Study Title:

Exploratory basket trial of cabozantinib plus atezolizumab in advanced and progressive neoplasms of the endocrine system – The CABATEN study

Protocol Number: GETNE-T1914

EudraCT: 2019-002279-32

Acronym: CABATEN STUDY

Sponsor: Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE)
C/ Balmes 243, Escalera A 5º1ª
08006 Barcelona
Phone: +34 93 434 44 12
E-mail: getne@getne.org

Coordinating Investigators:

Jaume Capdevila, M.D., Ph.D.
Vall d'Hebrón University Hospital
Medical Oncology Department
P. Vall d'Hebron, 119-129
08035 - Barcelona
Phone: +34 93 274 60 85
E-mail: jcapdevila@vhio.net

Enrique Grande. M.D., Ph.D.
MD Anderson Cancer Center Madrid
Medical Oncology Department.
Calle de Arturo Soria, 270,
28033 - Madrid
Phone: +34 91 787 86 00
e-mail: egrande@mdanderson.es

Sponsor Signature Page

Protocol Number: GETNE-T1914

Study Title: Exploratory basket trial of cabozantinib plus atezolizumab in advanced and progressive neoplasms of the endocrine system – **The CABATEN study**

EudraCT Number: 2019-002279-32

Version number and date: Protocol version 4.0 February 18th 2022

I have received and read the Investigator's Brochure for Cabozantinib and Atezolizumab. I have read the **GETNE-T1914 - CABATEN STUDY** protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol and I agree to conduct this trial in accordance with all provisions of the protocol, GCPs and the Declaration of Helsinki.

Dr. Jaume Capdevila

Sponsor signature **Signature date (DD-MM-YYYY)**

Dr. Jaume Capdevila

Coordinating Investigator signature **Signature date (DD-MM-YYYY)**

Dr. Enrique Grande

Coordinating Investigator signature **Signature date (DD-MM-YYYY)**

Investigator's Agreement

Protocol Number: GETNE-T1914

Study Title: Exploratory basket trial of cabozantinib plus atezolizumab in advanced and progressive neoplasms of the endocrine system – **The CABATEN study**

EudraCT Number: 2019-002279-32

Version number and date: Protocol version 4.0 February 18th 2022

I have received and read the Investigator's Brochure for Cabozantinib and Atezolizumab. I have read the **GETNE T1914 - CABATEN STUDY** protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol and I agree to conduct this trial in accordance with all provisions of the protocol, GCPs and the Declaration of Helsinki.

_____

Investigator Printed Name

_____

Investigator Signature

_____

Date:

1. Synopsis

<table>
<tr><td colspan="2">Sponsor:
GETNE (Spanish Group of Neuroendocrine and Endocrine Tumors)
C/ Balmes 243, Escalera A 5º1ª
08006 Barcelona
Phone: +34 93 434 44 12
E-mail: getne@getne.org</td></tr>
<tr><td colspan="2">Investigational Products:
Cabozantinib - 40 mg and 20 mg film-coated tablets
Atezolizumab - Atezolizumab 1200 mg concentrate for solution for infusion</td></tr>
<tr><td colspan="2">Title of Study:
Exploratory basket trial of cabozantinib plus atezolizumab in advanced and progressive neoplasms of the endocrine system – The CABATEN study</td></tr>
<tr><td colspan="2">Protocol number: GETNE-T1914</td></tr>
<tr><td colspan="2">EudraCT: 2019-002279-32</td></tr>
<tr><td colspan="2">Coordinating Investigators:
Jaume Capdevila, M.D., Ph.D.
Vall d’Hebrón University Hospital
Medical Oncology Department
P. Vall d’Hebron, 119-129
08035 - Barcelona
Phone: +34 93 274 60 85
E-mail: jcapdevila@vhio.net

Enrique Grande. M.D., Ph.D.
MD Anderson Cancer Center Madrid
Medical Oncology Department.
Calle de Arturo Soria, 270,
28033 - Madrid
Phone: +34 91 787 86 00
e-mail: egrande@mdanderson.es</td></tr>
<tr><td colspan="2">Principal Investigators:
In attached document</td></tr>
<tr><td colspan="2">Study center(s):
15 sites in Spain, detailed in attached document</td></tr>
<tr><td>Studied period:
First patient recruited: 8/10/2020</td><td>Phase of development:
2</td></tr>
</table>

Recruitment Period: 24 months: 8 months (Stage 1), 16 months (stage 2) **Last patient out:** 1Q 2023 (Stage I); 2023 (stage 2) **Estimated End of Study:** 1Q 2024	

Objectives:

Primary objective:

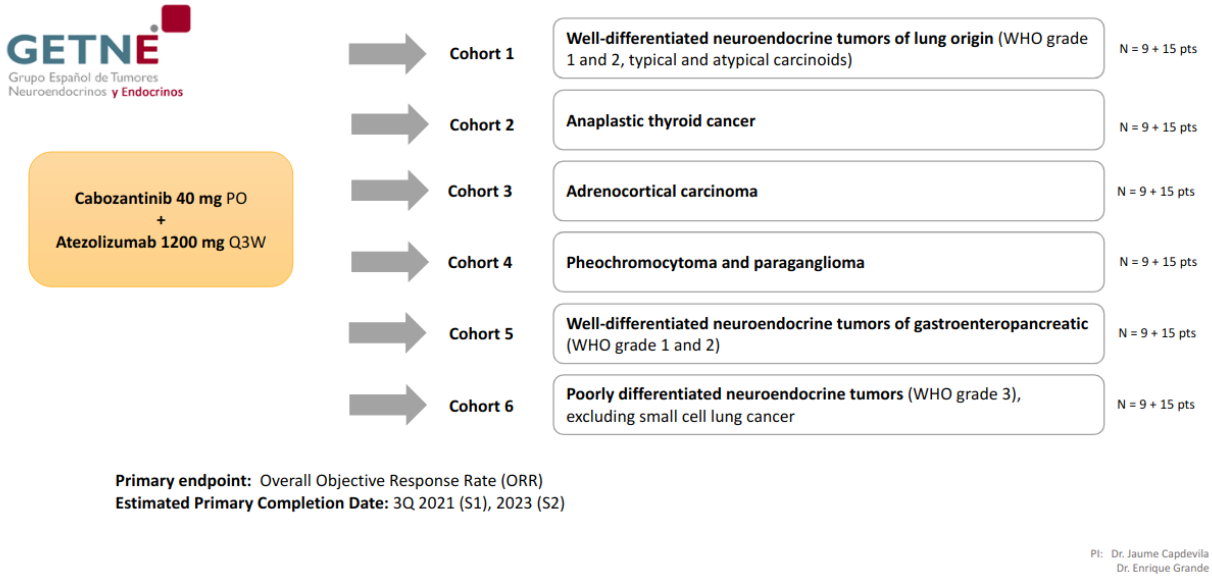
- To assess the efficacy of cabozantinib plus atezolizumab combination by means of radiological objective response rate (ORR) in advanced endocrine tumors.

Secondary objectives:

- Safety Profile
- Duration of Response (DoR)
- Progression-free Survival (PFS)
- Overall Survival (OS)
- Biomarkers
- Quality of Life (QoL)

Study Design:

*Exploratory basket trial of **CAB**ozantinib plus **AT**ezolizumab in advanced and progressive neoplasms of the **EN**docrine system – The **CABATEN** study*



This is a multicohort phase II study of cabozantinib plus atezolizumab in advanced and progressive tumors from the endocrine system.

Dosing scheme:

- Level 0 (starting dose): cabozantinib 40 mg qd + atezolizumab 1200 mg iv every 21 days (one cycle).
- Level -1: cabozantinib 20 mg qd + atezolizumab 1200 mg iv every 21 days (one cycle).

Cohorts of tumor types:

1. Well-differentiated neuroendocrine tumors of lung origin or thymus (WHO grade 1 and 2, typical and atypical carcinoids)

2. Anaplastic thyroid cancer
3. Adrenocortical carcinoma
4. Pheochromocytoma and paraganglioma
5. Well-differentiated neuroendocrine tumors of gastroenteropancreatic origin (WHO grade 1 and 2)
6. Poorly differentiated neuroendocrine tumors (WHO grade 3), excluding small cell lung cancer

Number of patients (planned):

Minimum of 54 patients and maximum of 144 patients, depending on the efficacy results, following the Simon-II optimal two-stage design, as further described in this protocol.

Eligibility criteria:

1. Inclusion criteria:

Patients eligible for inclusion in this study must meet all the following criteria:

1. Male or female subjects ≥ 18 years old.
2. Willingness to participate in the study by signing ICF approved by the trial Central Ethic Committee (CEIm).
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Measurable disease per RECIST 1.1 as determined by the investigator.
5. Patients with advanced and progressive neuroendocrine tumors histopathologically confirmed (as per local pathology report), meeting one of the following (according to WHO 2010 classification):
    a. Cohort 1: Well-differentiated neuroendocrine tumours of the lung and thymus (WHO grade 1 and 2, typical and atypical carcinoids) after progression to somatostatin analogs, targeted agents, PRRT, and/or chemotherapy.
    b. Cohort 2: Advanced anaplastic thyroid cancer in first-line or after progression to chemotherapy or investigational drugs, that underwent prior primary tumor surgical resection or not. In patients that primary tumor has not been resected, the risk of aerodigestive compression or bleeding should be ruled out to ensure no interference with the administration of the investigational product and undesirable potential side effects related to the route of administration.
    c. Cohort 3: Adrenocortical carcinoma after progression to chemotherapy and/or mitotane.
    d. Cohort 4: Pheochromocytoma and paraganglioma after progression to peptide receptor radionuclide therapy (PRRT) if indicated. Prior chemotherapy and biological therapy, such as somatostatin analogs, are allowed.
    e. Cohort 5: Well-differentiated neuroendocrine tumours of digestive system (WHO grade 1 and 2) after progression to somatostatin analogs, targeted agents, PRRT, and/or chemotherapy.
    f. Cohort 6: Grade 3 neuroendocrine neoplasm (WHO grade 3, including NET and NEC G3) of any origin, excluding small cell lung cancer, after progression to chemotherapy or targeted agents/PRRT.

    Note: Patients will be eligible for inclusion after progression to one of the lines aforementioned, without limit in the number of treatment lines.

6. Recovery from toxicity related to any prior treatments to ≤ Grade 1, unless the AE(s) are clinically non-significant and/or stable on supportive therapy.
7. Ability to swallow tablets.
8. 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 ≤ 1.5X 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. AST (SGOT)/ALT (SGPT) ≤ 2.5X institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 3X ULN.
    f. Measured creatinine clearance (CL) > 40 mL/min or Calculated creatinine CL > 40 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:

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

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 from their inclusion in the study and until 5 months after the last dose of study treatment (i.e condom with spermicide + IUD or cervical caps)(see section 9.6.1 of this protocol).
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, intrauterine device (IUD) or cervical caps), for the duration of the study and for 4 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.

2. Exclusion criteria

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

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

2. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks or 5 half-lives of the agent, whichever is longer. Patients should have been out of mitotane for at least 4 weeks.

3. Receipt of any type of anticancer antibody (including investigational antibody) or systemic chemotherapy within 2 weeks before starting treatment.

4. Current or prior use of immunosuppressive medication within 2 weeks before the first dose of cabozantinib and atezolizumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

5. 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.

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

7. History of allogeneic organ transplant.

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

9. Receipt of radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks before inclusion. Subjects with clinically relevant ongoing complications from prior radiation therapy that have not completely resolved are not eligible (e.g, radiation esophagitis or other inflammation of the viscera).

10. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before inclusion. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of study treatment.

11. Concomitant anticoagulation with oral anticoagulants (e.g, warfarin, direct thrombin and factor Xa inhibitors) or platelet inhibitors (e.g, clopidogrel), except for the following allowed anticoagulants:

    - Low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH).

    - Anticoagulation with therapeutic doses of LMWH in subjects without known brain metastases and who are on a stable dose of LMWH for at least 6 weeks before inclusion and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumour.

12. The subject has uncontrolled, significant intercurrent or recent illness 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. Moderate to severe hepatic impairment (child-pugh B or C).
   iv. Requirement for hemodialysis or peritoneal dialysis.
   v. Uncontrolled diabetes mellitus.
   vi. History of solid organ transplantation.

13. 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.

14. Corrected QT interval calculated by the Fridericia formula (QTcf) > 500 ms within 28 days before study treatment.

    Note: if a single ECG shows a QTCf with an absolute value > 500 ms, two additional EGGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these 3 consecutive results for qtcf will be used to determine eligibility.

15. Pregnant or lactating females.

16. Inability to swallow tablets.

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

18. Diagnosis of another malignancy within 3 years before study treatment, except for superficial skin cancers, or localised, low grade tumours deemed cured and not treated with systemic therapy.

Investigational products, dosage and mode of administration:

- Cabozantinib 40 mg or 20 mg tablets, oral administration, once daily, continuously.
- Atezolizumab 1200 mg administered intravenously, every three weeks (cycle).

Duration of treatment:

All the subjects will be treated with the combination of cabozantinib and atezolizumab until disease progression, unacceptable toxicity or patient consent withdrawal (whichever occurs first).

Reference therapy, dosage and administration:

Not applicable, this is a single arm study that will include patients receiving the same treatment.

Criteria for evaluation:

Efficacy assessments: RECIST V1.1 assessments will be performed on images from CT scans (preferred) or MRI, both preferably with intravenous (i.v.) contrast, of the neck, chest, abdomen (including liver and adrenal glands) and pelvis. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and through follow-up. Baseline assessments should be performed no more than 28 days before the date of inclusion and, ideally, as close as possible to the start of treatment and q12w ± 2w until objective disease progression/death (whichever comes first). Image assessments by CT scan or MRI may be performed q8w ± 2w if required by local standard clinical practice or by investigator criteria, as long as the frequency of assessments is maintained. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit.

The primary endpoint definition is as follows:

- **Overall Response Rate (ORR):** includes patients with partial (PR) and complete response (CR) as best response according to RECIST v 1.1.

The efficacy secondary endpoints will be studied as follows:

- **Duration of response (DoR) as per RECIST 1.1:** DOR calculated as the time from the date of first documented CR or PR to the first documented progression or death due to underlying cancer.
- **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. Those patients who are alive and have not progressed at the last follow-up will be censored at the date of the last image available. Patient with no additional image test other than that at baseline will be censored to the day after inclusion.
- **Overall Survival (OS)**: Median Overall Survival (mOS) is calculated as the time from date of inclusion to date of death due to any cause.
- **Quality of Life (QoL):** Quality of Life will be analyzed descriptively by QoL questionnaires (EQ-5D-5L, EORTC QLQ-C30 see appendix 2 and 3).

Safety assessments: The assessment of adverse events will include the type of event (including symptoms, physical exam findings and laboratory abnormalities), the incidence, the severity, the timing, the seriousness, and the 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 event 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 9.3.2.

Translational substudy (optional):

- **Tumor biopsies:** Collection of the most recent archived, tumor-biopsy sections for identification of predictive biomarkers.
- **Blood samples:** Somatic alterations in tumours including proteomics, transcriptomics, metabolics i.e. metabolic pathways of insulin growth factor, among others. No germinal line determinations will be performed. The levels of IGF-1 in serum (others biomarkers may be analysed) will be measured using the blood samples collected from the patients at the different time-points, according to table 2 "Schedule of assessments". The evolution of biomarkers will be evaluated individually and for the different groups of patients.

Statistical methods:

Simon-II optimal two-stage design was applied for sample size estimation. We hypothesize that the experimental therapy will improve the probability of expected objective response rate in refractory settings less than 5% in historical cohorts to 20% in the current study. With 80% of power (0.2) and unilateral alpha (0.1), 24 patients per cohort are needed to demonstrate the primary hypothesis. The Simon-II design suggested to observe ≥ 1 patient with objective response within the first 9 patients included in the first stage. If ≥ 1 out of 9 patients in each cohort achieve an objective radiological response in the first stage, study will continue recruiting 15 additional patients up to 24 patients per cohort. if ≥3 out of a total of 24 patients achieve a radiological objective response at the final analysis, the study should be declared positive. If stage I is reached only in one cohort, recruitment will continue in the successful cohort and stopped in the non-effective cohorts.

An overall description will be made of the variables included in the study. Absolute and relative frequency distributions (percentages) of qualitative variables will be presented, as well as measures of central tendency and dispersion (mean, standard deviation, median, minimum, and maximum values) of quantitative variables. The missing data will not be inputed and will be left as lost (missing value), however it will be presented.

The individual and summary on results of vital signs, ECG parameters, clinical laboratory data (haematology, serum biochemistry, and urinalysis) will be presented in tabular form. The values outside the reference range will be flagged. Clinically significantly abnormal values will be listed in tabular form. AEs will be tabulated by system organ class and preferred term after medical coding using the latest version of the NCI-CTCAE v5.0.

Main analyses populations:

- Intent-to-Treat (ITT)
- Per Protocol (PP)
- Safety population (SP)

INDEX

List of Abbreviations and Definitions of Terms

The following abbreviations and specialist terms are used in this study protocol.

Table 1. Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
5-HIAA	5-Hydroxyindoleacetic acid
ADL	Activities of Daily Living
ADR	Adverse drug reaction
AE	Adverse event
AP	Anatomic pathology
ASCO	American Society of Clinical Oncology
AUC	Area Under Curve
BED	Biological efficacious dose
beta-hCG	Beta-human chorionic gonadotropin
BID	bis in die, (Latin for "twice daily")
BMI	Body mass index
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CIs	Confidence intervals
CK	Creatine kinase (CK), also known as creatine phosphokinase (CPK) or phosphocreatine kinase
CL/F	Apparent total clearance of the drug from plasma after administration
Cmax	Maximum (or peak) serum concentration
CB	Clinical benefit
CDR	Control disease rate
CEA	Carcinoembryonic Antigen
CGA	Chromogranin A
CR	Complete Response
CRF	Controlled Release Form
CSR	Central Serous Retinopathy
CTCAE	Common Terminology Criteria for Adverse Events
CT Scan	Computed Tomography Scan
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicity
DM	Distant metastasis
DR	Duration of response
DVP	Data Validation Plan
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	United States Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence in situ hybridization
FU	Follow-up
GCP	Good Clinical Practice
GEP-NET	Gastroenteropancreatic Neuroendocrine Tumors
GH	Growth hormone
Hb	Haemoglobin
H/E	Haematoxylin/eosin

HFSR	Hand Foot Skin Reaction
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IM	Intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intention To Treat
KA	Keratoacanthoma
Ke	Elimination rate constant
KPS	Karnofsky Performance Status
LLN	Lower Limit of Normality
LVEF	Left Ventricular Ejection Fraction
LOCF	Last Observation Carried Forward
MAP	Mitogen-Activated Protein
MASCC	Multinational Association of Supportive Care
MDM2	Mouse double minute 2 homolog
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
MEN	Multiple endocrine neoplasms
MLPA	Multiplex ligation-dependent probe amplification
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition Scan
NET	Neuroendocrine Tumor
NSE	Neuron-Specific Enolase
OAE	Other significant adverse event
ORR	Overall response rate
OS	Overall Survival
OTEL	Open To Enrolment Letter
P2RD	Phase two recommended dose
PCR	Polymerase Chain Reaction
PD	Progression disease
PE	Physical examination
PET-CT	Positron emission tomography–computed tomography
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PLGA	Poly (lactic-co-glycolic acid)
pNET	Pancreatic NET
PP	Per Protocol
PR	Partial Response
PRT	Primary retroperitoneal tumours
PS	Performance Status
QD	Quaque die, every day “once daily”
QLQ 30	Quality of Life Questionnaire Core 30
QoL	Quality of Life
RDD	Retinal Degenerative Disease
RECIST	Response Evaluation Criteria In Solid Tumours
REEC	Registro Español de Estudios Clínicos (Spanish Registry of Clinical Studies)
RLS	Retroperitoneal Liposarcoma

RP	Retroperitoneum
RP2D	Recommended Phase II dose
RVO	Retinal Vein Occlusion
Rx	Radiography
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SBP	Systolic Blood Pressure
SC	Subcutaneous
SCC	Squamous Cell Carcinoma
SD	Stable disease
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SP	Safety Population
SRS	Stereotactic Radiosurgery
SSAs	Somatostatin Analogues
SSTR	Somatostatin Receptors
SUSAR	Suspected unexpected serious adverse reaction
Sx	Surgery
Tmax	Time of the sample identified as Cmax
TR	Translational Research
TTLR	Time to Local Relapse
ULN	Upper Limit of Normality
Vd/F	Apparent volume of distribution after non-intravenous administration
VS	Vital signs
VMAT	Volumetric Modulated Arc Therapy
WBC	White Blood Count
WBRT	Whole Brain Radiotherapy
WHO	World Health Organization

2. INTRODUCTION

2.1. DISEASE BACKGROUND

Neuroendocrine tumours (NETs) comprise a heterogeneous group of neoplasms originating from neural crest cells, endocrine glands, endocrine islets or the diffuse endocrine system, which explains the heterogeneity in the characteristics of these tumours and their clinical presentation (1). Although considered rare malignancies, available data suggest an increase in the incidence of NETs over the past 30 years, with around 7 cases per 100,000 populations per year (2), with NETs of pancreatic, intestinal, and bronchopulmonary origin as the most common types.
Clinical diagnoses of NETs are reliable at the advanced stages when many subjects present with metastases and inoperable disease, thereby receiving first line therapy towards controlling the progression of the disease and relieving associated symptoms (2).

Well and poorly-differentiated neuroendocrine tumours of lung origin

The origin and tumour development of neuroendocrine neoplasms are discussed controversially, but most theories point to an association with Kulchitsky cells (or enterochromaffin cells), which are normally present in the bronchial mucosa and are part of the diffuse neuroendocrine system, comprising single cells or clusters of 4 to 10 cells (3,4,5).

NETs were first described as carcinoid tumours by Siegfried Oberndorfer in 1904, and are developed from hormone producing (endocrine) cells which can be found throughout the foregut (thymus, lung, bronchi, and trachea), midgut (small intestine, gallbladder, and pancreas), and hindgut (Colon, excluding appendix, rectum), with the small intestine (30.4 %) and the lung (29.8 %) (5,6) as the most common locations. NETs of the lung are also characterised by their abilities to take up and decarboxylate the amine precursors (APUD system cells) (7,8,9).

