GI gastrointestinal; NCI National Cancer Institute.

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

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

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

J) Management Guidelines for Dermatologic Events

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

CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.
Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

a Atezolizumab may be withheld for a longer period of time (i.e., 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent

of 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

b If corticosteroids have been initiated, they must be tapered over 1 month to the equivalent of 10 mg/day oral prednisone before atezolizumab can be resumed.

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

- For suspected SCARs the patients should be referred to a dermatologist for further diagnosis and management
- Atezolizumab should be withheld for patients with suspected SJS or TEN
- Atezolizumab should be permanently withdrawn for any grade confirmed SJS or TEN
- Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

K) Management Guidelines for Neurologic Disorders

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

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

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

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

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

L) Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	● **Permanently discontinue atezolizumab and contact Medical Monitor.** [a] ● **Refer patient to neurologist. Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If 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**

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

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

M) Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	**Continue atezolizumab.** **Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.**
Renal event, Grade 2	**Withhold atezolizumab for up to 12 weeks after event onset.** [a] **Refer patient to renal specialist.** **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.** **If event resolves to Grade 1 or better, resume atezolizumab.** [b] **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.** [c]
Renal event, Grade 3 or 4	**Permanently discontinue atezolizumab and contact Medical Monitor.** **Refer patient to renal specialist and consider renal biopsy.** **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.** **If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.**

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

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

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

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

N) Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	**Continue atezolizumab.** **Refer patient to rheumatologist or neurologist.** **Initiate treatment as per institutional guidelines.**
Immune-mediated myositis, Grade 2	● **Withhold atezolizumab for up to 12 weeks after event onset a and contact Medical Monitor.** ● **Refer patient to rheumatologist or neurologist.** ● **Initiate treatment as per institutional guidelines.** ● **Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.** ● **If event resolves to Grade 1 or better, resume atezolizumab. [b]** ● **If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]**
Immune-mediated myositis, Grade 3	● **Withhold atezolizumab for up to 12 weeks after event onset a and contact Medical Monitor.** ● **Refer patient to rheumatologist or neurologist.** ● **Initiate treatment as per institutional guidelines.** ● **Respiratory support may be required in more severe cases.** ● **Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.** ● **If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, resume atezolizumab. b If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]** ● **For recurrent events, treat as a Grade 4 event.**
Immune-mediated myositis, Grade 4 (CTCAE v5.0 guidelines only)	● **Permanently discontinue atezolizumab and contact Medical Monitor. [c]** ● **Refer patient to rheumatologist or neurologist.** ● **Initiate treatment as per institutional guidelines.** ● **Respiratory support may be required in more severe cases. Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 12 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.**

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

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

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

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