According to the World Health Organization (WHO) classification 2004, NETs share common morphological, immunohistochemical and molecular characteristics and can be divided into three main entities (10):

- Carcinoid tumours: typical (TC) or atypical (AC),
- Large cell neuroendocrine carcinomas (LCNEC),
- Small cell carcinomas (SCLC).

These are further summarised into two groups according to their biological aggressiveness:

- Well-differentiated low grade (G1) typical and intermediate grade (G2) atypical carcinoids,
- Poorly-differentiated high grade (G3) LCNEC and SCLC.

Unlike those of typical and atypical carcinoids, genetic and epigenetic characteristics of LCNEC and SCLC are not closely related, and there are no precursor lesions known for SCLCs and LCNECs (10,11).

Anaplastic thyroid cancer
Anaplastic thyroid cancer (ATC) occurs in less than 2 % of all thyroid cancer cases but uniformly lethal; and it affects 1–2 individuals per million every year in the United States.
Patients are usually in their sixth or seventh decade of life at the time of disease presentation, and average median survival has been reported as 5 months, with < 20 % of survivors at 1 year after diagnosis (12,13).
ATC is thought to originate from differentiated thyroid cancers of follicular cell origin, as a result of dedifferentiation. Up to 80 % of ATC occurs in the setting of a long-standing goitre, possibly in the background of an undiagnosed, well-differentiated thyroid cancer (15).
Dedifferentiation is associated with gains and deletions in multiple chromosomal regions and involves a complex process involving multiple events, including cell cycle derangement and signal transduction

pathway disturbances (16-18). Due to its extremely aggressive behaviour, the American Joint Committee on Cancer (AJCC) defines all of ATC stages as stage IV, which is further staged into IVa, IVb, and IVc, depending on the extension of the primary tumour, lymph node involvement, or presence of distant metastases (DM). Although survival rates have not significantly improved in six decades, multimodality treatments including surgery, radiation, chemotherapy, and targeted therapy are considered the best strategy for improving outcome in patients diagnosed with ATC (14).

Adrenocortical carcinoma

Adrenocortical carcinoma (ACC) is a rare malignancy with an incidence of 0.7–2.0 cases/million inhabitants/year (19) whose malignancy features relies on careful investigations of the clinical, biological, and imaging features before surgery and the anatomopathological examination after tumour removal. Most patients present with excess steroid hormone or abdominal mass effects, but about 15 % of patients with ACC are initially diagnosed incidentally (20).

The stage classification proposed by the European Network for the Study of Adrenal Tumours (ENSAT) is recommended (21). Pathology reports define the Weiss score, the resection status, and the proliferative index, including the mitotic count and the Ki67 index.
As far as the treatment is concerned, the complete resection of the tumour is the first option for tumours that are limited to the adrenal gland.

In metastatic disease, mitotane is the cornerstone of initial treatment, and cytotoxic drugs should be added in case of progression. Recently, the First International Randomised (FIRM-ACT) Trial in metastatic ACC reported the association between mitotane and etoposide/doxorubicin/cisplatin (EDP) as the new standard in first line treatment of ACC. In the last few years, new targeted therapies, including the IGF-1 receptor inhibitors, have been investigated, but their efficacy remains limited. Thus, new treatment concepts are urgently needed (19).

Pheochromocytoma and paraganglioma

Pheochromocytomas and paragangliomas (PPGLs) are highly vascular neuroendocrine tumours that arise from chromaffin cells of the adrenal medulla or their neural crest progenitors located outside of the adrenal gland, respectively (22). PPGLs are estimated to occur in about 2–8 of 1 million persons per year and about 0.1 % of hypertensive patients harbour a PPGL. About 10 % of patients with PPGL present with adrenal incidentaloma (23). According to 2017–WHO classification of tumours (fourth edition) based on their location/origin, the neuroendocrine tumours are classified as tumours of the adrenal medulla and extra-adrenal paraganglia (24). These tumours are derived either from sympathetic tissue in adrenal or extra-adrenal abdominal locations (sympathetic PPGLs) or from parasympathetic tissue in the thorax or head and neck (parasympathetic PPGLs). Sympathetic PPGLs frequently produce considerable amounts of catecholamines, and in approximately 80 % of patients, they are found in the adrenal medulla (22,25). The remaining 20 % of these tumours are located outside of the adrenal glands, in the prevertebral and paravertebral sympathetic ganglia of the chest, abdomen, and pelvis. Extra-adrenal PPGLs in the abdomen most commonly arise from a collection of chromaffin tissue around the origin of the inferior mesenteric artery (the organ of Zuckerkandl) or aortic bifurcation. In contrast, most parasympathetic PPGLs are chromaffin-negative tumours mostly confined to the neck and at the base of the skull region along the glossopharyngeal and vagal nerves, and only 4 % of these tumours secrete catecholamines (25). These head and neck PGLs were formerly known as glomus tumour or carotid body tumours. Most PPGLs represent sporadic tumours and about 35 % of PPGLs are of familial origin with about 20 known susceptibility genes making them the most hereditary amongst all human tumours (26,27). Based on these genetic mutations and pathogenetic pathways, PPGLs can be classified into three broad clusters—cluster 1, cluster 2, and cluster 3. Cluster 1 includes mutations involving in overexpression of vascular endothelial growth factor (VEGF) (due to pseudohypoxia) and impaired DNA methylation leading to increased vascularization. Cluster 2 involves the activation of the mutations of Wnt-signalling pathway (Wnt receptor signalling and Hedgehog signalling). The activation of Wnt and Hedgehog signalling is secondary to somatic mutations of Cold shock

domain containing E1(CSDE1) and Mastermind like transcriptional coactivator 3 (MAML3) genes (28). Abnormal activation of kinase signalling pathways like PI3Kinase/AKT, RAS/RAF/ERK, and mTOR pathways account for cluster 3 mutations (24). On the other hand, based on biochemical secretory patterns, PPGLs can be characterised into three different phenotypical categories—noradrenergic phenotype (predominant norepinephrine secreting), adrenergic phenotype (predominant epinephrine secreting), and dopamine secreting. These biochemical phenotypes of PPGL lead to a constellation of symptoms (based on the predominant hormone secreted) leading to different clinical manifestations.

Well-differentiated neuroendocrine tumours of gastroenteropancreatic origin

Gastroenteropancreatic neuroendocrine neoplasms (NENs) are rare tumours defined by the expression of specific diagnostic biomarkers (29-31). Cell differentiation is a major prognostic marker of neuroendocrine neoplasms (32, 33). Indeed, regardless of the stage or the location of the primary tumour, it has been highlighted (31) that well-differentiated lesions have a better prognosis than poorly differentiated ones [32, 34-36).

In 2010, the World Health Organization (WHO) classification of neuroendocrine neoplasms was reviewed and the crucial role of the proliferative rate was validated (37-42). The WHO Classification 2010 defined three groups of tumours (Grades 1-3) according to the combination of the morphological characteristics, mitotic index, and Ki-67 index (43). Grades 1 and 2 corresponded to well-differentiated neuroendocrine tumours (NETs), whereas grade 3 corresponded to poorly differentiated lesions called neuroendocrine carcinomas (NECs). Initially, it was assumed that no NET with a mitotic or a Ki-67 index above 20 % could exist.

The majority of gastroenteropancreatic NENs are classified in the well-differentiated category because they retain the organoid architecture typical of neuroendocrine organs and have a relatively low proliferative rate. It is stated that all gastroenteropancreatic NETs—with the exception of the pancreatic microadenomas, gastrin-driven type 1 neuroendocrine tumours in the stomach are potentially malignant neoplasms. Different classifications have been used to distinguish pure neuroendocrine tumours from mixed endocrine-exocrine tumours, and to distinguish within pure neuroendocrine tumours according to their behaviour (well-differentiated NETs with benign behaviour, well-differentiated NETs with uncertain behaviour, well-differentiated NETs with malignant behaviour, and poorly differentiated endocrine carcinomas with high-grade malignant behaviour) (44, 45). These classifications are based on their site of origin, size, gross and/or microscopic tumour extension, vascular invasion, and/or proliferative activity (Ki-67 index), as well as their syndromic clinical/functioning features.

High-grade neuroendocrine neoplasms (WHO G3) of the pancreas include both well-differentiated neuroendocrine tumour (WD-NET) and poorly differentiated neuroendocrine carcinoma (PD-NEC). According to the WHO classification scheme, the diagnosis of this group of tumours is based on both the histopathology of the tumour and the assessment of proliferation fraction. However, the former can be challenging due to the lack of well-defined histologic criteria, and the latter alone (i.e, > 20 mitoses/10 high-power fields or Ki67 > 20 %) may not sufficiently distinguish WD-NETs from PD-NECs. Given the considerable differences in treatment strategies and clinical outcome, additional practical modalities are required to facilitate the accurate diagnosis of high-grade pancreatic neuroendocrine neoplasms. We examined 33 cases of WHO G3 neuroendocrine neoplasms of the pancreas and attempted to classify them into WD-NET, small cell PD-NEC (PD-NEC-SCC), and large cell PD-NEC (PD-NEC-LCC), or to designate them as "ambiguous" when an uncertain diagnosis was rendered by any of the observers or there was any disagreement in classification among the three observers. To simplify the interpretation, both PD-NEC-SCC and PD-NEC-LCC were considered together as PD-NECs in the final analysis. The initial approach was to assess microscopically a single morphologically challenging hematoxylin and eosin section from each case without the knowledge of Ki67 values. This was performed independently by three pathologists to assess the degree of diagnostic concordance, and the immunohistochemical staining for surrogate biomarkers of known genotypes of WD-NET and PD-NEC was evaluated. Lastly, a clinicopathologic review was completed to

establish a final definitive classification. Loss of DAXX or ATRX protein expression defined WD-NET, and abnormal expression of p53, Rb, SMAD4 signified PD-NEC. When the chosen section displayed an element of WD histopathology, or other tumour sections contained WHO G1/G2 components, or there had been a prior established diagnosis of a primary WD-NET, the final diagnosis was considered a WD-NET with high-grade (G3) progression. If a component of conventional adenocarcinoma was present (in slides not seen in the initial review), the diagnosis was established as a combined adenocarcinoma and PD-NEC. All the three pathologists agreed on the morphologic classification of 33 % of the cases (6 WD-NET, 3 PD-NEC-SCC, and 2 PD-NEC-LCC), were conflicted on two cases, between PD-NEC-SCC and PD-NEC-LCC, and disagreed or were uncertain on the classification of the remaining 20 cases (61%), which were therefore categorised as ambiguous. In the group of cases in which all pathologists agreed on the classification, the six WD-NET cases had either loss of DAXX or ATRX or had evidence of a WD-NET based on additional or prior pathology slides. The seven PD-NEC cases had abnormal expression of p53, Rb, and/or SMAD4 or a coexisting adenocarcinoma. In the ambiguous group (n = 20), 14 cases were established as WD-NETs based upon the loss of DAXX or ATRX in seven cases and additional pathology evidence of high-grade progression from WD-NET in the other seven cases; five cases were established as PD-NEC based upon abnormal expression of p53, Rb, and/or SMAD4; one case remained undetermined with normal expression of all markers and no evidence of entity-defining histologic findings in other slides. On the basis of the final pathologic classifications, the disease-specific survival was 75 and 11 months for the WD-NET and PD-NEC groups, respectively. Thus, we conclude that morphologic diagnosis of high-grade pancreatic neuroendocrine neoplasms is challenging, especially when limited pathologic materials are available, and necessitates better defined criteria. The analysis of both additional sections and prior material, along with an immunohistochemical evaluation, can facilitate accurate diagnosis in the majority of cases and guide the appropriate clinical management and prognosis (46).

2.2. SYSTEMIC THERAPY FOR ADVANCED AND REFRACTORY TUMOURS FROM ENDOCRINE SYSTEM

Systemic alternatives for the treatment of metastatic disease includes radionuclides, ablative locoregional treatments (for liver affectation), and other pharmacological options including somatostatin analogs, interferon, and chemotherapy or targeted therapies (47). Not all NETs respond equally to systemic therapy, therefore careful selection of patients is imperative so as to maximise the chance of response and avoid unnecessary toxicity (48).

The degree of differentiation can determine both overall prognosis and probability of response to individual cytotoxic regimens, and therefore an accurate histological characterisation using the WHO classification and the TNM system plays a major role in disease management (49). The proliferation rate, measured by the Ki-67 index may be useful to steer medical treatments (50). Highly proliferative (Ki-67 > 20 %) and poorly differentiated or anaplastic pancreatic tumours behave aggressively, with rapid growth rate and early dissemination. However, this subtype of NET may be more sensitive to cytotoxic chemotherapy, which impairs mitosis in a greater proportion of the rapidly dividing cell population (48).

The foregut tumours (excluding those of thymic and bronchial origin), particularly the pancreatic NETs are most likely to respond to conventional cytotoxic chemotherapy. Midgut tumours often appear to be low proliferating tumours, and cytotoxic chemotherapy has only resulted in responses of short duration in < 10 % of patients. Therefore, in slow growing tumours, there is an interest to evaluate treatment modalities with mechanisms of action other than cell cycle arrest (48). Immune modulation using interferon-α (IFNα) administered subcutaneously at doses of 3–9 million units administered 3–7 days a week has been shown to produce RRs up to 50 % measured by biochemical criteria, with durable reduction in tumour growth in up to 15 % of patients and symptomatic improvement seen in 40–70 % of patients (51). Somatostatin analogues have been used in conjunction with IFN, and long-term survival gains have been suggested (52-54). However, the benefits of IFN have not definitively been shown to outweigh its toxicity so as yet, IFN is not generally adopted as routine treatment for NETs.

Borderline tumours with histological evidence of a well-differentiated phenotype but moderately raised Ki-67 of 2–15 % present management dilemmas that may be clarified by future correlative studies assessing proliferation indices with treatment outcomes (55,56).

In general, chemotherapy is more effective in tumours of pancreatic origin than in those of enteric origin, and in poorly differentiated tumours (NEC) or with high proliferative index (Ki-67) than in those with good histological differentiation and low proliferative index. It can be considered for use in G2 NET in which radiological progression is documented, or in G1 NET in progression after failure of other therapeutic options, although the optimal chemotherapy scheme must be evaluated in appropriately designed clinical trials for this purpose (57).

With hormonal and immunological therapies, a high percentage of control of symptoms related to hormonal secretion syndrome is achieved, but the antitumour effect is limited (58).

Classical cytotoxic agents have also shown limited activity in systemic control (59,60), and this could be related to the biology of these tumours.

The limited efficacy of these classic drugs has led to the investigation of new therapeutic agents that attempt to exploit the phenotypic characteristics of endocrine tumours. The more detailed knowledge of the molecular mechanisms related to cell growth, apoptosis, angiogenesis, and tumour invasion, has allowed the development of new targeted therapies in this field (61).

The inhibition of the angiogenesis pathway represents an attractive strategy in the treatment of tumours with rich vascularisation, such as GEP-NETs. Thus, from preclinical studies, two therapeutic strategies directed against angiogenesis have been developed: monoclonal antibodies directed against VEGF (bevacizumab) and small tyrosine kinase inhibitory molecules directed against mediators involved in the pathway (sunitinib, sorafenib, pazopanib, and vatalanib).

The PI3/AKT/mTOR pathway plays a fundamental role in the carcinogenesis of multiple neoplasms by participating in multiple processes as proliferation, growth, and cell survival. Preclinical studies have shown that PTEN, one of the inhibitory phosphatases of the AKT/PI3K/mTOR pathway, is inactive in most pancreatic NETs and may represent an interesting therapeutic target in these neoplasms. mTOR is a serine-threonine kinase involved in PI3K-AKT signalling pathway, an intracellular signalling pathway, which integrates the signalling of multiple stimuli such as growth factors, and is involved in the process of angiogenesis by regulating the translation and activity of hypoxia-inducible factor (HIF1-A) which is related to the expression of VEGF in situations of cellular hypoxia. In the clinic, two drugs directed against this pathway have been developed: temsirolimus and everolimus.

Therapy with somatostatin analogues (SST), marked with radioactive elements [radiometabolic therapy (RMT)], has been used for the treatment of patients with NET in the last decades. It is linked to different radionuclides such as 111In which provides a low response rate, and 90Y and 177Lu which due to their emission of β particles were more suitable for therapeutic use, with 177Lu-octreotate being the radiopharmaceutical of choice. Another radiopharmaceutical used for NET therapy is metaiodobenzylguanidine (MIBG), and treatment with MIBG is indicated in patients with tumours that are resistant to surgery or radiofrequency ablation. With MIBG, there are similar results to those obtained with the administration of subcutaneous octreotide and α-interferon without the need for frequent injections, decreasing the expense per patient and increasing their well-being. To date, there is no data from controlled trials with radiometabolic therapy (RMT) versus placebo or other therapies to evaluate the benefits of this therapy in terms of progression-free survival or overall survival.

Other options include anti-HER drugs, IGFR inhibitors, and histone deacetylase inhibitors.

During the last decade, new active drugs have been studied in advanced and/or refractory endocrine tumours due to a better knowledge of the biology of these neoplasms. However, following first line therapy with

somatostatin analogues, there is no clear information to date indicating a preferred treatment sequence, and therefore, the treatment approach should be individualised based on the characteristics of each NET patient. In conclusion, there is a need for novel therapies and immunotherapy that may lead to more effective personalised interventions.

3. TRIAL RATIONALE

Endocrine tumours from different origins (thyroid, lung, pancreas and digestive tract, adrenal gland and paraganglia) are characterised by being remarkably vascular and expressing several growth factors including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1), basic fibroblast growth factor (BFGF), and transforming growth factor (TGF)-α and -β. In addition, the expression of several receptors of these growth factors and ligands has been described, including VEGF receptors (VEGFR)-2 and -3, IGF receptors (IGFR), and PDGF receptors (PDGFR). The (over) expression of some of these factors has been linked to poor prognosis and decreased progression-free survival (PFS), as well as to tumour growth, aggressiveness, and disease extent in patients with endocrine tumours. Several targeted agents have been studied in the treatment of advanced endocrine tumours including antiangiogenic compounds (such as bevacizumab), inhibitors of multiple receptors with kinase activity (such as cabozantinib, sunitinib, sorafenib, lenvatinib, and vandetanib), and inhibitors of intracellular downstream effector proteins such as the mammalian target of rapamycin (MTOR) (e.g, everolimus). The overexpression of c-MET pathway has been described as one of the most important mechanism of resistance to antiangiogenic therapies in many cancer types including endocrine tumours.

It has been tested in several endocrine tumour types with promising results (62,63) and is currently on phase III for differentiated thyroid cancer and neuroendocrine tumours of the digestive system (NCT03690388, NCT03375320).

The activity of immune checkpoint inhibitors in endocrine cancers has been limited by their tumour biology, mostly low grade with low tumour mutational burden and low percentage of alterations in DNA repair genes. However, activity in high grade tumours such as MSI adrenocortical carcinomas or anaplastic thyroid cancers has been described with promising results. In addition to that, there is robust evidence supporting the existence of cumulative mutations that are leading to more aggressive behaviour of endocrine tumours as these tumours are becoming refractory to subsequent systemic treatments.

The rationale for the combination of cabozantinib and atezolizumab in endocrine tumours are as follows:

1. Cabozantinib has shown promising activity, in several endocrine tumour types, including thyroid cancer, neuroendocrine tumours, as well as pheochromocytoma and paragangliomas (62-64). Cabozantinib increased PFS on progressive medullary thyroid cancer and refractory differentiated thyroid cancer patients with a manageable toxicity profile (62-63). Preliminary results in 10 pheochromocytoma patients showed an ORR of 40% and a clinical benefit rate of 90% (64).

2. The efficacy of anti-PD-1/PD-L1 treatments (as atezolizumab) in monotherapy seems to be limited to high grade tumours such as anaplastic thyroid cancers and MSI adrenocortical carcinomas. However, in most well-differentiated endocrine neoplasms, including thyroid and neuroendocrine tumours, the immune system plays a crucial role in the control of tumour growth without systemic therapies which allows the inclusion of active surveillance strategies in all treatment guidelines. Recent data showed potential higher activity, measured by ORR, of anti-PD1 monotherapy in well-differentiated neuroendocrine tumours of the lung than in gastroenteropancreatic origins (NTC03167853)(65).

3. The combination of cabozantinib and atezolizumab may be active in endocrine tumours by overcoming the resistance to prior antiangiogenic drugs and sensitising the tumours to immunotherapy through the combination of multikinase inhibitors and anti-PD-L1 therapy (66-67).

4.

3.1. Rationale for dose

Results from the phase 1b COSMIC-021 study of cabozantinib in combination with atezolizumab in patients with previously untreated advanced renal cell carcinoma (RCC) were presented at the European Society for Medical Oncology (ESMO) 2018 Congress in Munich (68). This dose-escalation study primarily looked at the safety of cabozantinib + atezolizumab combination in untreated advanced RCC patients to determine the best dose to use in future clinical trials. The combination showed encouraging clinical activity in this group of patients, and the best dose of cabozantinib was found to be 40 mg in combination with the standard dose of atezolizumab (1200 mg/every 3 weeks) (68). Dosing selected for this trial is based in the aforementioned study.

4. Hypothesis and Objectives

4.1. Study Hypothesis

The main hypothesis is that the administration of cabozantinib plus atezolizumab will improve the probability of expected objective response rate in advanced and refractory tumours of the endocrine system. This study will be considered positive if the main hypothesis is achieved in at least one cohort of patients.

4.2. Study Objectives

Primary objective:

- To assess the efficacy of cabozantinib plus atezolizumab by means of radiological objective response rate (ORR) as per RECIST V1.1, in advanced endocrine tumours.

Secondary objectives:

- To evaluate the safety profile of cabozantinib and atezolizumab combination, according to NCI-CTCAE V5.0.
- Duration of response (DoR) as per RECIST V1.1.
- Progression-free survival (PFS): median PFS as per RECIST V1.1.
- Overall Survival (OS): median OS as per RECIST V1.1.
- Tumour biomarkers: translational substudy (optional).
- Quality of Life (QoL).

Study endpoints for these objectives are described in section 10.2 of this protocol.

5. Study Design

5.1. Overall Study Design

This is an open labelled, single arm, multicohort phase II multicentre clinical trial of cabozantinib plus atezolizumab in advanced and refractory tumours from the endocrine system.

The dose scheme includes the initial dose of cabozantinib 40 mg qd + atezolizumab (1200 mg) intravenously

administered every 21 days (one cycle). Dose adjustment of cabozantinib is allowed as per the PI criteria but dose reductions of atezolizumab are not expected. Additional information on the treatment, modifications, and dose delays is available in section 7 of this protocol.

The CABATEN trial will include patients with advanced and refractory tumours of endocrine system (additional details on the eligibility criteria of the study are found in section 6 of this protocol) and patients would be allocated to six different cohorts according to the following tumour types:

- Cohort 1: Well-differentiated neuroendocrine tumours of the lung and thymus (WHO grades 1 and 2, typical and atypical carcinoids) after progression to somatostatin analogs, targeted agents, PRRT, and/or chemotherapy.
- Cohort 2: Anaplastic thyroid cancer in first-line or after progression to chemotherapy or investigational drugs.
- Cohort 3: Adrenocortical carcinoma after progression to chemotherapy and/or mitotane.
- Cohort 4: Pheochromocytoma and paraganglioma after progression to peptide receptor radionuclide therapy (PRRT) if indicated, prior chemotherapy and biological therapy, such as somatostatin analogs, are allowed.
- Cohort 5: Well-differentiated neuroendocrine tumours of digestive system (WHO grades 1 and 2) after progression to somatostatin analogs, targeted agents, PRRT, and/or chemotherapy.
- Cohort 6: Grade 3 neuroendocrine neoplasm (WHO grade 3, including NET and NEC G3) of any origin, excluding small cell lung cancer, after progression to chemotherapy or targeted agents/PRRT.

The design includes screening phase, treatment phase (including medical consultation and drug administration Q3w ± 3 days), disease progression follow up by RECIST 1.1 every 12 weeks ± 2w (disease progression assessments may be performed every Q8w ± 2w if required by local standard clinical practice or by investigator criteria, as long as the frequency of the assessments is maintained), translational research with biopsies and blood samples and long term follow-up.

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.

The first administration of cabozantinib will be carried out after the infusion of the first atezolizumab cycle, the patient will take the treatment in the presence of a member of the Site staff who will advise the patient on the correct intake of the treatment (according to the indications of the section 7.1 of this protocol), discuss with the patient the process of completing the patient diary, and address the doubts that the patient may have at the time. In addition, patient must bring all medication bottle(s) (including empty ones) to each visit , for IMP adherence and compliance traceability purposes.

After the first supervised administration, cabozantinib will be self-administered by patients daily according to the indications of the Investigator staff and as indicated in section 7 of this protocol. Treatment with cabozantinib will be continuous until the progression of the disease and/or unacceptable toxicity, among others. Patients will attend follow-up visits with the study doctor every 3 weeks for clinical assessment, laboratory tests, laboratory determinations should be made within 72 hours prior to the date of administration of atezolizumab, in order to assess the relevance of administration of a new cycle (modifications, delays, etc.), according to what is specified in sections 7.1.2 and 7.2.2. Additionally, the study doctor may request patients to come to the centre more frequently in case of toxicity or discomfort of the patient. Additional information about the study's determinations is found in section 8 of this protocol.

Treatment and study determinations will be the same for all the patients, regardless of the cohort in which the patients are included.

This is a study with Simon's two-stage design; it requires that an event is observed in the first nine patients before continuing to the second stage where there is a possible inclusion of 15 additional patients (up to a maximum of 24 patients per cohort).

In addition, an optional biomarker study with tumour and blood samples will be performed (if it is feasible for the Sponsor), and it is detailed in the corresponding biological samples manual.

5.2. Patient Screening

Once all regulatory and sponsor requirements are completed confirming that the study is fully active in the corresponding site, ICFs can be offered to potential patients.

Screening slots will be assigned centrally by MFAR Clinical Research, and it is important to confirm slot availability before giving an ICF to any patient. 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 such as bone scans) 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. 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 the procedures that are needed to confirm patients' suitability for the trial protocol, such as clinical laboratory tests, imaging, and others are performed.

Screening determinations include ICF signature, eligibility assessments, tumour characteristics, ECG, clinical evaluation (AE, PE, ECOG, VS, BMI, and symptom control), laboratory determinations [FBE, Biochemistry, liver panel test function, pancreatic enzymes, serology, urinalysis, pregnancy test, concomitant medication, biological samples (optional tumour sample and blood samples for biomarkers)], and CT Scan / MRI. Additional information about screening procedures can be found in section 8 of this protocol.

5.3. Patient Inclusion and Cohort Assignment

After confirming that a patient fulfils all the eligibility criteria of the study (section 6 "Eligibility Criteria), 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.

5.4. Patient Treatment

All the subjects will be treated with the combination until disease progression, unacceptable toxicity, or patient consent withdrawal (whichever occurs first) according to section 7 of this protocol.

- Cabozantinib 40 mg or 20 mg tablets, oral administration once daily continuously.
- Atezolizumab 1200 mg administered intravenously (IV) every three weeks (cycle).

5.5. Patient Follow up After Treatment

5.5.1. End of treatment without progression

Patients ending treatment without progression should remain in the study, and should be followed up according to RECIST 1.1 every 12 weeks (± 2w) until progression or death. Follow up assessments may be

performed q8w ± 2w if required by local standard clinical practice or by investigator criteria, as long as the frequency of assessments is maintained. Please see section 8.1 of this protocol.

5.5.2. End of treatment due to progression

Information on subsequent treatments should include the list of post-treatment therapies, administered drugs, the date of initiation and discontinuation of each drug, and the date of subsequent progression. All data will be recorded in the medical record and in the eCRF as per section 8.1 of this protocol.

5.6. Translational Research

- Optional substudy involving tissue biopsies will be performed with samples obtained before treatment, for identification of predictive biomarkers.
- Blood samples: Analysis of somatic alterations in tumours including proteomics, transcriptomics, and metabolics i.e. metabolic pathways of insulin growth factor, among others. No germinal line determinations will be performed. The levels of IGF-1 in serum (others biomarkers may be analysed) will be measured using the blood samples collected from the patients at the different time-points, according to table 2 “Schedule of assessments”. The evolution of biomarkers will be evaluated individually and for the different groups of patients.

Information regarding biological samples collection, management, and shipments are provided in the biological sample manual.

5.7. Study Calendar

Date first patient enrolled: 08/10/2020

Estimated date last patient enrolled: 3Q 2022

Estimated date last patient completed: 3Q 2023

Estimated End of Study: 1Q 2024

6. Eligibility Criteria

6.1. Inclusion Criteria

Patients eligible for inclusion in this study must meet all the following criteria:

1. Male or female subjects ≥ 18 years old.
2. Willingness to participate in the study by signing ICF approved by the trial Central Ethic Committee (CEIm).
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Measurable disease per RECIST 1.1 as determined by the investigator.
5. Patients with advanced and progressive neuroendocrine tumors histopathologically confirmed (as per local pathology report), meeting one of the following (according to WHO 2010 classification):
    a. Cohort 1: Well-differentiated neuroendocrine tumours of the lung and thymus (WHO grade 1 and 2, typical and atypical carcinoids) after progression to somatostatin analogs, targeted agents, PRRT, and/or chemotherapy.
    b. Cohort 2: Advanced anaplastic thyroid cancer in first-line or after progression to chemotherapy or investigational drugs, that underwent prior primary tumor surgical

resection or not. In patients that primary tumor has not been resected, the risk of aerodigestive compression or bleeding should be ruled out to ensure no interference with the administration of the investigational product and undesirable potential side effects related to the route of administration.

c. Cohort 3: Adrenocortical carcinoma after progression to chemotherapy and/or mitotane.
d. Cohort 4: Pheochromocytoma and paraganglioma after progression to peptide receptor radionuclide therapy (PRRT) if indicated. Prior chemotherapy and biological therapy, such as somatostatin analogs, are allowed.
e. Cohort 5: Well-differentiated neuroendocrine tumours of digestive system (WHO grade 1 and 2) after progression to somatostatin analogs, targeted agents, PRRT, and/or chemotherapy.
f. Cohort 6: Grade 3 neuroendocrine neoplasm (WHO grade 3, including NET and NEC G3) of any origin, excluding small cell lung cancer, after progression to chemotherapy or targeted agents/PRRT.

   Note: Patients will be eligible for inclusion after progression to one of the lines aforementioned, without limit in the number of treatment lines.

6. Recovery from toxicity related to any prior treatments to ≤ Grade 1, unless the AE(s) are clinically non-significant and/or stable on supportive therapy.
7. Ability to swallow tablets.
8. 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 ≤ 1.5X 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. AST (SGOT)/ALT (SGPT) ≤ 2.5X institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 3X ULN.
   f. Measured creatinine clearance (CL) > 40 mL/min or Calculated creatinine CL > 40 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:

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

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 from their inclusion in the study and until 5 months after the last dose of study treatment (i.e condom with spermicide + IUD or cervical caps). (see section 9.6.1 of this protocol) .

10. Males should agree to abstain from sexual intercourse with a female partner or agree to use double barrier method of contraception (i.e. a condom with spermicide, in addition to having their female partner use some contraceptive measures such as intrauterine device, or cervical caps), for the duration of the study and for 4 months after participation in the study (see section 7.4.1 of this protocol).

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

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

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

2. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks or 5 half-lives of the agent, whichever is longer. Patients should have been out of mitotane for at least 4 weeks.

3. Receipt of any type of anticancer antibody (including investigational antibody) or systemic chemotherapy within 2 weeks before starting treatment.

4. Current or prior use of immunosuppressive medication within 2 weeks before the first dose of cabozantinib and atezolizumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

5. Active or prior documented autoimmune disease within the past 2 years

   *N*ote: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

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

7. History of allogeneic organ transplant.

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

9. Receipt of radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks before inclusion. Subjects with clinically relevant ongoing complications from prior radiation therapy that have not completely resolved are not eligible (e.g, radiation esophagitis or other inflammation of the viscera).

10. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before inclusion. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of study treatment.

11. Concomitant anticoagulation with oral anticoagulants (e.g, warfarin, direct thrombin and factor Xa inhibitors) or platelet inhibitors (e.g, clopidogrel), except for the following allowed anticoagulants:

    - Low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH).

    - Anticoagulation with therapeutic doses of LMWH in subjects without known brain metastases and who are on a stable dose of LMWH for at least 6 weeks before inclusion and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumour.

12. The subject has uncontrolled, significant intercurrent or recent illness 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

        vii. History of solid organ transplantation

13. 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.

14. Corrected QT interval calculated by the Fridericia formula (QTcf) > 500 ms within 28 days before study treatment

    Note: if a single ECG shows a QTCf with an absolute value > 500 ms, two additional EGGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these 3 consecutive results for qtcf will be used to determine eligibility.

15. Pregnant or lactating females.

16. Inability to swallow tablets.

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

18. Diagnosis of another malignancy within 3 years before study treatment, except for superficial skin cancers, or localised, low grade tumours deemed cured and not treated with systemic therapy.

6.3. Patient Withdrawal From the Trial

Patient is, at any time, free to withdraw from study (investigational product and study assessments), without prejudice to further treatment (withdrawal of consent).
Subjects that choose to withdraw early from the study will be voluntarily surveyed for reasons for withdrawal, including information of possible presence of any adverse events. If possible, he/she will be seen and assessed by an investigator.
Adverse events will be followed up and all study material (if any) should be returned by the patient. 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. Withdrawn patients will not be replaced.

If patient withdraws consent, he/she will be specifically asked if he/she is withdrawing consent to:

- To further participation in the study including any further follow up (e.g., survival calls).
- The use of her data generated from the study.
- The use of any samples.

Reasons for early withdrawal from the study should be documented in the eCRF and patient's records as:

- Study closed/terminated.
- Subject lost to follow-up.
- Investigator’s decision.
- Subject withdrew consent.
- Participation in another clinical trial.
- Major protocol violations that invalidates patient’s data.
- Death.

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

6.4. Premature Termination of the Trial

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)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

6.5. Definition of End of Trial

'Last patient last visit', as defined in this protocol, is 12 months after the enrolment of last patient. Subjects may continue to receive IMPs after the cut-off because treatment cannot be discontinued for ethical reasons, but in such cases, Sponsor agrees to continue with cabozantinib supply to sites to cover patient treatment until it's finalisation and atezolizumab for a maximum of 6 months after the end of the study (LPLV). For these 6 additional months (since LPLV), the principal investigators must inform on any suspicion on adverse events/special situations in patients receiving atezolizumab's, to the marketing authorisation holder, Roche's Pharmacovigilance Department (madrid.drug_safety@roche.com, Tel. +34 91.324.8183). Those events reported in patients receiving cabozantinib the marketing authorisation holder: Ipsen Pharmacovigilance Department (pharmacovigilance.spain@ipsen.com), Tel. +34 93.685.81.00.

7. Treatment of Subjects

7.1. Cabozantinib

7.1.1. Cabozantinib presentation and administration

Pharmaceutical form and route of administration: Cabozantinib is formulated as two distinct drug product types for oral administration: capsules and tablets. For this trial, tablets containing cabozantinib 20 mg and 40 mg will be supplied.

Strength: Tablet strengths are 20 and 40 mg (FBE weight). They are formulated from a wet granulation process that consists of mixing cabozantinib malate salt and excipients together; the granulation is subsequently further blended and then compressed into tablets and film-coated. Tablets are distinguished by shape.

Presentation: Commercial medication labeled for clinical trial, containing cabozantinib 20 mg or 40 mg in HDPE bottle with a polypropylene child-resistant closure and three silica gel desiccant canisters. Each bottle contains 30 film-coated tablets.

Administration instructions

Cabozantinib tablets are meant to be taken orally only and not to be opened or crushed for dissolving in liquid or administered through other routes including percutaneous endoscopic gastrostomy (PEG) tubes. Cabozantinib tablets should not be administered to subjects who do not have adequate swallowing capacity. Cabozantinib is meant to be taken without food (subjects should not eat for at least 2 h before and at least 1 h after taking cabozantinib) with a full glass (at least 8 ounces or 240 mL) of water. If a dose is missed, the missed dose should not be taken less than 12 h before the next dose.

Important dosage information:

- Stop treatment with cabozantinib at least 28 days prior to scheduled surgery, including dental surgery.
- Do not substitute cabozantinib tablets with cabozantinib capsules.
- Do not administer cabozantinib with food. Administer at least 1 hour before or at least 2 hours after eating.

- Patients should swallow cabozantinib tablets whole. Do not crush cabozantinib tablets.
- Patients do not take a missed dose within 12 hours of the next dose.
- Modify the dose for certain patients with hepatic impairment and for patients taking drugs known to strongly induce or inhibit CYP450.

7.1.2. Dose modifications

The allowed dosing schemes of this trial are:

- *Level 0 (starting dose): cabozantinib 40 mg qd + atezolizumab 1200 mg iv every 21 days (one cycle)*
- *Level -1: cabozantinib 20 mg qd + atezolizumab 1200 mg iv every 21 days (one cycle)*

If cabozantinib is temporarily or definitively interrupted for its toxicity, atezolizumab will be continued, unless the toxicity of cabozantinib prevents the administration of atezolizumab or increases the risk of atezolizumab toxicity. In this case, both treatments will be interrupted until toxicity resolution (or NCI CTCAE grade 1) or definitively.

If one of the two drugs is discontinued or interrupted due to toxicity, the administration of the other drug should continue according to the protocol schedule.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF and patient record.

As previously mentioned, cabozantinib dose reduction to 20 mg qd is allowed. Once reduced, dose re-escalation of cabozantinib is allowed in the opinion of the Principal Investigator, taking into account clinical benefit, type and degree of toxicity that produced the dose reduction.

Cabozantinib should be withheld for:

- Intolerable Grade 2 adverse reactions
- Grade 3 or 4 adverse reactions
- Osteonecrosis of the jaw

Upon resolution/improvement (i.e., return to baseline or resolution to Grade 1) of an adverse reaction, reduce the dose as follows:

- If previously receiving 40 mg daily dose, resume treatment at 20 mg daily.
- If previously receiving 20 mg daily dose, resume at 20 mg if tolerated, otherwise, discontinue cabozantinib.

Permanently discontinue cabozantinib for any of the following:

- Severe hemorrhage
- Development of gastrointestinal (GI) perforation or unmanageable fistula
- Serious thromboembolic event (e.g., myocardial infarction, cerebral infarction)
- Hypertensive crisis or severe hypertension despite optimal medical management
- Nephrotic syndrome
- Reversible posterior leukoencephalopathy syndrome

7.1.3. Cabozantinib Special warnings and precautions for use

1) Hepatic effects

Abnormalities of liver function tests (increases in alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) have been frequently observed in patients treated with cabozantinib. It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of cabozantinib treatment and to monitor closely during treatment. For patients with worsening of liver function tests

considered related to cabozantinib treatment (i.e. where no alternative cause is evident), the dose modification advice in section 7.1.2). Cabozantinib is eliminated mainly via the hepatic route. Closer monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment (see also section 7.1.2). A higher relative proportion of patients with moderate hepatic impairment (Child-Pugh B) developed 6 hepatic encephalopathy with cabozantinib treatment. Cabozantinib is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as cabozantinib has not been studied in this population and exposure might be increased in these patients.

2) Hepatic encephalopathy

In the HCC study (CELESTIAL), hepatic encephalopathy was reported more frequently in the cabozantinib than the placebo arm. Cabozantinib has been associated with diarrhoea, vomiting, decreased appetite and electrolyte abnormalities. In HCC patients with compromised livers, these non-hepatic effects may be precipitating factors for the development of hepatic encephalopathy. Patients should be monitored for signs and symptoms of hepatic encephalopathy.

3) Perforations and Fistulas

Fistulas, including fatal cases, occurred in 1% of cabozantinib-treated patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of cabozantinib-treated patients.

Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue cabozantinib in patients who experience a fistula which cannot be appropriately managed or a GI perforation.

4) Gastrointestinal (GI) disorders

Diarrhoea, nausea/vomiting, decreased appetite, and stomatitis/oral pain were some of the most commonly reported GI adverse reactions. Prompt medical management, including supportive care with antiemetics, antidiarrheals, or antacids, should be instituted to prevent dehydration, electrolyte imbalances and weight loss. Dose interruption or reduction, or permanent discontinuation of cabozantinib should be considered in case of persistent or recurrent significant GI adverse reactions.

Diarrhea occurred in 63% of patients treated with cabozantinib. Grade 3 diarrhea occurred in 11% of patients treated with cabozantinib.

Withhold cabozantinib until improvement to Grade 1 and resume cabozantinib at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard anti diarrhea treatments, or Grade 4 diarrhea.

5) Thrombotic Events

Cabozantinib increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of cabozantinib-treated patients. Fatal thrombotic events occurred in cabozantinib-treated patients.

Discontinue cabozantinib in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention

6) Hemorrhage

Severe and fatal hemorrhages occurred with cabozantinib. The incidence of Grade 3 to 5 hemorrhagic events was 5% in cabozantinib-treated patients. Discontinue cabozantinib for Grade 3 or 4 hemorrhage. Do not administer cabozantinib to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

7) Thrombocytopenia

In the HCC study (CELESTIAL), thrombocytopenia and decreased platelets were reported. Platelet levels should be monitored during cabozantinib treatment and the dose modified according to the severity of the thrombocytopenia (see section 7.1.2).

8) Wound Complications

Wound complications have been reported with cabozantinib. Stop cabozantinib at least 28 days prior to scheduled surgery. Resume cabozantinib after surgery based on clinical judgment of adequate wound healing. Withhold cabozantinib in patients with dehiscence or wound healing complications requiring medical intervention.

9) Hypertension and Hypertensive Crisis

Cabozantinib can cause hypertension, including hypertensive crisis. Hypertension was reported in 36% (17% Grade 3 and <1% Grade 4) of cabozantinib treated patients.

Do not initiate cabozantinib in patients with uncontrolled hypertension. Monitor blood pressure regularly during cabozantinib treatment. Withhold cabozantinib for hypertension that is not adequately controlled with medical management; when controlled, resume cabozantinib at a reduced dose. Discontinue cabozantinib for severe hypertension that cannot be controlled with antihypertensive therapy or for hypertensive crisis.

10) Palmar-Plantar Erythrodysesthesia

Palmar-plantar erythrodysesthesia (PPE) occurred in 44% of patients treated with cabozantinib. Grade 3 PPE occurred in 13% of patients treated with cabozantinib.

Withhold cabozantinib until improvement to Grade 1 and resume cabozantinib at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

11) Proteinuria

Proteinuria was observed in 7% of patients receiving cabozantinib. Monitor urine protein regularly during cabozantinib treatment. Discontinue cabozantinib in patients who develop nephrotic syndrome.

12) Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with cabozantinib. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue cabozantinib in patients who develop RPLS.

13) Prolongation of QT interval

Cabozantinib should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using cabozantinib, periodic monitoring with ontreatment ECGs and electrolytes (serum calcium, potassium, and magnesium) should be considered.

14) Biochemical laboratory test abnormalities

Cabozantinib has been associated with an increased incidence of electrolyte abnormalities (including hypo- and hyperkalemia, hypomagnesaemia, hypocalcaemia, hyponatremia). It is recommended to monitor biochemical parameters during cabozantinib treatment and to institute appropriate replacement therapy according to standard clinical practice if required. Cases of hepatic encephalopathy in HCC patients can be

attributed to the development of electrolyte disturbances. Dose interruption or reduction, or permanent discontinuation of cabozantinib should be considered in case of persistent or recurrent significant abnormalities (see section 7.1.2).

15) Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) occurred in <1% of patients treated with cabozantinib. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of cabozantinib and periodically during cabozantinib. Advise patients regarding good oral hygiene practices. Withhold cabozantinib for at least 28 days prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold cabozantinib for development of ONJ until complete resolution.

16) Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, cabozantinib can cause fetal harm when administered to a pregnant woman. Cabozantinib administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with cabozantinib and for 4 months after the last dose.

7.2. ATEZOLIZUMAB

7.2.1. Atezolizumab presentation and administration

Pharmaceutical form and route of administration: Preservative-free clear liquid solution for intravenous administration.

Strength: 60 mg/mL glass vials of 20-mL, nominal atezolizumab amount per vial, 1200 mg.

Presentation: Glass vials of 20-mL, commercial medication labeled for clinical trial.

Administration instructions:

Atezolizumab is for intravenous use. 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.

7.2.2. Atezolizumab dose modifications

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment if they experience toxicity that is considered to be related to study drug and requires a dose to be held. If atezolizumab is held because of related adverse events for 42 days beyond when the dose would have been given, then the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in section 8. Please see Section 7.2.3 for guidelines for the management of infusion related reactions.

Dose interruption of atezolizumab

Any toxicity observed during the study treatment phase could be managed by interruption of the dose of the study treatment if deemed appropriate by the Investigator. Repeated dose interruptions are allowed as required, for a maximum of 42 days on each occasion. If the interruption is any longer than this, the Coordinating Investigator must be informed and treatment restart should be discussed between the Sponsor study team and the investigator. If in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming atezolizumab after a hold of 42 days, the treatment may be restarted with the approval of the Coordinating Investigator.

If patients must be tapered off steroids used to treat adverse events, study treatment may be held for 42 days. The acceptable length of interruption will depend on agreement between the investigator and the Coordinating Investigator.

Study treatment must be interrupted until the patient recovers completely or the toxicity reverts to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0) grade 1 or less.

Treatment with atezolizumab must be temporarily or permanently interrupted if any NCI CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to the administration of atezolizumab. Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will depend on agreement between the investigator and the Coordinating Investigator.

If atezolizumab is temporarily or definitively interrupted for its toxicity, cabozantinib will be continued, unless the toxicity of atezolizumab prevents the administration of cabozantinib or increase the risk of cabozantinib toxicity. In this case, both treatments will be interrupted until toxicity resolution (or NCI CTCAE grade 1) or definitively.

If one of the two drugs is discontinued or interrupted due to toxicity, the administration of the other drug should continue according to the protocol schedule.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF and patient record. An occurrence of autoimmune disease will be declared in this study as a serious adverse event (SAE) at any time during atezolizumab treatment and at any time after the treatment has been stopped.

7.2.3. Atezolizumab *Special warnings and precautions for use*

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.

Most immune-mediated adverse reactions that occurs 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. Immune-mediated adverse reactions with atezolizumab 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.

1) Pulmonary events

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

2) Hepatic events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. 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 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(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, 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. 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. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly.

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

14) 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 10^9/L (100,000/µL)
    - ANC 1.0 <10^9/L (1000/µL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen <1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin >500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥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 10^9/L (181,000/μL)
    - AST ≥48 U/L
    - Triglycerides ≥1.761 mmol/L (156 mg/dL)
    - Fibrinogen ≤3.6 g/L (360 mg/dL)

More information provided in Appendix 1.

15) Severe Cutaneous Adverse Reactions (SCARs)

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.

The following recommendations should be followed:

- 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.

7.3. CONCOMITANT MEDICATIONS

Full and updated information regarding potential drug interactions and effects of food are available in the IBs (69,70) and SmPC of cabozantinib (71) and atezolizumab (72) allocated at investigator site file. However, general information regarding permitted/prohibited concomitant treatment is detailed below.

All medications (prescriptions or over-the-counter medications) on-going at the start of the trial or initiated during the study or until 30 days from the end of the last protocol treatment and different from the study medication will be documented.

All concomitant medications taken by the subject during the trial, starting from the date of signing the informed consent, will be recorded. The indication, dose, frequency, and dates of treatment will be recorded in the patient's medical records and in the appropriate section of the eCRF.

The patient must notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than the study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications, and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Surgical and Medical Procedures eCRF. Patients taking concomitant medications should maintain the same dose and dose schedule throughout the study if medically feasible.

Caution should be used regarding the use of herbal medications as there may be yet unknown interactions

with study treatment. Discontinuation of the use of herbal medications prior to study enrolment is encouraged.

Any medications that are considered necessary to protect subject's welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

Rescue medications may be administered to address anticipated adverse reactions or anticipated emergency situations.

7.3.1. Allowed concomitant treatment

- Antiemetics and antidiarrheal medications are allowed prophylactically according to standard clinical practice if clinically indicated.
- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (eg, ASCO or ESMO guidelines).
- Bisphosphonates can be used per standard of care if the benefit outweighs the risk per the Investigator's discretion.

  Note: osteonecrosis of the jaw has been reported in subjects using bisphosphonates. Oral examinations are recommended at screening to determine eligibility and periodically during the study. In addition, subjects should be advised regarding oral hygiene practice and to quickly report symptoms to the Investigator. Frequent monitoring for potentially overlapping toxicities with study treatment is recommended.

- Transfusions and hormone replacement should be utilized as indicated by standard clinical practice.
- Inhaled, intranasal, intra-articular, or topical corticosteroids are allowed if minimal systemic absorption. Systemic corticosteroids are allowed for control of infusion reactions or irAEs and must be tapered over ≥ 1 month to a dose level ≤ 10 mg/day of prednisone equivalent before next atezolizumab administration. Prophylactic steroid treatment for subjects with contrast allergies prior to tumor imaging is allowed.
- Individualized anticoagulation therapy with heparin is allowed if it can be provided safely and effectively under the following circumstances:
    - Low dose LMWH for prophylactic use are allowed if clinically indicated and the benefit outweighs the risk per the investigator's discretion.
    - Therapeutic doses of LMWH after first dose of study treatment are allowed if clinically indicated (eg, for the treatment of DVT), and the benefit outweighs the risk per the investigator's discretion. For management of thromboembolic complications while on study, refer to Section 7.1.2 and 7.1.3
    - Accepted clinical guidelines regarding appropriate management while receiving anticoagulation therapy with heparins must be followed. This includes, but is not limited to, subject education regarding potential adverse drug reactions, monitoring laboratory parameters, dose adjustments (eg, due to kidney dysfunction, platelet decrease).
    - For restrictions on oral anticoagulants see Section 7.3.3.

Additional information on potential drug interactions with cabozantinib, atezolizumab are summarized in Section 7.4.1 and 7.4.2 respectively

7.3.2. Prohibited concomitant treatment

The following therapies are prohibited until study treatment has been permanently discontinued:

- Any investigational agent or investigational medical device.
- Therapeutic doses of oral anticoagulants (eg, warfarin or other coumarin-related agents, direct thrombin or direct FXa inhibitors, or antiplatelet agents such as clopidogrel, or chronic use of aspirin above low dose levels for cardioprotection per local applicable guidelines).
- Any non-protocol systemic anticancer treatment (eg, chemotherapy, immunotherapy, radionuclides, drugs or herbal products used specifically for the treatment of the cancer under investigation).
- Concomitant use of denosumab with atezolizumab is prohibited due to a potential for increased risk of infections.
- Immunosuppressive agents including immunosuppressive doses of systemic corticosteroids with exceptions as stated in Section 7.2.3 and 7.3.1.

The following therapies should be avoided until study treatment has been permanently discontinued or until otherwise specified:

- Local anticancer treatment including palliative radiation, ablation, embolization, or surgery with impact on tumor lesions should not be performed until radiographic progression per RECIST 1.1 has been established. If clinically unavoidable the investigator should consult the Sponsor prior to the procedure for safety guidance.
- Erythropoietic stimulating agents (eg, epoetin alfa and darbepoetin alfa) should not be used based on a report of increased risk of tumor recurrence/progression associated with erythropoietin (Wright et al 2007).
- Concomitant medications that are known to prolong the QTc interval should be avoided in subjects until they have permanently discontinued cabozantinib or sorafenib treatment (refer to http://www.qtdrugs.org for a list of drugs which have the potential to prolong the QTc interval).
- Live vaccines are prohibited while on study and until 5 months after last atezolizumab dose (eg, intranasal influenza, measles, mumps, rubella, oral polio, Bacillus Calmette-Guérin, yellow fever, varicella, and TY21a typhoid vaccines). The use of inactivated (killed) vaccines for the prevention of infectious disease requires Sponsor approval.
- Chronic co-administration of cabozantinib or sorafenib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease concentrations of these study drugs and should be avoided. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.
- Caution must be used when discontinuing treatment with a strong CYP3A4 inducer in a subject who has been concurrently receiving a stable dose of cabozantinib or sorafenib, as this could significantly increase the exposure to these study drugs.
- Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase concentrations of study drug and should be avoided. Grapefruit, star fruit, and Seville oranges may also increase plasma concentrations of these study drugs and should be avoided.

Additional information on potential drug interactions with cabozantinib, atezolizumab are summarized in Section 7.4.1 and 7.4.2 respectively

7.4 POTENTIAL DRUG INTERACTIONS

7.4.1 Potential Drug Interactions with Cabozantinib

Cytochrome P450: Data from a clinical drug interaction study (Study XL184-008) show that clinically relevant steady-state concentrations of cabozantinib appear to have no marked effect on the area under the plasma concentration-vs-time curve (AUC) of co-administered rosiglitazone, a CYP2C8 substrate. Therefore, cabozantinib is not anticipated to markedly inhibit CYP2C8 in the clinic, and by inference, is not anticipated to markedly inhibit other CYP450 isozymes that have lower [I]/Ki values compared with CYP2C8 (ie, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP3A4). In vitro data indicate that cabozantinib is unlikely to induce CYP enzymes, except for possible induction of CYP1A1 at high cabozantinib concentrations (30 µM).

Cabozantinib is a CYP3A4 substrate and a weak substrate for CYP2C9 (but not a CYP2D6, CYP2C8, CYP2C19, CYP2B6, or CYP1A2 substrate), based on data from in vitro studies. Results from a clinical pharmacology study, XL184-006, showed that concurrent administration of cabozantinib with the strong CYP3A4 inducer, rifampin, resulted in an approximately 77% reduction in cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Chronic co-administration of cabozantinib with strong inducers of the CYP3A4 family (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's Wort) may significantly decrease cabozantinib concentrations. The chronic use of strong CYP3A4 inducers should be avoided. Other drugs that induce CYP3A4 should be used with caution because these drugs have the potential to decrease exposure (ie, AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme induction potential is recommended.

Results from a clinical pharmacology study, XL184-007, showed that concurrent administration of cabozantinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in a 38% increase in the cabozantinib exposure (AUC values) after a single dose of cabozantinib in healthy volunteers. Co-administration of cabozantinib with strong inhibitors of the CYP3A4 family (eg, boceprevir, conivaptan, posaconazole, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, saquinavir, ritonavir, lopinavir, telaprevir, telithromycin, and voriconazole) may increase cabozantinib concentrations. Grapefruit, star fruit and Seville oranges may also increase plasma concentrations of cabozantinib and should be avoided. Strong CYP3A4 inhibitors should be avoided and other drugs that inhibit CYP3A4 should be used with caution because these drugs have the potential to increase exposure (ie, AUC) to cabozantinib. Selection of alternate concomitant medications with no or minimal CYP3A4 enzyme inhibition potential is recommended.

Please refer to the drug interaction tables at the following website for lists of substrates, inducers, and inhibitors of selected CYP450 isozyme pathways:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions

Other Interactions: Food may increase exposure levels of cabozantinib by 57%, fasting recommendations should be followed. In vitro data suggest that cabozantinib is unlikely to be a substrate for P-glycoprotein, but has the potential to inhibit the P-glycoprotein transport activity (IC50=7.0 µM) at high concentrations. Subject should be cautioned regarding taking substrates of P-glycoprotein (eg, fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan). Therefore, subjects are cautioned regarding taking drugs containing a P-glycoprotein substrate. In addition, cabozantinib was shown to be a substrate of drug transporter multidrug resistance-associated protein 2 (MRP2) in an in vitro assay. Administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors (eg, cyclosporine, efavirenz, emtricitabine) should be approached with caution. Additional details related to these overall conclusions can be found in the investigator brochure.

Administration of the proton pump inhibitor (PPI) esomeprazole resulted in no clinically-relevant effect on cabozantinib plasma PK in healthy volunteers. Therefore, concomitant use of gastric pH modifying agents (ie, PPIs, H2 receptor antagonists, and antacids) is not contraindicated in subjects administered cabozantinib.

The effect of cabozantinib on the pharmacokinetics on contraceptive steroids has not been investigated. Since it cannot be guaranteed that there are no changes on the contraceptive effect, it is recommended to use an additional contraceptive method, such as a barrier method.

From in vitro data, cannabinoids have been shown to be CYP3A4 inhibitors. Investigators should be mindful that an increase in cabozantinib exposure with cannabinoid use could potentially exist although it seems unlikely.

Additional details regarding potential drug interactions with cabozantinib can be found in the Investigator's Brochure.

7.4.2 Potential Drug Interactions with Atezolizumab

Cytochrome P450 enzymes, as well as conjugation/glucuronidation reactions, are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted. There are no known interactions with other medicinal products or other form of interactions. For additional details refer to the local prescribing information and the atezolizumab Investigator's Brochure.

7.5. Treatment 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.

The investigator or designee must maintain an accurate record of the shipment and the dispensing of study treatments in the IWRS system designed for this trial (access to IWRS system will be created by study monitors during site initiation visit, or can be requested by email to: investigacion@mfar.net).

Compliance with the IMP schema is critical for patients and trial outcomes, and any deviation from the IMP schema may jeopardise trial results or may affect patient safety; for these reasons, non-compliance may be considered a protocol deviation. When an investigational product is dispensed in a clinical trial, the investigator or a person designated by the investigator will ensure high level of compliance with the investigational product administration procedures.

All the stages from IMP will be documented in the corresponding forms to guarantee traceability during the procedure.

For this trial, IMP 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.

At study close-out, and as appropriate during the study, the investigator will return all used and unused study treatment, packaging, and drug labels to the Sponsor, designated monitor, or to the Sponsor's address provided in the Investigator Site File at each site.

Upon approval by the Sponsor's delegate and after accountability has been confirmed by the Sponsor or designated monitor, the study drug supply will be destroyed at Sponsor's vendor, as appropriate.

7.6. Study Drug Supply, Labelling, Dispensing and Handling

7.6.1. Study Drug Supply

The Sponsor will supply cabozantinib and atezolizumab The Investigator or responsible site personnel must

instruct the clinical site staff as per protocol. Study drug(s) will be managed by authorised site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the patient's record and the eCRF.

7.6.2. Study drug labelling

Study drug will be open labelled. Medication labels will be created in the local language and will comply with the legal requirements of each participating country, including storage conditions for the drugs, batch number and expiration date, among others. The patient number should be hand-written by the investigator or its staff at the drug delivery time.

7.6.3. Study drug storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated site personnel have access.

Upon receipt, the study drugs should be stored according to the instructions specified on the drug labels and Investigator's Brochure of cabozantinib and atezolizumab. Study drug is to be stored in a secure locked area while under the responsibility of the Investigator. Receipt and dispensing of study medication must be recorded by an authorised person at the Investigator's site.

Records of drug formulation, batch number, and number of blisters/bottles dispensed must be recorded in the IWRS system of this trial and in pharmacy source records.

8. STUDY ASSESSMENTS

8.1. SCHEDULE FOR TESTS AND DETERMINATIONS

Study assessments should be performed following the indications of this schedule of determinations and when clinically indicated according treating clinician (i.e: more frequent determinations in case of toxicities).

Table 2. Schedule for test and determinations throughout the study period

	Screening	C1	C2	C3	C4	C5	C6	C7 to PD	EOT	Up to EOS
Week	-4 To -1	0	Q3w ±3 days unless dosing needs to be held for toxicity reasons					Q3w ±3 days unless dosing needs to be held for toxicity reasons		
Day	-28 To -1	1[a]	Q21 Days ±3 days unless dosing needs to be held for toxicity reasons					Q21 Days ±3 days unless dosing needs to be held for toxicity reasons		
Informed Consent										
Informed Consent[b]	X									
Consent and Collection of Specimens for Future Biomedical Research	X									
Study Procedures										
Medical History	X									
Physical Exam (Full)	X									
Targeted Physical Exam (Based On Symptoms)		X	X	X	X	X	X	X	X	
Vital Signs[c]	X	X	X	X	X	X	X	X	X	
ECG[d]	X	As clinically indicated							X	
Prior and Concomitant Medications	<----------									
Demography, Including Baseline Characteristics And Tobacco Use	X									
Eligibility Criteria	X									
Laboratory Assessments										
Clinical Chemistry[e]	X	X[f]	X	X	X	X	X	X	X	
Hematology[e]	X	X[f]	X	X	X	X	X	X	X	
TSH[g] (Reflex Free T3 Or Free T4[h])	X	X	X	X	X	X	X	X	X	
Hepatitis B, C and HIV[i]	X									
Urinalysis	X								X	
Tumor markers[q]	X	q12w ± 2w until objective disease progression or death (whichever occurs first).								
Pregnancy Test[j]	X	If clinically indicated								
Monitoring										
ECOG Performance Status	X	X	X	X	X	X	X	X	X	
QoL (EQ-5D-5L, EORTC QLQ-C30)[p]	X		X		X		X	q6w	X	
AE/SAE/AESI Assessment[k]		X	X	X	X	X	X	X	X	
Post-treatment Follow-up[l]										X
IMPs Administration										
Cabozantinib[m]		X (p.o. daily, until PD or unacceptable toxicity)								
Atezolizumab[m]		X (IV. q3w, 21 days ±3 days until PD or unacceptable toxicity)								
Biological samples collection										
Tumor Biopsy (Archival, If Available)	X									
Processed blood samples[n]	X		X						X	
Efficacy Evaluations										
Tumor evaluation (CT scan or MRI) (RECIST 1.1) [o]	X	q12w ± 2w until objective disease progression/death (whichever comes first).								X

Note: all assessments on treatment days are to be performed prior to atezolizumab infusion, unless otherwise indicated. C: cycle; ECG: electrocardiogram; IM: intramuscular; LFT: liver function test; QxW: every x weeks; T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone. EOT: end of treatment, EOS: end of study.

a) Every effort should be made to minimise the time between inclusion and start of treatment. (i.e. within 1 day of inclusion)
b) Informed consent of study procedures may be obtained prior to the 28-day screening window. If laboratory or imaging procedures were performed for different reasons prior to signing consent, these can be used for the screening purposes with the consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of inclusion.
c) Body weight is to be recorded at each visit along with vital signs.
d) Any clinically significant abnormalities detected require triplicate ECG results.
e) Complete blood count that includes total white blood cell count with leukocyte formula, haemoglobin, 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. 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 function include alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT) tests. Tests for pancreatic enzymes include lipase and amylase.
f) If clinical chemistry screening and haematology assessments are performed within 14 days prior to day 1 (first infusion day), they do not need to be repeated at day 1.
g) If TSH is measured within 14 days prior to C1D1 (first infusion day), it does not need to be repeated at day 1.
h) Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
i) Serology including HIV, hepatitis B (HBsAg and anti-HBc), and hepatitis C virus (HCV).
j) Women of childbearing potential are required to have a pregnancy test within 72 hours prior to the first dose of the study drug, and every 3 cycles (9 weeks) thereafter (if clinically indicated). Latest pregnancy results (maximum 9 weeks old) must be available and reviewed by the treating physician or investigator prior to commencing a new cycle of infusion. A urine or serum pregnancy test is acceptable.
k) For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed.
l) Post-treatment follow up: all patients will be followed up according to RECIST 1.1 every 12 weeks (+/-14 days) up to disease progression or death (whichever occurs first), regardless of the reason for ending the treatment. Follow up assessments may be performed q8w ± 2w if required by local standard clinical practice or by investigator criteria, as long as the frequency of assessments is maintained. Neuroendocrine markers are to be analysed according to local practice. The follow-up period according to this protocol is 12 months considering last patient inclusion. Information on subsequent treatments should include the list of post-treatment therapies, the drugs administered, and the date of initiation and discontinuation of each drug. All the data will be recorded in the medical record and in the eCRF.
m) The initial dose of atezolizumab will be administered before cabozantinib and must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. For the rest of the cycles, cabozantinib will be self-administered by the patients daily and as per principal investigator indications. 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.
n) Biomarker study: Collection of the most recent archived tumour-biopsy sections. Processed blood samples at baseline, day 1 of cycle 2 (D1C2), 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).
o) CT Scan or MRI is to be performed at baseline and q12w ± 2w until the objective disease progression or death (whichever comes first). Image assessments by CT scan or MRI may be performed q8w ± 2w if required by local standard clinical practice or by investigator criteria, as long as the frequency of assessments is maintained. The schedule of q12w ± 2 week (q8w ± 2w when applicable) 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. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. 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.
p) EQ-5D-5L and EORTC QLQ-C30 Questionnaires (appendix 2 and 3) will be done prior to the start of treatment (at screening) and every 2 cycles (q6w, 42 days) thereafter until PD.
q) Tumor markers should be analyzed at screening and every 12 weeks ± 2 weeks to determine the non-radiological response. The markers to collect are NSE in tumors from cohort 1, CGA in tumors from cohort 5, cortisol in functionant tumors from cohort 3, metanephrines and adrenaline in functionant tumors from cohort 4. Norepinephrine, 5-HIAA and CEA may be collected when considered.

8.2. Clinical Evaluation, Laboratory Tests and Follow-up

Study procedures and timing are summarised in the Schedule for test and determinations (section 8.1).

- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before inclusion. The investigator will maintain a patient log to record the details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Patient log will remain at the site at all time and will be available for monitoring and audit purposes.

8.2.1. Before treatment start

Informed Consent

For this study a single informed consent has been generated that includes the general information of the clinical trial and a section for the collection of samples for future research. The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. The informed consent will adhere to EC requirements, applicable laws and regulations.

The following recommendations should be considered for informed consent procedure:

- Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative dated signature on a consent form along with the dated signature of the person conducting the consent discussion.
- All fields aimed at collecting information of the patient and investigator performing the informed consent procedure should be completed. Any finding on signed consent forms could be considered as GCP breach.
- A copy of the signed and dated consent form should be given to the subject before participation in the trial. The initial informed consent form, any subsequent revised written informed consent form, and any written information provided to the subject must receive the EC approval or favourable opinion in advance of use.
- The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented through a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative dated signature.
- *Consent and Collection of Specimens for Future Biomedical Research:*
    - In accordance with Annex VIIIA - Guide for the elaboration of patient information sheet and informed consent of the AEMPS, taking into account that Future Biomedical Research will be offered to all patients, the information related to this part of the study will be included in a section of the general informed consent form. In this section, participation implications will be clearly explained, detailing the risk and benefit, answering all of patient's questions, and obtaining written informed consent before collection of biological samples.

    - The patient may accept or NOT to participate in this optional collection of biological samples by marking the corresponding box YES/NO in the section of informed consent. Site staff obtaining the informed consent must verify that the patient has correctly completed all the sections including their willingness to participate or not in the collection of samples.
- The Principal Investigator or the designee should clearly indicate in patient records that the patient has signed the informed consent stating his willingness to participate in the GETNE T-1914 - CABATEN Study indicating the level of acceptance, clinical part +/- sample collection.

Medical History

- A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, any diagnosed condition that are considered to be clinically significant by the Investigator, and/or relevant medical history taking into consideration the eligibility criteria (section 6.1 and 6.2).
- Any autoimmune disorders, regardless of the onset date, should be recorded.

Physical Exam

- *Full Physical Exam:* The investigator or clinical designee will perform a full physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history.
- *Targeted Physical Exam (prior treatment administration):* Additional physical exams (targeted) should be performed based on investigator criteria as specified in the Trial Flow Chart-Section 8.1, considering the disease under study, patients' symptoms, and prior physical exams. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

Vital Signs

- The investigator or qualified designee will take vital signs as specified in the Trial Flow Chart-Section 8.1.
- Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Body weight is to be recorded at each visit along with vital signs, but height will be measured at screening only.

12-Lead Electrocardiogram (ECG)

A standard 12-lead ECG will be performed at baseline and at the end of the treatment visit using local standard procedure. Any clinically significant abnormalities detected require triplicate ECG results and should be recorded as medical history or adverse event, and monitored if needed. No new ECGs will be performed unless clinically indicated.

Prior and concomitant medications review

- *Prior Medications:*

  The investigator or qualified designee will review prior medication use including any protocol-specified washout requirement, and record prior medication taken by the subject within 4 weeks of first dose of the study treatment.
- *Concomitant Medications:*
    - The investigator or qualified designee will record the medication, if any, taken by the subject during the trial from the time of signing the informed consent form until the Safety Follow-up Visit.
    - All medications related to reportable SAEs should be recorded

      .

Demography, Including Baseline Characteristics And Tobacco Use

- Date of birth (month/year of birth) or age at informed consent, race, and sex.
- Smoking history: never smoke (≤ 100 cigarettes/life time), former smoker (≥ 1 year), smoker, unknown)
- Tobacco use: pack/year and cigarettes/day.

Eligibility Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that each subject qualifies for the trial. More details on criteria for patients' eligibility are in section 6.1 and 6.2.

Laboratory Assessments

The summary of the procedures required is summarised in Table 2 and flow chart (Section 8.1 and the corresponding footnotes). Laboratory tests for screening should be performed within 7 days prior to study enrolment. If performed < 14 days prior to the first dose of trial therapy, the screening laboratory tests will serve as cycle 1 day 1 laboratory tests. If not, laboratory tests will need to be performed again on day 1 of cycle 1. Laboratory determinations include full clinical chemistry panel (including albumin, alkaline phosphatase, LDH, calcium, magnesium, phosphorus, sodium, potassium, creatinine, creatine kinase, direct bilirubin, indirect bilirubin, total bilirubin, total protein, urea, uric acid, amylase, lipase, glucose, ALT, AST, ALP, GGT), hematological counts (total white blood cell count with leukocyte formula, haemoglobin, and platelet count), TSH hormone levels, serology (HIV, HBV, and HCV), urianalysis and tumor markers (NSE in tumors from cohort 1, CGA in tumors from cohort 5, cortisol in functionant tumors from cohort 3, metanephrines and, adrenaline in functionant tumors from cohort 4. Norepinephrine, 5-HIAA and CEA may be collected when considered).

Pregnancy test

A serum pregnancy test must be performed at screening (at the local laboratory) within ≤ 72 hours before the *first dose of study treatment (if clinically indicated).*

Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG performance status at screening, prior to the administration of each dose of trial treatment and as specified in the Table of Schedule of Assessments (Table 2). It is **important to collect ECOG Status in patient's record and eCRF.**

Biological samples collection

Tumour Biopsy (Archival, If Available)

- If available, it is mandatory that archival tumour tissue samples are analysed in this trial.
- Either pre-existing archived or newly-obtained (fresh tissue) biopsy specimens from either primary or metastatic tumour, whichever is the most recent.
- Tumour tissue specimen submitted in FFPE block is acceptable.

Processed blood samples:

- Serum and plasma samples to be collected at baseline, D1C2, and at progression.
- Blood samples are to be stored at site at -80ºC, and are to be sent at the end of study (1 dry ice shipment per site).

Tumour Imaging

The site study team must review pre-trial images to confirm that the subject has at least one target lesion (i.e. meets measurability requirements) as per RECIST 1.1.

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. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Patients with known baseline brain lesions are not eligible for this study, but brain CT scan or MRI is neither required at baseline nor in the follow-up in the absence of neurological signs or symptoms. Additional anatomical imaging should be carried out 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.

Quality of life (QoL)

The QoL measured by the self administered questionnaires EQ-5D-5L and EORTC QLQ-C30(appendix 2 and 3) will be performed at screening, no more than 28 days before the date of inclusion and, ideally, should be performed as close as possible to the start of treatment.

8.2.2. Assessment during treatment

Physical Exam

- *Targeted Physical Exam (prior treatment administration):* Additional physical exams (targeted) should be performed based on investigator criteria as specified in the Trial Flow Chart (Section 8.1), considering the disease under study, patient symptoms, and prior physical exams. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

Vital Signs

- The investigator or qualified designee will take vital signs as specified in the Trial Flow Chart (Section 8.1).
- Vital signs should include temperature, pulse, respiratory rate, weight, and blood pressure. Body weight is to be recorded at each visit along with vital signs; however, height will be measured at screening only.

Laboratory Assessments

The summary of the procedures required is summarised in Section 8.1 and the corresponding footnotes. It is recommended that laboratory tests be performed < 3 days prior to the next dose of trial therapy in order to have the results to decide on the continuity of study treatment (dose modifications and delays, among other relevant clinical decisions).
Laboratory determinations include full clinical chemistry panel (including albumin, alkaline phosphatase, LDH, calcium, magnesium, phosphorus, sodium, potassium, creatinine, creatine kinase, direct bilirubin, indirect bilirubin, total bilirubin, total protein, urea, uric acid, amylase, lipase, glucose, ALT, AST, ALP, GGT), hematological counts (total white blood cell count with leukocyte formula, haemoglobin, and platelet count), TSH hormone levels, and tumor markers.
Tumor markers should be analyzed at screening and every 12 weeks ± 2 weeks until PD or death (whichever occurs first) to determine the non-radiological response. The markers to collect are NSE in tumors from cohort 1, CGA in tumors from cohort 5, cortisol in functionant tumors from cohort 3, metanephrines and, adrenaline in functionant tumors from cohort 4. Norepinephrine, 5-HIAA and CEA may be collected when considered.

Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG performance status **prior to the administration** of each dose of atezolizumab as specified in the Table of Schedule of Assessments (Table 2). It is **important to**

collect ECOG Status in patient's record and eCRF.

Adverse Event (AE)/Serious Adverse Events (SAE) assessment

- The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart, and subsequently if clinically indicated.
- Adverse events will be graded and recorded throughout the trial and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterised in terms of seriousness, causality, toxicity grading, and action taken with regard to trial treatment.
- All AEs of unknown etiology associated with study treatment exposure should be evaluated to determine if it is possibly an ECI of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

Tumour Imaging

- q12w ± 2w until the objective disease progression or death (whichever comes first). Image assessments by CT scan or MRI may be performed q8w ± 2w if required by local standard clinical practice or by investigator criteria, as long as the frequency of assessments is maintained.

Biological samples collection

Processed blood samples:

- Serum and plasma samples to be collected at D1C2.
- Blood 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).

Pregnancy test

Women of childbearing potential are required to have a pregnancy test within 72 hours prior to the first dose of the study drug, and every 3 cycles (9 weeks) thereafter (if clinically indicated). Latest pregnancy results (maximum 9 weeks old) must be available and reviewed by the treating physician or investigator prior to commencing a new cycle of infusion. A urine or serum pregnancy test is acceptable.

Quality of life

The questionnaires EQ-5D-5L and EORTC QLQ-C30 will be fulfilled every two cycles by the patient during the visit, before the knowledgement of tumor assessment and before the administration of each dose of atezolizumab as specified in the Table of Schedule of Assessments (Table 2).

8.2.3. End of treatment Visit

Physical Exam

- *Targeted Physical Exam (prior treatment administration):* Additional physical exams (targeted) should be performed based on investigator criteria as specified in the Trial Flow Chart-Section 8.1, considering the disease under study, patient symptoms, and prior physical exams. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

Vital Signs

- The investigator or qualified designee will take vital signs as specified in the Trial Flow Chart-Section 8.1.

- Vital signs should include temperature, pulse, respiratory rate, weight, and blood pressure. Body weight is to be recorded at each visit along with vital signs; however, height will be measured at screening only.

12-Lead Electrocardiogram (ECG)

A standard 12-lead ECG will be performed at baseline and at end of treatment visit using local standard procedure. Any clinically significant abnormalities detected require triplicate ECG results and should be recorded as medical history or adverse event, and monitored if needed. No new ECGs will be performed unless clinically indicated.

Laboratory Assessments

The summary of the procedures required is summarised in Section 8.1 and in the corresponding footnotes. It is recommended that laboratory tests be performed < 3 days prior to the EOT visit.

Laboratory determinations include full clinical chemistry panel (including albumin, alkaline phosphatase, LDH, calcium, magnesium, phosphorus, sodium, potassium, creatinine, creatine kinase, direct bilirubin, indirect bilirubin, total bilirubin, total protein, urea, uric acid, amylase, lipase, glucose, ALT, AST, ALP, GGT), hematological counts (total white blood cell count with leukocyte formula, haemoglobin, and platelet count), TSH hormone levels, and tumor markers (NSE in tumors from cohort 1, CGA in tumors from cohort 5, cortisol in functionant tumors from cohort 3, metanephrines and, adrenaline in functionant tumors from cohort 4. Norepinephrine, 5-HIAA and CEA may be collected when considered).

Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG performance status. It is **important to record ECOG Status in patient's record and eCRF.**

Adverse Event (AE)/Serious Adverse Events (SAE) assessment

- The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated.
- Adverse events will be graded and recorded throughout the trial and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterised in terms of seriousness, causality, toxicity grading, and action taken with regards to trial treatment.
- All AEs of unknown etiology associated with study treatment exposure should be evaluated to determine if it is possibly an ECI of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

Biological samples collection

Processed blood samples:

- Serum and plasma samples to be collected at progression.
- Blood samples are to be stored at site at -80 ºC and are to be sent at the end of the study (1 dry ice shipment per site).

Quality of life

The QoL EQ-5D-5L, EORTC QLQ-C30 questionnaires (appendix 2 and 3) will be fulfilled by the patient during the EOT visit.

8.2.4. Post-treatment (Follow-up)

8.2.4.1. Progression Free Survival follow-up

After the end of the treatment visit, clinical procedures and assessment will be performed as previously explained and reflected in the summary table 2 (section 8.1), all patients will be followed by RECIST 1.1 every 12 weeks (+/-14 days) up to disease progression or death (whichever occurs first), independently of the reason for ending the treatment. Follow up assessments may be performed every 8 weeks (± 14 days) if required by local standard clinical practice or by investigator criteria, as long as the frequency of assessments is maintained. The follow-up period according to this protocol is 12 months considering last patient inclusion.

8.2.4.2. Overall Survival (Long term follow-up)

Follow-up after disease progression will be carried out according to local practice. The follow-up period according to this protocol is 12 months considering last patient inclusion. Information on subsequent treatments should include the list of post-treatment therapies, the drugs administered, the date of initiation/discontinuation of each drug and date of progression. All the data will be recorded in the medical record and in the eCRF.

Survival information may be obtained through telephone contact with the patient, patient's family or by contact with the patient's current physician. Survival data will be collected up to the time of the final overall survival (OS) analysis, and at this point, Investigators will be notified that no further data collection for the study is required.

The status of ongoing, withdrawn (from the study), and lost to follow-up patients at the time of an OS analysis should be obtained by the site personnel by checking the patient's notes and hospital records, contacting the patient's general clinician, and checking publicly available death registries.

9. ASSESSMENT OF SAFETY

Sites should record all adverse events both in patient's medical record and in eCRF according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0, following the Table of assessment (Table 2, Section 8.1). For patients who are still on treatment at the end of trial, and for the additional 6 months with provision of both investigational products, any suspicion on adverse events/special situation should be reported to sponsor. Those events reported in patients receiving atezolizumab the marketing authorisation holder: Roche's Pharmacovigilance Department (madrid.drug_safety@roche.com, Tel. +34 91.324.8183). Those events reported in patients receiving cabozantinib the marketing authorisation holder: Ipsen's Pharmacovigilance Department (pharmacovigilance.spain@ipsen.com, Tel. +34 93.685.81.00).

9.1. SAFETY PARAMETERS

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

9.2. ADVERSE AND SERIOUS ADVERSE EVENTS

9.2.1. Definitions

Definitions regarding safety and pharmacovigilance to be applied in this study are defined below.

9.2.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be the development of a new medical condition, or the deterioration of a pre-existing medical condition. This includes any unfavorable and unintended sign (e.g. tachycardia, enlarged liver), symptom (e.g. nausea, chest pain) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram) temporally associated with the use of a medicinal product, whether or not considered related.

This requirement includes specific events or symptoms associated with cancer progression or general clinical deterioration to ensure potential toxicities are not overlooked. Radiographic progression without associated clinical sequelae is not considered an AE; terms such as 'disease progression' should be avoided. Pre-existing medical conditions that worsen during a study will be recorded as AEs. Abnormal laboratory values, ECG findings, or vital signs are to be recorded as AEs if they meet the criteria described in Section 9.3.

All untoward events that occur after informed consent through 30 days (100 days for SAEs and AESIs) after the date of the decision to permanently discontinue study treatment (defined as the later of the date of the decision to discontinue all study treatment or the date of the last dose of any study treatment) are to be recorded by the investigational site.

At each scheduled and unscheduled visit, AEs are to be identified and assessed based upon study procedures, routine and symptom-directed clinical investigations, and subject query/report.

Assessment of the relationship of the AEs to study treatment by the investigator will be based on the following two definitions:

- Not Related: An event is assessed as not related to study treatment if it is attributable to another cause and/or there is no evidence to support a causal relationship.
- Related: 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.

9.2.1.2. Severity of Events

Assessment of adverse events, safety, and toxicity will be performed according to the National Cancer Institute Common Toxicity Criteria (version 5.0) from the time of Informed Consent for the pre-registration phase until the end of study. The following definitions should be considered when evaluating the severity of oncology events when not present in NCI-CTCAE version 5.0:

Severity of Events	
Grade	**Definition**
1	Mild adverse event
2	Moderate adverse event
3	Severe and undesirable adverse event
4	Life-threatening or disabling adverse event
5	Death related to adverse event

9.2.1.3. 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.

9.3. SERIOUS ADVERSE EVENT (SAE)

9.3.1. Definitions

The SAE definition and reporting requirements are in accordance with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Topic E2A.

An SAE is any AE occurring at any dose that:

- Results in death.
- Is immediately life-threatening (ie, in the opinion of the investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
- Requires inpatient hospitalization or results in prolongation of an existing hospitalization.
- Results in significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect.

- Is an important medical event that may not be immediately life-threatening, result in death, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

9.3.2. SAE Reporting

As soon as an investigator becomes aware of an AE that meets the criteria for an SAE, the investigator will document the SAE to the extent that information is available.

SAEs, regardless of causal relationship, must be reported to the Sponsor or designee within 24 hours of the investigator's knowledge of the event by submitting the completed SAE report form and any other pertinent SAE information as indicated on the SAE Reporting form (or in the SAE Reporting form Completion Guidelines) and confirming the report was received. Forms for reporting SAEs and contact information will be provided to the study sites.

Reporting Information for safety reports
To report initial or follow-up information to Ipsen/Roche, a completed Clinical Study Serious Adverse Event (SAE) report form should be sent to the following within 24 hours of becoming aware of the event: **Serious Adverse Events** **All serious adverse events must be reported by fax within 24 h to MFAR Clinical Research, S.L. by fax (+ 34 93 253 11 68) or e-mail to investigacion@mfar.net**

SAEs that must be recorded on an SAE Reporting form include the following:

- All SAEs that occur after informed consent and through 100 days after the date of the decision to permanently discontinue study treatment (ie, the later of the date of the decision of the investigator to permanently discontinue study treatment or the date of the last dose of any study treatment taken by the subject) or the date the subject is deemed to be a screen failure.

- Any SAEs assessed as related to study treatment or study procedures, even if the SAE occurs more than 100 days after the date of the decision to permanently discontinue study treatment.

Note: If the subject does not meet the eligibility criteria during screening, then SAEs only need to be reported from the time the subject signs the informed consent until the day when the subject has been determined to not be eligible for study participation.

SAEs that occur after the initiation of study treatment through 100 days after the date of the decision to permanently discontinue of study treatment must also be recorded on the CRF page.

The minimum information required for SAE reporting includes identity of Investigator, site number, subject number, and an event description. Other important information requiring timely reporting are the SAE term(s), the reason why the event is considered to be serious (ie, the seriousness criteria), and the Investigator's assessment of the relationship of the event to study treatment. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment because of the event, and the outcome/resolution of the event will be recorded on the SAE form.

In all cases, the Investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the Investigator may be required to provide supplementary information as requested by the Sponsor's Drug Safety personnel or designee.

When reporting SAEs, the following additional points will be noted:

- When the diagnosis of an SAE is known or suspected, the Investigator will report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description.
- Death will not be reported as an SAE, but as an outcome of a specific SAE, unless the event preceding the death is unknown. Terms of "Unexplained Death" or "Death from unknown origin" may be used when the cause is unknown. In these circumstances the cause of death must be investigated and the diagnosis amended when the etiology has been identified. If an autopsy was performed, the autopsy report should be provided.
- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
    - Elective or previously scheduled surgeries or procedures for preexisting conditions that have not worsened after initiation of treatment (eg, a previously scheduled ventral hernia repair). SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.
    - Prespecified study hospitalizations for observation.
    - Events that result in hospital stays of fewer than 24 hours and that do not require admission (eg, an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics).
- SAEs must be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

9.3.2. SAE Regulatory Reporting

The Sponsor's Drug Safety group (or designee) will process and evaluate all SAEs and AESIs as the reports are received. For each SAE received, the Sponsor will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met.

The Sponsor's Drug Safety group (or designee) will assess the expectedness of each SAE to the study treatment using the current reference safety information (RSI) for each study drug. RSI for this trial will be the last version of study treatment Investigator Brochure. If information on the expectedness has been made available by the reporting investigator, this should be taken into consideration by Sponsor. If Sponsor disagrees with the investigator's expectedness assessment, both the opinion of the investigator and the sponsor should be provided in the report.

The Sponsor or its designee is responsible for reporting relevant SAEs to the relevant regulatory authorities, and participating investigators, in accordance with FDA regulations (21 Code of Federal Regulations [CFR] 312.32), ICH guidelines, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Reporting of SAEs by the Investigator to his or her IRB/ECs will be done in accordance with the standard operating procedures and policies of the IRB/EC. Adequate documentation must be maintained showing that the IRB/EC was properly notified.

MFAR Clinical Research on behalf of GETNE will forward safety reports received to both IPSEN and ROCHE within one working day, following agreed procedures (signed IPSEN agreement and ROCHE SDEA) in order they can fulfill the corresponding legal requirement regarding pharmacovigilance as MAH of cabozantinib and atezolizumab respectively.

All adverse events will be processed by MFAR/Ipsen/Roche according to their relevant Standard Operating Procedures. This includes the follow up of adverse event reports with the Investigator through MFAR Clinical Research, as required. If an AE occurs with a "non Ipsen/Roche product", the Investigator should

consider informing the competent authority in the Member State where the event occurred or to the marketing authorisation holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).

The Sponsor through MFAR Clinical Research ensures that the reporting requirements and timelines for reporting, as defined in the respective applicable laws, are followed. A Development Safety Update Report (DSUR) will be provided to the local investigators for filing into the investigator's file. MFAR Clinical Research will submit the DSUR to the involved ECs and involved Regulatory Agencies.

9.4. Adverse Events of Special Interest

Adverse events of special interest (AESIs) consist of immune-mediated AEs associated with ICIs, cases of potential DILI, and suspected transmission of an infectious agent by the study treatment (Table 3).

AESIs will be reported to the Sponsor or designee using the SAE reporting form irrespective of whether the event is serious or nonserious; all AESIs must be reported within 24 hours using the SAE process as described in Section 9.3.

Guidance for management of immune-mediated AEs associated is provided in Investigator's Brochure for atezolizumab.

Table 3. Adverse Events of Special Interest

Category	Event
DILI	● Cases of potential Drug-induced Liver Injury (DILI) that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations: ○ Treatment-emergent ALT or AST > 3 × baseline value in combination with total bilirubin > 2 × ULN (of which ≥ 35% is direct bilirubin). ○ Treatment-emergent ALT or AST > 3 × baseline value in combination with clinical jaundice.
Other	● Suspected transmission of an infectious agent by the study treatment, as defined below: ○ Any organism, virus, or infectious particle (eg, 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.
irAE	● Systemic lupus erythematosus
irAE	● Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, HLH and MAS
irAE	● Nephritis
irAE	● Ocular toxicities (eg, uveitis, retinitis)
irAE	● ≥ Grade 2 cardiac disorders (eg, atrial fibrillation, myocarditis, pericarditis)
irAE	● Vasculitis
irAE	● Autoimmune hemolytic anemia

irAE	● Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; irAE, immune-related adverse event; ULN, upper limit of normal.

9.4.1 General Information on Immune-Related Adverse Events

The immune-modulating properties of checkpoint-inhibitors, such as the anti-PD-L1 antibody atezolizumab, are able to unbalance immunologic tolerance and generate a subset of AEs (called irAEs) with an autoimmune inflammatory pathomechanism. Immune-related adverse events may involve any organ or tissue (Michot et al 2016). Most irAEs occur within the first 12 weeks of exposure to ICIs but some of them may appear with a delayed onset. Diagnosis of irAEs should be based on exposure to an ICI and a reasonable immune-based mechanism of the observed AE. Whenever possible, histologic examination or other immune-based diagnostic evaluations should be used to support the diagnosis. Other etiologic causes including AEs from tumor progression should be ruled out.

The spectrum of irAEs is wide and can be general or organ-specific. Examples of general irAEs in subjects treated with ICIs are fatigue, fever, and chills. Organ-specific irAEs consist of dermatitis (rash, pruritus, vitiligo, oral mucositis, and gingivitis), enterocolitis (diarrhea with abdominal pain and clinical or radiological evidence of colonic inflammation), and endocrinopathies (pituitary, thyroid, adrenal, testes). Diagnosis of endocrine dysfunction is challenging with relatively nonspecific symptoms. Additional laboratory testing of the endocrine axes may be helpful: prolactin (pituitary-hypothalamic function), FT4 and TSH (pituitary-thyroid function), luteinizing hormone (LH) and follicle-stimulating hormone (FSH; pituitary-gonadal function), adrenocorticotropic hormone (ACTH) and cortisol (pituitary-adrenal function).

Additional organ-specific irAEs include hepatitis (AST/ALT increases, hepatomegaly, periportal edema, periportal lymphadenopathy, lymphocyte infiltrates periportal and surrounding primary biliary ducts) and pneumonitis (acute interstitial pneumonia). Less frequent irAEs include neurologic syndromes (myasthenia gravis, Guillian-Barré syndrome, aseptic meningitis), ocular AEs (uveitis), renal AEs (interstitial nephritis), cardiac AEs (myocarditis), muscular AEs (myositis), and pancreatic AEs (lipase increase).

9.5. Follow-Up of Adverse Events

Non-serious AEs are to be recorded in the CRF until 30 days after the date of the decision to discontinue study treatment (the later of the date of the decision by the investigator to permanently discontinue study treatment or the date of the last dose of any study treatment taken by the subject). The status of unrelated SAEs that are ongoing after the date of the decision to discontinue study treatment will be documented as of the 100-day FU-2 visit.

All AESIs (regardless of seriousness) and all related SAEs that are ongoing 100 days after the date of the decision to discontinue study treatment (the later of the date of the decision by the investigator to permanently discontinue study treatment or the date of the last dose of any study treatment taken by the subject), and AEs assessed as related that led to study treatment discontinuation that are ongoing 100 days after the date of the decision to discontinue study treatment, are to be followed until either:

- the AE has resolved
- the AE has improved to Grade 2 or lower
- The Investigator determines that the event has become stable or irreversible.

Further details on follow-up procedures are summarized in section 8.1 study determinations chart.

9.6. Other Safety Considerations

9.6.1. Pregnancy

Use of highly effective methods of contraception is very important during the study and for 5 months after the last dose of study treatment. If a subject becomes pregnant during the study, she will be taken off study treatment. She will be followed through the end of her pregnancy and the infant should have follow up for at least 6 months after birth. Furthermore, male subjects are required to use condoms in order to avoid transmission of study treatment in semen for 5 months after their last dose of study treatment. If a female partner of a male subject becomes pregnant during the study, the Sponsor will ask the pregnant female partner to be followed through the end of her pregnancy and for the infant to be followed for at least 6 months after birth. Both male and female subjects should seek advice and consider fertility preservation before receiving study treatment.

The Investigator must inform the Sponsor of the pregnancy. Forms for reporting pregnancies will be provided to the study sites upon request. The outcome of a pregnancy (for a subject or for the partner of a subject) and the medical condition of any resultant offspring must be reported to the Sponsor or designee. Any birth defect or congenital anomaly must be reported as an SAE and any other untoward events occurring during the pregnancy must be reported as AEs or SAEs, as appropriate.

Females should not breastfeed while receiving study treatment and for the following periods after discontinuing study treatment:

- **Combination cabozantinib plus atezolizumab:** at least 5 months from the last dose of atezolizumab or 4 months from the last dose of cabozantinib, whichever is later
- **Single-agent cabozantinib:** at least 4 months from the last dose of cabozantinib
- **Single-agent atezolizumab:** at least 5 months from the last dose of atezolizumab

9.6.2. Medication Errors/Overdose/Drug abuse/Drug misuse

Medication error is defined as accidental deviation in the administration of a drug (e.g. wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered). In some cases, a medication error may be intercepted prior to administration of the drug.

Any study medication overdose, misuse, abuse, or study medication error (excluding missed doses) that results in an AE or SAE requires reporting to the Sponsor or designee according to the guidance for AE and SAE reporting (Sections 9.1 and 9.2, respectively).

In case of overdose, the Coordinating Investigator or designee should be contacted promptly to discuss how to proceed. Any AEs that occur as a result of an overdose have to be treated according to clinical standard practice.

Please refer to the Investigator's Brochure for additional management recommendations for an overdose of cabozantinib and/or atezolizumab.

In addition, all study medication overdose, misuse, abuse or medication error, regardless of whether they result in an adverse event, should be recorded on the Adverse Event CRF

9.6.2 Lack of Efficacy or Worsening of study disease:

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1 criteria. In rare cases, the

determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

10. STATISTICS

10.1. SAMPLE SIZE CALCULATION

Simon-II optimal two-stage design was applied for sample size estimation. We hypothesise that the experimental therapy will improve the probability of expected objective response rate in refractory settings, from less than 5 % in previous reports, to 20 % in the current study. With 80 % of power (0.2) and unilateral alpha (0.1), 24 patients per cohort are needed to demonstrate the primary hypothesis. The Simon-II design suggested the observation of ≥ 1 patient with objective response within the first nine patients included in the first stage. If ≥ 1 out of nine patients in each cohort achieve an objective radiological response in the first stage, the study will continue to recruit 15 additional patients up to 24 patients per cohort. If ≥ 3 out of a total of 24 patients achieve a radiological objective response at the final analysis, the study should be declared positive. If stage I is reached only in one cohort, recruitment will continue in the successful cohort and stopped in the non-effective cohorts.

10.2. STUDY ENDPOINTS

10.2.1. Primary endpoint

Overall Response Rate (ORR): includes patients with partial (PR) and complete response (CR) as best response according to RECIST v 1.1.

10.2.2. Secondary endpoints

- **Safety profile of cabozantinib and atezolizumab:** The number of patients with AEs and SAEs, changes in laboratory values, vital signs, ECGs, and results of physician examinations graded according to the CTCAE v 5.0. This will be analysed using descriptive statistics techniques such as frequency and contingency tables. The final statistical analysis of this endpoint is expected to be performed within 6 months after database closure, which is expected at 12 months after last patient inclusion. However, interim analysis may be performed when analysing other primary endpoints.
- **Duration of response (DOR) as per RECIST 1.1:** DOR calculated as the time from the date of first documented CR or PR to the first documented progression or death due to underlying cancer.
- **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). Patient with no additional image test other than that at baseline will be censored to the day after inclusion.
- **Overall Survival (OS)**: Median Overall Survival (mOS) is calculated as the time from date of inclusion to date of death due to any cause.
- **Biomarkers:** To be determined according to study results and Sponsor feasibility.
- **Quality of Life (QoL):** Quality of Life will be analyzed descriptively by QoL questionnaires (EQ-5D-5L, EORTC QLQ-C30, see appendix 2 and 3).

10.3. EFFICACY ASSESSMENT

Body CT scan or MRI will be performed at baseline and every 12 weeks (± 2 week) until progression. Body CT scan or MRI may be performed every 8 weeks (± 2 week) if required by local standard clinical practice

or by investigator criteria, as long as the frequency of assessments is maintained. All target and non-target lesions in the initial evaluation will be measured according to the aforementioned timeline, until disease progression. Imaging tests will be performed using the same method each time.

10.3.1. Time-point efficacy assessment

Table 4. Criteria for disease evaluation for target lesions

CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

Table 5. Criteria for disease evaluation for non-target lesions

CR	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/ non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
PD	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

Table 6. Overall Response Assessment (RECIST 1.1)

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

10.4. Definition of Study Populations

Data will be analysed in the following populations:

1. Intent-To-Treat (ITT): All patients that has been enrolled in the trial.
2. Evaluable population per protocol (PP): All patients fulfilling all eligibility criteria without

any protocol deviation that makes patient invalid for the primary endpoint evaluation.

3. Safety population: All patients receiving at least one dose of treatment.

10.5. Safety Analysis

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.

Assessment of adverse events, safety, and toxicity will be performed according to the National Cancer Institute Common Toxicity Criteria (version 5.0) from the time of Informed Consent for the pre-registration phase until the end of study. Safety and tolerability of study medication will be determined by evaluating the type, incidence, frequency, severity, seriousness and causality of adverse effects. Physical examinations, and laboratory tests will also be assessed. Any signs and/or symptoms associated with the worsening of the existing tumour at baseline (in severity or frequency) during the trial should be reported as adverse event.

10.6. Statistical Analysis

For each categorical variable, the results will be summarised by frequencies and percentages. For each continuous variable, the results will be summarised by descriptive statistics such as median, range, and interquartile range or by means, standard deviations, and 95 % confidence intervals (CIs). For proportions, point estimates and exact 95 % confidence intervals will be calculated. 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. Laboratory values will be expressed as absolute values and in grades (ordinal categorical variables) according to NCI CTCAE v 5.0.

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

10.7. Statistical Methods

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

Continuous data will be presented with the number of observations, mean value, standard deviation, minimum, maximum, and median. Categorical data will be presented as counts and percentages. Individual subject data will be listed.

Vital signs, ECG parameters, clinical laboratory data (haematology, serum biochemistry, and urinalysis) will be presented in tabular form. Values outside the reference range will be flagged, and the clinically significantly abnormal values will be listed in tabular form. Adverse events will be tabulated by system organ class and preferred term after medical coding using the according to NCI CTCAE v 5.0.

11. Direct access to source data/documents

11.1. Source Data Definition

Source data is defined as all data in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial.

The Investigator must keep a file (medical file and original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information listed below and should be as complete as possible.

- Subject's full name, date of birth, sex, height, and weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to CT or MRI scan images, ECG recordings, and laboratory results. Such documents must bear the subject number and the date of the procedure. Where possible, this information should be printed by the instrument used to perform the assessment or measurement. Medical evaluation of such records will be performed as necessary; all evaluations will be documented, signed, and dated by the Investigator.

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts will be signed and dated by the Investigator, countersigned by the Monitor, and will be secured in a safe place at the site.

According to the directives of the European Parliament 95/46 and Regulation Regulation No. 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, the information obtained in the course of the clinical trial may only be used by the Sponsor of clinical trial to evaluate the results in compliance with the directive mentioned.

11.2. Study Oversight and Study Monitoring

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 IRB

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

12. REGULATORY

12.1. AUDITS AND INSPECTIONS

Authorised representatives of Sponsor, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board 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.

12.2. INDEPENDENT ETHICAL COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB) 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 or IRB, 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.

12.3. ETHICAL CONDUCT OF THE STUDY

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki, and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements including:

- Oviedo Convention, of 4 April 1997 on Human Rights and Biomedicine, ratified in 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 concerning clinical information and documentation, in accordance with Law 41/2002 of 14 November, a basic regulatory 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 3 July, on Biomedical Research.

12.4. WRITTEN INFORMED CONSENT

The Principal Investigator(s) at each centre will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided. The patient's signed and

dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) will retain the original signed ICF and this form will be made available for reviewing during monitoring visits. A copy of the signed ICF will be provided to the patient. The Principal Investigator will document the informed consent procedure in the patient medical records.

12.5. Insurance

An insurance policy in accordance with spanish regulatory requirements will be contracted so all patients in this clinical study will be protected with a policy that will meet the conditions stipulated by the RD 1090/2015.

13. Quality Control and Quality Assurance

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

14. Data Handling and Record Keeping

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 data server located at the Data Centre maintained by Claranet SAU located at "Calle Juan Gris, 10-18, 08014 Barcelona". The physical access to the Data Centre is restricted to authorised Claranet personnel, and the 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 are 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).

14.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring

any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, drug stocks, drug accountability records, subject charts and study source documents, and other records relating to study conduct.

14.2. Retention of Records

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor during Sponsor audits, and for inspection by Health Authorities during and after the trial. Moreover, the file must be safely archived for at least 25 years (as per local requirements) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject Informed Consent Forms. If archiving the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

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.

15. Publication Policy

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 authorised clinical trials in scientific journals, and inform the Ethical Committee of Clinical Research that approved the study.

After completion of the trial, the clinical publication will be carried out by the Sponsor in collaboration with the Coordinating Investigator and Principal Investigators. The order of authors will strictly depend on the Sponsor Publication Policy, the contribution to the clinical trial and number of eligible patients included by the Investigators. Coordinating investigator, will be first or last authors, and the number of the rest of the authors will depend on the above rule and the requirements of the congresses and/or journals.

The first publication will include the results of the analysis of the primary endpoints and will include data from all trial sites that provided valuable data. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require written authorisation by the Sponsor before submission.

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 study outcome will be reported prematurely or in a sensationalistic way. 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 - Registro Español de Estudios Clínicos) and Clinical trials.gov before enrolling the first patient.

16. List of References

1. Kulke MH, Benson AB, III, Bergsland E, et al. Neuroendocrine tumors. J Natl Compr Canc Netw. 2012;10:724-64.
2. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol. 2017;3:1335-42. doi:10.1001/jamaoncol.2017.0589.
3. Travis WD. Advances in neuroendocrine lung tumors. Ann. Oncol. 2010;21:ii65–ii71. doi: 10.1093/annonc/mdq380.
4. Rekhtmann N. Neuroendocrine tumors of the lung. Arch. Pathol. Lab. Med. 2010;134:1628–38.
5. Bertino EM. Pulmonary neuroendocrine/carcinoid tumors. Cancer. 2009;115:4434–4441. doi: 10.1002/cncr.24498.
6. Taal BG, Visser O. Epidemiology of neuroendocrine tumours. Neuroendocrin. 2004;80:3–7. doi: 10.1159/000080731.
7. Chong S. Teaching points for neuroendocrine tumors of the lung: Clinical, pathologic, and imaging findings. Radiographics. 2006;26:41–58. doi: 10.1148/rg.261055057.
8. Moran CA. Neuroendocrine carcinomas of the lung. Am. Soc. Clin. Pathol. 2009;131:206–21. doi: 10.1309/AJCP9H1OTMUCSKQW.
9. Valente M, Catena L., Milione M., Pusceddu S., Formisano B., Bajetta E. Common diagnostic challenges in the histopathologic diagnosis of neuroendocrine lung tumors: A case report. Case Rep. Oncol. 2010;3:202–7. doi: 10.1159/000317313.
10. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC, editors. World Health Organization Classification of Tumours, Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. IARC Press; Lyon, France: 2004. pp. 19–25.
11. Zander DS, Popper HH, Jagirdar J, Haque AK, Cagle PT, Barrios R. Molecular Pathology Of Lung Diseases. Springer; New York, NY, USA: 2008.
12. Kebebew E, Greenspan FS, Clark OH, et al. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. Cancer 2005;103:1330-5.
13. Smallridge RC, Copland JA. Anaplastic thyroid carcinoma: pathogenesis and emerging therapies. Clin Oncol (R Coll Radiol) 2010;22:486-97.
14. Kebebew E. Anaplastic thyroid cancer: rare, fatal, and neglected. Surgery 2012;152:1088-9.
15. O'Neill JP, Shaha AR. Anaplastic thyroid cancer. Oral Oncol 2013;49:702-6.
16. Hunt JL, Tometsko M, LiVolsi VA, et al. Molecular evidence of anaplastic transformation in coexisting well-differentiated and anaplastic carcinomas of the thyroid. Am J Surg Pathol. 2003;27:1559-64.
17. Kadota M, Tamaki Y, Sekimoto M, et al. Loss of heterozygosity on chromosome 16p and 18q in anaplastic thyroid carcinoma. Oncol Rep. 2003;10:35-8.
18. Kitamura Y, Shimizu K, Tanaka S, et al. Allelotyping of anaplastic thyroid carcinoma: frequent allelic losses on 1q, 9p, 11, 17, 19p, and 22q. Genes Chromosomes Cancer. 2000;27:244-51.
19. Libé R. Adrenocortical carcinoma (ACC): diagnosis, prognosis, and treatment. Front Cell Dev Biol. 2015;3:45.
20. Else T, Kim AC, Sabolch A, Raymond VM, Kandathil A, Caoili EM, Jolly S, Miller BS, Giordano TJ, Hammer GD. Review Adrenocortical carcinoma. Endocr Rev. 2014; 35:282-326.
21. Libé R, Borget I, Ronchi CL, Zaggia B, Kroiss M, Kerkhofs T, et al. Prognostic factors in Stage III-IV adrenocortical carcinomas (ACC): an European Network for the Study of Adrenal Tumor (ENSAT) study. Ann Oncol. 2015;26:2119-25.
22. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Pheochromocytoma. Lancet (London, England). 2005;366:665-75.
23. Kopetschke R, Slisko M, Kilisli A, et al. Frequent incidental discovery of pheochromocytoma: data from a German cohort of 201 pheochromocytoma. Eur J Endocrinol. 2009;161:355-61.
24. Lam AK. Update on Adrenal Tumours in 2017 World Health Organization (WHO) of Endocrine Tumours. Endocr Pathol. 2017;28:213-27.

25. Eisenhofer G, Lenders JW, Pacak K. Biochemical diagnosis of pheochromocytoma. Front Horm Res. 2004;31:76-106.
26. Gupta G, Pacak K. Precision Medicine: An update on genotype/biochemical phenotype relationship in pheochromocytoma/paraganglioma patients.. Endocr Pract. 2017;23:690-704.
27. Pillai S, Gopalan V, Smith RA, Lam AK. Updates on the genetics and the clinical impacts on pheochromocytoma and paraganglioma in the new era. Crit Rev Oncol Hematol.. 2016;100:190-208.
28. Eisenhofer G, Huynh TT, Pacak K, et al. Distinct gene expression profiles in norepinephrine- and epinephrine-producing hereditary and sporadic pheochromocytomas: activation of hypoxia-driven angiogenic pathways in von Hippel-Lindau syndrome. Endocr Relat Cancer. 2004;11:897-911.
29. Yao JC, Hassan M, Phan A, et al. One hundred years after “carcinoid”: Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26:3063–72.
30. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008;9:61–72.
31. Baudin E. Gastroenteropancreatic endocrine tumors: Clinical characterization before therapy. Nat Clin Pract Endocrinol Metab. 2007;3:228–239.
32. Madeira I, Terris B, Voss M, et al. Prognostic factors in patients with endocrine tumours of the duodenopancreatic area. Gut. 1998;43:422–7.
33. Faggiano A, Sabourin JC, Ducreux M, et al. Pulmonary and extrapulmonary poorly differentiated large cell neuroendocrine carcinomas: Diagnostic and prognostic features. Cancer. 2007;110:265–74.
34. Rindi G, Azzoni C, La Rosa S, et al. ECL cell tumor and poorly differentiated endocrine carcinoma of the stomach: Prognostic evaluation by pathological analysis. Gastroenterology. 1999;116:532–42.
35. Mitry E, Baudin E, Ducreux M, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. Br J Cancer. 1999;81:1351–5.
36. Lepage C, Bouvier AM, Phelip JM, et al. Incidence and management of malignant digestive endocrine tumours in a well defined French population. Gut. 2004;53:549–3.
37. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364:514–23.
38. Travis WD, Rush W, Flieder DB, et al. Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. Am J Surg Pathol. 1998;22:934–44.
39. Ekeblad S, Skogseid B, Dunder K, et al. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. Clin Cancer Res. 2008;14:7798–7803.
40. Strosberg JR, Fine RL, Choi J, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer. 2011;117:268–75.
41. Panzuto F, Boninsegna L, Fazio N, et al. Metastatic and locally advanced pancreatic endocrine carcinomas: Analysis of factors associated with disease progression. J Clin Oncol. 2011;29:2372–7.
42. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364:501–13.
43. Rindi G, Inzani F, Solcia E. Pathology of gastrointestinal disorders. Endocrinol Metab Clin North Am. 2010;39:713–27.
44. Solcia E, Klöppel G, Sobin LH. 2nd ed. Berlin, Germany: Springer; 2000. Histological Typing of Endocrine Tumours: WHO International Histological Classification of Tumours.
45. Heitz PU, Komminoth P, Perren A, et al. Geneva, Switzerland: World Health Organization; 2004. Pancreatic endocrine tumours: Introduction. In: Pathology and Genetics: Tumours of Endocrine Organs. WHO Classification of Tumors; pp. 177–82.
46. Tang LH, Basturk O, Sue JJ, Klimstra DS. A Practical Approach to the Classification of WHO Grade 3 (G3) Well-differentiated Neuroendocrine Tumor (WD-NET) and Poorly Differentiated Neuroendocrine Carcinoma (PD-NEC) of the Pancreas. Am J Surg Pathol. 2016;40:1192-202.
47. García-Carbonero, et al. Manual de diagnóstico y tratamiento de los tumores neuroendocrinos 4 de Octubre de 2013 - ISBN: 978-84-695-8312-8.

48. Basu B, Sirohi B, Corrie P. Systemic therapy for neuroendocrine tumours of gastroenteropancreatic origin.Volume 17: Issue 1. Page(s): R75–R90.
49. Vilar E, Salazar R, Pérez-García J, Cortes J, Oberg K, Tabernero J. Chemotherapy and role of the proliferation marker Ki-67 in digestive neuroendocrine tumors. Endocr Relat Cancer. 2007;14:221-32.
50. Vilar E, Salazar R, Pérez-García J, Cortes J, Oberg K, Tabernero J. Chemotherapy and role of the proliferation marker Ki-67 in digestive neuroendocrine tumors. Endocr Relat Cancer. 2007;14: 221-32.
51. Oberg K, Funa K & Alm G. Effects of leukocyte interferon on clinical symptoms and hormone levels in patients with mid-gut carcinoid tumors and carcinoid syndrome. N Engl J Med. 1983;309 129–133
52. Ducreux M, Ruszniewski P, Chayvialle JA, Blumberg J, Cloarec D, Michel H, Raymond JM, Dupas JL, Gouerou H, Jian R, Genestin E, Hammel P, Rougier P. The antitumoral effect of the long-acting somatostatin analog lanreotide in neuroendocrine tumors. Am J Gastroenterol. 2000;95:3276-81.
53. Filosso PL, Croce S, Oliaro A, Ruffini E. Long-term survival of patients treated with octreotide for metastatic well differentiated neuroendocrine carcinoma of the lung. J Cardiovasc Surg (Torino). 2000;41:773-6
54. Faiss S, Pape UF, Böhmig M, et al. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors--the International Lanreotide and Interferon Alfa Study Group. J Clin Oncol. 2003;21:2689-96.
55. Solcia 2000 Solcia E1, Rindi G, Larosa S, Capella C. Morphological, molecular, and prognostic aspects of gastric endocrine tumors. Microsc Res Tech. 2000;48:339-48.
56. O'Toole D, Salazar R, Falconi M, Kaltsas G, Couvelard A, de Herder WW, Hyrdel R, Nikou G, Krenning E, Vullierme MP, Caplin M, Jensen R, Eriksson B; Frascati Consensus Conference; European Neuroendocrine Tumor Society. Rare functioning pancreatic endocrine tumors. Neuroendocrinology. 2006;84:189-95.
57. García-Carbonero R, Salazar R, Sevilla I, Isla D. SEOM clinical guidelines for the diagnosis and treatment of gastroenteropancreatic neuroendocrine tumours (GEP NETS). Clin Transl Oncol 2011; 13: 545-551.08. Pavel M, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, Anlauf M, Wiedenmann B, Salazar R; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology. 2012; 95:157-76.
58. Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-Controlled, Double Blind, Prospective, randomized study on the effect of octreotide lar in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009;27:4656-63.
59. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG. Phase II/III Study of doxorubicin with fluorouracil compared with streptozotocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. J Clin Oncol. 2005; 23:4897-904.
60. Vilar E, Salazar R, Pérez-García J, Cortes J, Oberg K, Tabernero J. Chemotherapy and role of the proliferation marker Ki-67 in digestive neuroendocrine tumors. Endocr Relat Cancer. 2007;14: 221-32.
61. Missiaglia E, Dalai I, Barbi S, et al. Pancreatic endocrine tumors: expression profiling evidences a role for AKT– mTOR pathway. J Clin Oncol. 2010;28:245–55.
62. Agarwal N, Vaishampayan U, Green M, di Nucci F, Chang P, Scheffold C, Pal S. Phase 1b study (COSMIC-021) of cabozantinib in combination with atezolizumab: Results of the dose escalation stage. Ann Oncol. 2018;29: viii303-31.
63. Maria E Cabanillas, Jonas A de Souza, Susan Geyer, Lori J Wirth, Michael E Menefee, Stephen V Liu, Komal Shah, John Wright, Manisha H Shah. Cabozantinib As Salvage Therapy for Patients With Tyrosine Kinase Inhibitor-Refractory Differentiated Thyroid Cancer: Results of a Multicenter Phase II International Thyroid Oncology Group Trial. J Clin Oncol. 2017 Oct 10;35(29):3315-3321. doi: 10.1200/JCO.2017.73.0226. Epub 2017 Aug 17.
64. Rossella Elisei, Martin J Schlumberger, Stefan P Müller, Patrick Schöffski, Marcia S Brose, Manisha H Shah, Lisa Licitra, Barbara Jarzab, Viktor Medvedev, Michael C Kreissl, Bruno Niederle, Ezra E W

Cohen, Lori J Wirth, Haythem Ali, Colin Hessel, Yifah Yaron, Douglas Ball, Barry Nelkin, Steven I Sherman. Cabozantinib in Progressive Medullary Thyroid Cancer. J Clin Oncol. 2013 Oct 10;31(29):3639-46. doi: 10.1200/JCO.2012.48.4659. Epub 2013 Sep 3

65. Jimenez C, Pool M, Busaidy N, Habra MA, Waguespack S, Jessop A. A phase 2 study to evaluate the effects of cabozantinib in patients with unresectable metastatic pheochromocytomas and paragangliomas. International Symposium on Pheochromocytoma and Paraganglioma.Sydney, Australia: (2017).
66. J.C. Yao, J. Strosberg, N. Fazio, et al. Activity & safety of spartalizumab (PDR001) in patients (pts) with advanced neuroendocrine tumors (NET) of pancreatic (Pan), gastrointestinal (GI), or thoracic (T) origin, & gastroenteropancreatic neuroendocrine carcinoma (GEP NEC) who have progressed on prior treatment (Tx). Annals of Oncology 29 (Supplement 8): viii467–viii478, 2018
67. Marilina García-Aranda and Maximino Redondo. Targeting Protein Kinases to Enhance the Response to anti-PD-1/PD-L1 Immunotherapy. Camilo Jimenez. Treatment for Patients With Malignant Pheochromocytomas and Paragangliomas: A Perspective From the Hallmarks of Cancer.
68. Investigator Brochure of Cabozantinib version 15, July, 2019.
69. Investigator Brochure RO5541267 TECENTRIQ (Atezolizumab Version 15, July 2019 and Addendum Number 2, December 2019).
70. SmPC Cabozantinib, last updated 10/04/2019 available at:https://www.ema.europa.eu/en/medicines/human/EPAR/cometriq
71. SmPC Atezolizumab, last updated 03/09/2018 available at: https://www.ema.europa.eu/en/medicines/human/EPAR/tecentriq

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 methylprednisone. ● 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 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
In patients without HCC	
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] ● Refer patient to GI specialist for evaluation and confirmatory biopsy. ● 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 3ULN to 10ULN **or** **AST/ALT is ULN to 3ULN at baseline and increases to 5ULN to 10 ULN** **or** **AST/ALT is 3ULN to 5ULN at baseline and increases to 8ULN to 10ULN**	● 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 1-2 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 10ULN or total bilirubin increases to 3ULN	● 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 baseline, taper corticosteroids over ≥1 month.

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 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 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 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 both 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, Grades 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	● Withhold atezolizumab for up to 12 weeks after event onset. a

(pan-hypopituitarism), Grade 2 or 3	● 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.

[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.

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 2-4	● Permanently discontinue atezolizumab and contact Medical Monitor. [a] ● Refer patient to cardiologist. ● Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. ● Initiate treatment with 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. 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 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, next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretics, 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	● Permanently discontinue atezolizumab and contact Medical Monitor. [e] ● Administer symptomatic treatment. [c] ● For hypotension, administer IV fluid bolus and vasopressor as needed. ● Monitor cardiopulmonary and other organ function closely;

vasopressin) **<u>and/or</u>** **hypoxia requiring high-flow oxygen d by nasal cannula, face mask, non-rebreather mask, or venturi mask**	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. [e] ● 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 [f] 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; IV= intravenous; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI National Cancer Institute.
Note: These management guidelines have been adapted from the NCCN guidelines for the management of CAR T-cell-related toxicities (Version 2.2019).

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (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 who 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] 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 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.

f Refer to *Riegler et al. (2019)*.

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 Grade 3.
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 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, biopsy. ● Initiate treatment with topical corticosteroids. ● Consider treatment with higher-potency topical corticosteroids if event does not improve. ● If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	● Withhold atezolizumab for up to 12 weeks after event onset.[a] ● Refer patient to dermatologist for evaluation and, if indicated, biopsy.. ● Initiate treatment with 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, 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..

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	● 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 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.

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 closely, including creatinine and urine protein, 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	● 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 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.

N) Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	● Permanently discontinue atezolizumab and contact Medical Monitor. ● Consider patient referral to hematologist. ● Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. ● Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. ● If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). ● If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH hemophagocytic lymphohistiocytosis; IVintravenous; MAS macrophage activation syndrome.

O) Severe skin adverse reactions related to the immune system (SCARS)

Event	Management
Skin reaction Grade 3	● Temporary discontinue atezolizumab and start corticosteroid treatment with prednisona 1-2 mg/kg/day or equivalent. ● Treatment with atezolizumab can be resumed if the event improves to ≤ Grade 1 in 12 weeks, and corticosteroids have been reduced to ≤ 10 mg of prednisolone or equivalent per day.
Skin reaction Grade 4	● Permanently discontinue atezolizumab and start corticosteroid treatment.
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	● Temporary discontinue atezolizumab and contact Medical Monitor for confirmation. ● If SJS or NET is confirmed, atezolizumab should be permanently discontinued. ● Caution should be exercised when considering the use of atezolizumab in a patient who has previously had serious or life-threatening skin adverse reactions with prior treatment with other immunostimulatory anticancer drugs.

SJS Stevens-Johnson syndrome; TEN Toxic epidermal necrolysis.

Appendix 2. EORTC QLQ-C30 Questionnaire (Version 3.0 Spanish)

EORTC QLQ-C30 (version 3)

Estamos interesados en conocer algunas cosas sobre usted y su salud. Por favor, responda a todas las preguntas personalmente, rodeando con un círculo el número que mejor se aplique a su caso. No hay contestaciones "acertadas" o "desacertadas". La información que nos proporcione será estrictamente confidencial.

Por favor escriba sus iniciales: |_|_|_|_|
Su fecha de nacimiento (día, mes año): |_|_| |_|_| |_|_|_|_|
Fecha de hoy (día, mes, año): |_|_| |_|_| |_|_|_|_|

		No	Un poco	Bastante	Muchísimo
1.	¿Tiene alguna dificultad para realizar actividades que requieran un gran esfuerzo, como llevar una bolsa de compras o una maleta pesada?	1	2	3	4
2.	¿Tiene alguna dificultad para dar un paseo largo?	1	2	3	4
3.	¿Tiene alguna dificultad para dar un paseo corto fuera de su casa?	1	2	3	4
4.	¿Tiene que permanecer en cama o sentado/a en una silla durante el día?	1	2	3	4
5.	¿Necesita ayuda para comer, vestirse, asearse o ir al baño?	1	2	3	4

Durante la semana pasada:

		No	Un poco	Bastante	Muchísimo
6.	¿Tuvo algún impedimento para hacer su trabajo u otras actividades cotidianas?	1	2	3	4
7.	¿Tuvo algún impedimento para realizar sus hobbies o actividades recreativas?	1	2	3	4
8.	¿Se quedó sin aliento?	1	2	3	4
9.	¿Tuvo algún dolor?	1	2	3	4
10.	¿Tuvo que detenerse a descansar?	1	2	3	4
11.	¿Tuvo dificultades para dormir?	1	2	3	4
12.	¿Se sintió débil?	1	2	3	4
13.	¿Se sintió sin apetito?	1	2	3	4
14.	¿Sintió náuseas?	1	2	3	4
15.	¿Tuvo vómitos?	1	2	3	4

Por favor, continúe en la página siguiente

Durante la semana pasada:		**No**	**Un poco**	**Bastante**	**Muchísimo**
16.	¿Tuvo estreñimiento?	1	2	3	4
17.	¿Tuvo diarrea?	1	2	3	4
18.	¿Se sintió cansado/a?	1	2	3	4
19.	¿Interfirió algún dolor en sus actividades diarias?	1	2	3	4
20.	¿Tuvo alguna dificultad para concentrarse en cosas como leer el diario o ver televisión?	1	2	3	4
21.	¿Se sintió nervioso/a?	1	2	3	4
22.	¿Se sintió preocupado/a?	1	2	3	4
23.	¿Se sintió irritable?	1	2	3	4
24.	¿Se sintió deprimido/a?	1	2	3	4
25.	¿Tuvo dificultades para recordar cosas?	1	2	3	4
26.	¿Ha interferido su estado físico o el tratamiento médico en su vida familiar?	1	2	3	4
27.	¿Ha interferido su estado físico o el tratamiento médico en sus actividades sociales?	1	2	3	4
28.	¿Le ha causado problemas económicos su estado físico o el tratamiento médico?	1	2	3	4

Por favor, en las siguientes preguntas encierre en un círculo el número del 1 al 7 que mejor se aplique a usted

29. En general, ¿cómo valoraría su estado de salud durante la semana pasada?

1	2	3	4	5	6	7
Pésimo						Excelente

30. En general, ¿cómo valoraría su calidad de vida durante la semana pasada?

1	2	3	4	5	6	7
Pésimo						Excelente

Appendix 3. EuroQol-5D questionnaire (Spanish)

Marque con una cruz como ésta ☒ las afirmaciones que describen mejor su estado de salud en el día de hoy.

Movilidad

- No tengo problemas para caminar ❑
- Tengo algunos problemas para caminar ❑
- Tengo que estar en cama ❑

Cuidado-Personal

- No tengo problemas con mi cuidado personal ❑
- Tengo algunos problemas para lavarme o vestirme solo ❑
- Soy incapaz de lavarme o vestirme solo ❑

Actividades Habituales *(ej, trabajar, estudiar, hacer tareas domésticas, actividades familiares o realizadas durante el tiempo libre)*

- No tengo problemas para realizar mis actividades habituales ❑
- Tengo algunos problemas para realizar mis actividades habituales ❑
- Soy incapaz de realizar mis actividades habituales ❑

Dolor/Malestar

- No tengo dolor ni malestar ❑
- Tengo un dolor o malestar moderado ❑
- Tengo mucho dolor o malestar ❑

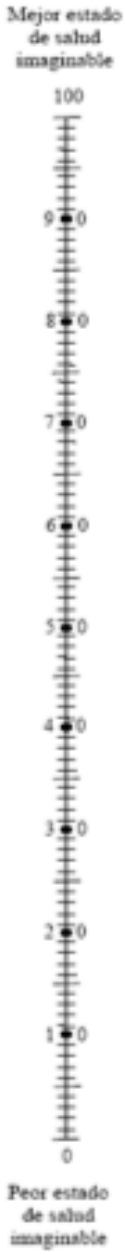
Angustia/Depresión

- No estoy angustiado o deprimido ❑
- Estoy moderadamente angustiado o deprimido ❑
- Estoy muy angustiado o deprimido ❑

Para ayudar a la gente a describir lo bueno o malo que es su estado de salud hemos dibujado una escala parecida a un termómetro en la cual se marca con un 100 el mejor estado de salud que pueda imaginarse y con un 0 el peor estado de salud que pueda imaginarse.

Nos gustaría que nos indicara en esta escala, en su opinión, lo bueno o malo que es su estado de salud en el día de hoy. Por favor, dibuje una línea desde el casillero abajo hasta el punto que en su opinión indique lo bueno o malo que es su estado de salud en el día de hoy.

Su estado de salud hoy



Sponsor: Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE)

CABATEN

Exploratory basket trial of cabozantinib plus atezolizumab in advanced and progressive neoplasms of the endocrine system

STATISTICAL ANALYSIS PLAN

27th of October 2020 (version 1.1)

Written by: Clara de Caralt

Reviewed by: Jordi Curto

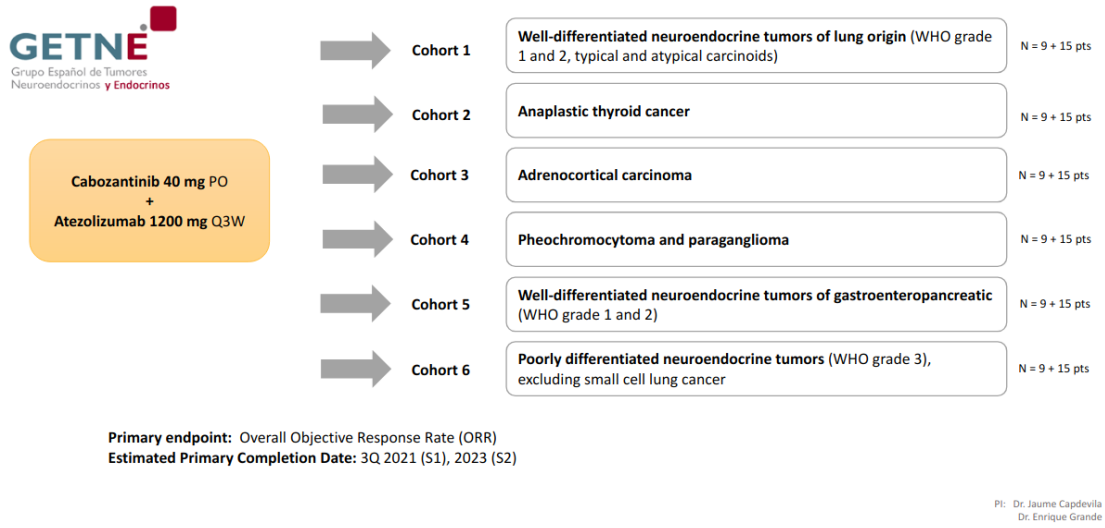
GENERAL INFORMATION

TITLE

Exploratory basket trial of cabozantinib plus atezolizumab in advanced and progressive neoplasms of the endocrine system

STUDY DESIGN

*Exploratory basket trial of **CAB**ozantinib plus **AT**ezolizumab in advanced and progressive neoplasms of the **EN**docrine system – The **CABATEN** study*



This is a multicohort phase II study of cabozantinib plus atezolizumab in advanced and progressive tumors from endocrine system.

Dosing scheme:

- Level 0 (starting dose): cabozantinib 40 mg qd + atezolizumab 1200 mg iv every 21 days (one cycle).
- Level -1: cabozantinib 20 mg qd + atezolizumab 1200 mg iv every 21 days (one cycle).

Cohorts of tumor types:

1. Well-differentiated neuroendocrine tumors of lung origin or thymus (WHO grade 1 and 2, typical and atypical carcinoids)
2. Anaplastic thyroid cancer
3. Adrenocortical carcinoma
4. Pheochromocytoma and paraganglioma
5. Well-differentiated neuroendocrine tumors of gastroenteropancreatic origin (WHO grade 1 and 2)

6. Poorly differentiated neuroendocrine tumors (WHO grade 3), excluding small cell lung cancer

TREATMENT

All the subjects will be treated with the combination until disease progression, unacceptable toxicity, or patient consent withdrawal (whichever occurs first) according to section 7 of the protocol.

- Cabozantinib 40 mg or 20 mg tablets, oral administration once daily continuously.
- Atezolizumab 1200 mg administered intravenously (IV) every three weeks (cycle).

Dosing scheme:

- Level 0 (starting dose): cabozantinib 40 mg qd + atezolizumab 1200 mg iv every 21 days (one cycle).
- Level -1: cabozantinib 20 mg qd + atezolizumab 1200 mg iv every 21 days (one cycle).

SPONSOR

GETNE (Spanish Group of Neuroendocrine and Endocrine Tumors)

C/ Pau Alsina, 64-68, Esc. B entresuelo 5ª, 08024 Barcelona

Phone: +34 93 434 44 12

E-mail: getne@getne.org

STUDY CHIEF INVESTIGATOR

Jaume Capdevila, M.D., Ph.D. Vall d'Hebrón University Hospital Medical Oncology Department P. Vall d'Hebron, 119-129 08035 – Barcelona

Phone: +34 93 274 60 85 E-mail: jcapdevila@vhio.net

Enrique Grande. M.D., Ph.D. MD Anderson Cancer Center Madrid Medical Oncology Department. Calle de Arturo Soria, 270, 28033 – Madrid

Phone: +34 91 787 86 00 e-mail: egrande@mdanderson.es

MONITORING ORGANISATION (CRO)

MFAR Clinical Research

C/ Sinfonía, 28, 2ª planta Nº1 - 28054 Madrid

Tel: 93.434.44.12

Sponsor: Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE)

Fax: 93.253.11.68

e-mail: investigacion@mfar.net

www.mfar.es

INDEX OF CONTENTS DE CONTENIDOS

INDEX OF TABLES

INDEX OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation Explanation

ADL	Activities of Daily Living
ADR	Adverse drug reaction
AE	Adverse event
AP	Anatomic pathology
ASCO	American Society of Clinical Oncology
AUC	Area Under Curve
BED	Biological efficacious dose
beta-hCG	Beta-human chorionic gonadotropin
BID	bis in die, (Latin for "twice daily")
BMI	Body mass index
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CIs	Confidence intervals
CK	Creatine kinase (CK), also known as creatine phosphokinase (CPK) or phosphocreatine kinase
CL/F	Apparent total clearance of the drug from plasma after administration
Cmax	Maximum (or peak) serum concentration
CB	Clinical benefit
CDR	Control disease rate
CR	Complete Response
CRF	Controlled Release Form
CSR	Central Serous Retinopathy
CTCAE	Common Terminology Criteria for Adverse Events
CT Scan	Computed Tomography Scan
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicity
DM	Distant metastasis
DR	Duration of response
DVP	Data Validation Plan
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	United States Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence in situ hybridization
FU	Follow-up
GCP	Good Clinical Practice
GEP-NET	Gastroenteropancreatic Neuroendocrine Tumors
GH	Growth hormone
Hb	Haemoglobin
H/E	Haematoxylin/eosin
HFSR	Hand Foot Skin Reaction
IB	Investigator Brochure
ICF	Informed Consent Form

ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IM	Intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intention To Treat
KA	Keratoacanthoma
Ke	Elimination rate constant
KPS	Karnofsky Performance Status
LLN	Lower Limit of Normality
LVEF	Left Ventricular Ejection Fraction
LOCF	Last Observation Carried Forward
MAP	Mitogen-Activated Protein
MASCC	Multinational Association of Supportive Care
MDM2	Mouse double minute 2 homolog
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
MEN	Multiple endocrine neoplasms
MLPA	Multiplex ligation-dependent probe amplification
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition Scan
NET	Neuroendocrine Tumor
OAE	Other significant adverse event
ORR	Overall response rate
OS	Overall Survival
OTEL	Open To Enrolment Letter
P2RD	Phase two recommended dose
PCR	Polymerase Chain Reaction
PD	Progression disease
PE	Physical examination
PET-CT	Positron emission tomography–computed tomography
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PLGA	Poly (lactic-co-glycolic acid)
pNET	Pancreatic NET
PP	Per Protocol
PR	Partial Response
PRT	Primary retroperitoneal tumours
PS	Performance Status
QD	Quaque die, every day “once daily”
QLQ 30	Quality of Life Questionnaire Core 30
QoL	Quality of Life
RDD	Retinal Degenerative Disease
RECIST	Response Evaluation Criteria In Solid Tumours
REEC	Registro Español de Estudios Clínicos (Spanish Registry of Clinical Studies)
RLS	Retroperitoneal Liposarcoma
RP	Retroperitoneum
RP2D	Recommended Phase II dose
RVO	Retinal Vein Occlusion
Rx	Radiography

SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SBP	Systolic Blood Pressure
SC	Subcutaneous
SCC	Squamous Cell Carcinoma
SD	Stable disease
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SP	Safety Population
SRS	Stereotactic Radiosurgery
SSAs	Somatostatin Analogues
SSTR	Somatostatin Receptors
SUSAR	Suspected unexpected serious adverse reaction
Sx	Surgery
Tmax	Time of the sample identified as Cmax
TR	Translational Research
TTLR	Time to Local Relapse
ULN	Upper Limit of Normality
Vd/F	Apparent volume of distribution after non-intravenous administration
VS	Vital signs
VMAT	Volumetric Modulated Arc Therapy
WBC	White Blood Count
WBRT	Whole Brain Radiotherapy
WHO	World Health Organization

1. MATERIAL AND METHODS

1.1. INTRODUCTION

1.1.1. BACKGROUND

Neuroendocrine tumours (NETs) comprise a heterogeneous group of neoplasms originating from neural crest cells, endocrine glands, endocrine islets or the diffuse endocrine system, which explains the heterogeneity in the characteristics of these tumours and their clinical presentation (1). Although considered rare malignancies, available data suggest an increase in the incidence of NETs over the past 30 years, with around 7 cases per 100,000 populations per year (2), with NETs of pancreatic, intestinal, and bronchopulmonary origin as the most common types.

Clinical diagnoses of NETs are reliable at the advanced stages when many subjects present with metastases and inoperable disease, thereby receiving first line therapy towards controlling the progression of the disease and relieving associated symptoms (2).

Well and poorly-differentiated neuroendocrine tumours of lung origin

The origin and tumour development of neuroendocrine neoplasms are discussed controversially, but most theories point to an association with Kulchitsky cells (or enterochromaffin cells), which are normally present in the bronchial mucosa and are part of the diffuse neuroendocrine system, comprising single cells or clusters of 4 to 10 cells (3,4,5).

NETs were first described as carcinoid tumours by Siegfried Oberndorfer in 1904, and are developed from hormone producing (endocrine) cells which can be found throughout the foregut (thymus, lung, bronchi, and trachea), midgut (small intestine, gallbladder, and pancreas), and hindgut (Colon, excluding appendix, rectum), with the small intestine (30.4 %) and the lung (29.8 %) (5,6) as the most common locations. NETs of the lung are also characterised by their abilities to take up and decarboxylate the amine precursors (APUD system cells) (7,8,9).

According to the World Health Organization (WHO) classification 2004, NETs share common morphological, immunohistochemical and molecular characteristics and can be divided into three main entities (10):

- Carcinoid tumours: typical (TC) or atypical (AC),
- Large cell neuroendocrine carcinomas (LCNEC),
- Small cell carcinomas (SCLC).

  These are further summarised into two groups according to their biological aggressiveness:

- Well-differentiated low grade (G1) typical and intermediate grade (G2) atypical carcinoids,
- Poorly-differentiated high grade (G3) LCNEC and SCLC.

  Unlike those of typical and atypical carcinoids, genetic and epigenetic characteristics of LCNEC and SCLC are not closely related, and there are no precursor lesions known for SCLCs and LCNECs (10,11).

Anaplastic thyroid cancer

Anaplastic thyroid cancer (ATC) occurs in less than 2 % of all thyroid cancer cases but uniformly lethal; and it affects 1–2 individuals per million every year in the United States. Patients are usually in their sixth or seventh decade of life at the time of disease presentation, and average median survival has been reported as 5 months, with < 20 % of survivors at 1 year after diagnosis (12,13). ATC is thought to originate from differentiated thyroid cancers of follicular cell origin, as a result of dedifferentiation. Up to 80 % of ATC occurs in the setting of a long-standing goitre, possibly in the background of an undiagnosed, well-differentiated thyroid cancer (15).

Dedifferentiation is associated with gains and deletions in multiple chromosomal regions and involves a complex process involving multiple events, including cell cycle derangement and signal transduction pathway disturbances (16-18). Due to its extremely aggressive behaviour, the American Joint Committee on Cancer (AJCC) defines all of ATC stages as stage IV, which is further staged into IVa, IVb, and IVc, depending on the extension of the primary tumour, lymph node involvement, or presence of distant metastases (DM). Although survival rates have not significantly improved in six decades, multimodality treatments including surgery, radiation, chemotherapy, and targeted therapy are considered the best strategy for improving outcome in patients diagnosed with ATC (14).

Adrenocortical carcinoma

Adrenocortical carcinoma (ACC) is a rare malignancy with an incidence of 0.7–2.0 cases/million inhabitants/year (19) whose malignancy features relies on careful investigations of the clinical, biological, and imaging features before surgery and the anatomopathological examination after tumour removal. Most patients present with excess steroid hormone or abdominal mass effects, but about 15 % of patients with ACC are initially diagnosed incidentally (20).

The stage classification proposed by the European Network for the Study of Adrenal Tumours (ENSAT) is recommended (21). Pathology reports define the Weiss score, the resection status, and the proliferative index, including the mitotic count and the Ki67 index. As far as the treatment is concerned, the complete resection of the tumour is the first option for tumours that are limited to the adrenal gland.

In metastatic disease, mitotane is the cornerstone of initial treatment, and cytotoxic drugs should be added in case of progression. Recently, the First International Randomised (FIRM-ACT) Trial in metastatic ACC reported the association between mitotane and etoposide/doxorubicin/cisplatin (EDP) as the new standard in first line treatment of ACC. In the last few years, new targeted therapies, including the IGF-1 receptor inhibitors, have been investigated, but their efficacy remains limited. Thus, new treatment concepts are urgently needed (19).

Pheochromocytoma and paraganglioma

Pheochromocytomas and paragangliomas (PPGLs) are highly vascular neuroendocrine tumours that arise from chromaffin cells of the adrenal medulla or their neural crest progenitors located outside of the adrenal gland, respectively (22). PPGLs are estimated to occur in about 2–8 of 1 million persons per year and about 0.1 % of hypertensive patients harbour a PPGL. About 10 % of patients with PPGL present with adrenal incidentaloma (23). According to 2017–WHO classification of tumours (fourth edition) based on their location/origin, the neuroendocrine tumours are classified as tumours of the adrenal medulla and extra-adrenal paraganglia (24). These tumours are derived either from sympathetic tissue in adrenal or extra-adrenal abdominal

locations (sympathetic PPGLs) or from parasympathetic tissue in the thorax or head and neck (parasympathetic PPGLs). Sympathetic PPGLs frequently produce considerable amounts of catecholamines, and in approximately 80 % of patients, they are found in the adrenal medulla (22,25). The remaining 20 % of these tumours are located outside of the adrenal glands, in the prevertebral and paravertebral sympathetic ganglia of the chest, abdomen, and pelvis. Extra-adrenal PPGLs in the abdomen most commonly arise from a collection of chromaffin tissue around the origin of the inferior mesenteric artery (the organ of Zuckerkandl) or aortic bifurcation. In contrast, most parasympathetic PPGLs are chromaffin-negative tumours mostly confined to the neck and at the base of the skull region along the glossopharyngeal and vagal nerves, and only 4 % of these tumours secrete catecholamines (25). These head and neck PGLs were formerly known as glomus tumour or carotid body tumours. Most PPGLs represent sporadic tumours and about 35 % of PPGLs are of familial origin with about 20 known susceptibility genes making them the most hereditary amongst all human tumours (26,27). Based on these genetic mutations and pathogenetic pathways, PPGLs can be classified into three broad clusters—cluster 1, cluster 2, and cluster 3. Cluster 1 includes mutations involving in overexpression of vascular endothelial growth factor (VEGF) (due to pseudohypoxia) and impaired DNA methylation leading to increased vascularization. Cluster 2 involves the activation of the mutations of Wnt-signalling pathway (Wnt receptor signalling and Hedgehog signalling). The activation of Wnt and Hedgehog signalling is secondary to somatic mutations of Cold shock domain containing E1(CSDE1) and Mastermind like transcriptional coactivator 3 (MAML3) genes (28). Abnormal activation of kinase signalling pathways like PI3Kinase/AKT, RAS/RAF/ERK, and mTOR pathways account for cluster 3 mutations (24). On the other hand, based on biochemical secretory patterns, PPGLs can be characterised into three different phenotypical categories—noradrenergic phenotype (predominant norepinephrine secreting), adrenergic phenotype (predominant epinephrine secreting), and dopamine secreting. These biochemical phenotypes of PPGL lead to a constellation of symptoms (based on the predominant hormone secreted) leading to different clinical manifestations.

Well-differentiated neuroendocrine tumours of gastroenteropancreatic origin

Gastroenteropancreatic neuroendocrine neoplasms (NENs) are rare tumours defined by the expression of specific diagnostic biomarkers (29-31). Cell differentiation is a major prognostic marker of neuroendocrine neoplasms (32, 33). Indeed, regardless of the stage or the location of the primary tumour, it has been highlighted (31) that well-differentiated lesions have a better prognosis than poorly differentiated ones [32, 34-36).

In 2010, the World Health Organization (WHO) classification of neuroendocrine neoplasms was reviewed and the crucial role of the proliferative rate was validated (37-42). The WHO Classification 2010 defined three groups of tumours (Grades 1-3) according to the combination of the morphological characteristics, mitotic index, and Ki-67 index (43). Grades 1 and 2 corresponded to well-differentiated neuroendocrine tumours (NETs), whereas grade 3 corresponded to poorly differentiated lesions called neuroendocrine carcinomas (NECs). Initially, it was assumed that no NET with a mitotic or a Ki-67 index above 20 % could exist.

The majority of gastroenteropancreatic NENs are classified in the well-differentiated category because they retain the organoid architecture typical of neuroendocrine organs and have a relatively low proliferative rate. It is stated that all gastroenteropancreatic NETs—with the exception of the pancreatic microadenomas, gastrin-driven type 1 neuroendocrine tumours in the stomach are potentially malignant neoplasms. Different classifications have been used to distinguish pure neuroendocrine tumours from mixed endocrine-exocrine tumours, and to distinguish within pure neuroendocrine tumours according to their behaviour (well-differentiated NETs with benign behaviour, well-differentiated NETs with uncertain behaviour,

well-differentiated NETs with malignant behaviour, and poorly differentiated endocrine carcinomas with high-grade malignant behaviour) (44, 45). These classifications are based on their site of origin, size, gross and/or microscopic tumour extension, vascular invasion, and/or proliferative activity (Ki-67 index), as well as their syndromic clinical/functioning features.

High-grade neuroendocrine neoplasms (WHO G3) of the pancreas include both well-differentiated neuroendocrine tumour (WD-NET) and poorly differentiated neuroendocrine carcinoma (PD-NEC). According to the WHO classification scheme, the diagnosis of this group of tumours is based on both the histopathology of the tumour and the assessment of proliferation fraction. However, the former can be challenging due to the lack of well-defined histologic criteria, and the latter alone (i.e, > 20 mitoses/10 high-power fields or Ki67 > 20 %) may not sufficiently distinguish WD-NETs from PD-NECs. Given the considerable differences in treatment strategies and clinical outcome, additional practical modalities are required to facilitate the accurate diagnosis of high-grade pancreatic neuroendocrine neoplasms. We examined 33 cases of WHO G3 neuroendocrine neoplasms of the pancreas and attempted to classify them into WD-NET, small cell PD-NEC (PD-NEC-SCC), and large cell PD-NEC (PD-NEC-LCC), or to designate them as "ambiguous" when an uncertain diagnosis was rendered by any of the observers or there was any disagreement in classification among the three observers. To simplify the interpretation, both PD-NEC-SCC and PD-NEC-LCC were considered together as PD-NECs in the final analysis. The initial approach was to assess microscopically a single morphologically challenging hematoxylin and eosin section from each case without the knowledge of Ki67 values. This was performed independently by three pathologists to assess the degree of diagnostic concordance, and the immunohistochemical staining for surrogate biomarkers of known genotypes of WD-NET and PD-NEC was evaluated. Lastly, a clinicopathologic review was completed to establish a final definitive classification. Loss of DAXX or ATRX protein expression defined WD-NET, and abnormal expression of p53, Rb, SMAD4 signified PD-NEC. When the chosen section displayed an element of WD histopathology, or other tumour sections contained WHO G1/G2 components, or there had been a prior established diagnosis of a primary WD-NET, the final diagnosis was considered a WD-NET with high-grade (G3) progression. If a component of conventional adenocarcinoma was present (in slides not seen in the initial review), the diagnosis was established as a combined adenocarcinoma and PD-NEC. All the three pathologists agreed on the morphologic classification of 33 % of the cases (6 WD-NET, 3 PD-NEC-SCC, and 2 PD-NEC-LCC), were conflicted on two cases, between PD-NEC-SCC and PD-NEC-LCC, and disagreed or were uncertain on the classification of the remaining 20 cases (61%), which were therefore categorised as ambiguous. In the group of cases in which all pathologists agreed on the classification, the six WD-NET cases had either loss of DAXX or ATRX or had evidence of a WD-NET based on additional or prior pathology slides. The seven PD-NEC cases had abnormal expression of p53, Rb, and/or SMAD4 or a coexisting adenocarcinoma. In the ambiguous group (n = 20), 14 cases were established as WD-NETs based upon the loss of DAXX or ATRX in seven cases and additional pathology evidence of high-grade progression from WD-NET in the other seven cases; five cases were established as PD-NEC based upon abnormal expression of p53, Rb, and/or SMAD4; one case remained undetermined with normal expression of all markers and no evidence of entity-defining histologic findings in other slides. On the basis of the final pathologic classifications, the disease-specific survival was 75 and 11 months for the WD-NET and PD-NEC groups, respectively. Thus, we conclude that morphologic diagnosis of high-grade pancreatic neuroendocrine neoplasms is challenging, especially when limited pathologic materials are available, and necessitates better defined criteria. The analysis of both additional sections and prior material, along with an immunohistochemical evaluation, can facilitate accurate diagnosis in the majority of cases and guide the appropriate clinical management and prognosis (46).

1.2. PURPOSE OF THE ANALYSIS

1.2.1. STUDY OBJECTIVES

Primary objective:

To assess the efficacy of cabozantinib plus atezolizumab combination by means of radiological objective response rate (ORR) in advanced endocrine tumors.

Secondary objectives are:

- Safety Profile
- Duration of Response (DoR)
- Progression-free Survival (PFS)
- Overall Survival (OS)
- Biomarkers

1.2.2. ENDPOINTS

Primary endpoint:

Overall Response Rate (ORR): includes patients with confirmed partial (PR) and complete response (CR) as best response according to RECIST v 1.1.

Secondary endpoints:

- **Safety profile of cabozantinib and atezolizumab:** The number of patients with AEs and SAEs, changes in laboratory values, vital signs, ECGs, and results of physician examinations graded according to the CTCAE v 5.0. This will be analysed using descriptive statistics techniques such as frequency and contingency tables. The final statistical analysis of this endpoint is expected to be performed within 6 months after database closure, which is expected at 12 months after last patient inclusion. However, interim analysis may be performed when analysing other primary endpoints.
- **Duration of response (DOR) as per RECIST 1.1:** DOR calculated as the time from the date of first documented CR or PR to the first documented progression or death due to underlying cancer.
- **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). Patient with no additional image test other than that at baseline will be censored to the day after inclusion.
- **Overall Survival (OS)**: Median Overall Survival (mOS) is calculated as the time from date of inclusion to date of death due to any cause.
- **Biomarkers:** To be determined according to study results and Sponsor feasibility.

1.3. STUDY METHODS

This is an open labelled, single arm, multicohort phase II multicentre clinical trial of cabozantinib plus atezolizumab in advanced and refractory tumours from endocrine system.

The design includes screening phase, treatment phase (including medical consultation and drug administration Q3w ± 3 days) unless otherwise specified, disease progression follow up by RECIST 1.1 every 12 weeks, translational research with biopsies and blood samples and long term follow-up.

This is a study with Simon's two-stage design; it requires that an event is observed (confirmed response) in the first nine patients before continuing to the second stage where there is a possible inclusion of 15 additional patients (up to a maximum of 24 patients per cohort).

1.3.1. INCLUSION-EXCLUSION CRITERIA

1.3.1.1 INCLUSION CRITERIA

Patients eligible for inclusion in this study must meet all the following criteria:

1. Male or female subjects ≥ 18 years old.
2. Willingness to participate in the study by signing ICF approved by the trial Central Ethic Committee (CEIm).
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Measurable disease per RECIST 1.1 as determined by the investigator.
5. Patients with advanced and progressive neuroendocrine tumors histopathologically confirmed (as per local pathology report), meeting one of the following (according to WHO 2010 classification):
    a. Cohort 1: Well-differentiated neuroendocrine tumours of the lung and thymus (WHO grade 1 and 2, typical and atypical carcinoids) after progression to somatostatin analogs, targeted agents, PRRT, and/or chemotherapy.
    b. Cohort 2: Advanced anaplastic thyroid cancer in first-line or after progression to chemotherapy or investigational drugs, that underwent prior primary tumor surgical resection or not. In patients that primary tumor has not been resected, the risk of aerodigestive compression or bleeding should be ruled out to ensure no interference with the administration of the investigational product and undesirable potential side effects related to the route of administration.
    c. Cohort 3: Adrenocortical carcinoma after progression to chemotherapy and/or mitotane.
    d. Cohort 4: Pheochromocytoma and paraganglioma after progression to peptide receptor radionuclide therapy (PRRT) if indicated. Prior chemotherapy and biological therapy, such as somatostatin analogs, are allowed.

e. Cohort 5: Well-differentiated neuroendocrine tumours of digestive system (WHO grade 1 and 2) after progression to somatostatin analogs, targeted agents, PRRT, and/or chemotherapy.

f. Cohort 6: Grade 3 neuroendocrine neoplasm (WHO grade 3, including NET and NEC G3) of any origin, excluding small cell lung cancer, after progression to chemotherapy or targeted agents/PRRT.

6. Recovery from toxicity related to any prior treatments to ≤ Grade 1, unless the AE(s) are clinically non-significant and/or stable on supportive therapy.

7. Ability to swallow tablets.

8. 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 ≤ 1.5X 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. AST (SGOT)/ALT (SGPT) ≤ 2.5X institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 3X ULN.

   f. Measured creatinine clearance (CL) > 40 mL/min or Calculated creatinine CL > 40 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:

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

1.3.1.2 EXCLUSION CRITERIA

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

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

2. Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks or 5 half-lives of the agent, whichever is longer. Patients should have been out of mitotane for at least 4 weeks.

3. Receipt of any type of anticancer antibody (including investigational antibody) or systemic chemotherapy within 2 weeks before starting treatment.

4. Current or prior use of immunosuppressive medication within 2 weeks before the first dose of cabozantinib and atezolizumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

5. 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.

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

7. History of allogeneic organ transplant.

8. 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.

9. Receipt of radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks before inclusion. Subjects with clinically relevant ongoing complications from prior radiation therapy that have not completely resolved are not eligible (e.g, radiation esophagitis or other inflammation of the viscera).

10. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks before inclusion. Eligible subjects must be neurologically asymptomatic and without corticosteroid treatment at the time of study treatment.

11. Concomitant anticoagulation with oral anticoagulants (e.g, warfarin, direct thrombin and factor Xa inhibitors) or platelet inhibitors (e.g, clopidogrel), except for the following allowed anticoagulants:

    - Low-dose aspirin for cardioprotection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH).

    - Anticoagulation with therapeutic doses of LMWH in subjects without known brain metastases and who are on a stable dose of LMWH for at least 6 weeks before inclusion and who have had no clinically significant hemorrhagic complications from the anticoagulation regimen or the tumour.

12. The subject has uncontrolled, significant intercurrent or recent illness 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. Moderate to severe hepatic impairment (child-pugh B or C).

iv. Requirement for hemodialysis or peritoneal dialysis.

v. Uncontrolled diabetes mellitus.

vi. History of solid organ transplantation.

13. 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.

14. Corrected QT interval calculated by the Fridericia formula (QTcf) > 500 ms within 28 days before study treatment.

    Note: if a single ECG shows a QTCf with an absolute value > 500 ms, two additional EGGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these 3 consecutive results for qtcf will be used to determine eligibility.

15. Pregnant or lactating females.

16. Inability to swallow tablets.

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

18. Diagnosis of another malignancy within 3 years before study treatment, except for superficial skin cancers, or localised, low grade tumours deemed cured and not treated with systemic therapy.

1.3.2. STUDY VARIABLES

	Screening	C1	C2	C3	C4	C5 to PD	EOT	Up to EOS
Week	-4 To -1	0	Q3w ±3 days unless dosing needs to be held for toxicity reasons					
Day	-28 To -1	1[a]	Q21 Days ±3 days unless dosing needs to be held for toxicity reasons					
Informed Consent								
Informed Consent[b]	X							
Consent and Collection of Specimens for Future Biomedical Research	X							
Study Procedures								
Medical History	X							
Physical Exam (Full)	X							
Targeted Physical Exam (Based On Symptoms)		X	X	X	X	X	X	
Vital Signs[c]	X	X	X	X	X	X	X	
ECG[d]	X	As clinically indicated					X	
Prior and Concomitant Medications	<----------						---------->	
Demography, Including Baseline Characteristics And Tobacco Use	X							
Eligibility Criteria	X							
Laboratory Assessments								
Clinical Chemistry[e]	X	X[f]	X	X	X	X	X	
Hematology[e]	X	X[f]	X	X	X	X	X	
TSH[g] (Reflex Free T3 Or Free T4[h])	X	X	X	X	X	X	X	
Hepatitis B, C and HIV[i]	X							
Urinalysis	X						X	
Pregnancy Test[j]	X	if clinically indicated						
Monitoring								
ECOG Performance Status	X	X	X	X	X	X	X	
AE/SAE/AESI Assessment[k]		X	X	X	X	X	X	
Post-treatment Follow-up[l]								X

IMPs Administration								
Cabozantinib[m]		X (p.o. daily, until PD or unacceptable toxicity)						
Atezolizumab[m]		X	X	X	X	X		
Biological samples collection								
Tumor Biopsy (Archival, If Available)	(X)							
Processed blood samples[n]	X		X				X	
Efficacy Evaluations								
Tumor evaluation (CT scan or MRI) (RECIST 1.1)[o]	X	q12w ± 1w until confirmed objective disease progression/death (whichever comes first).						(X)
Note: all assessments on treatment days are to be performed prior to atezolizumab infusion, unless otherwise indicated. C: cycle; ECG: electrocardiogram; IM: intramuscular; LFT: liver function test; QxW: every x weeks; T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone. EOT: end of treatment, EOS: end of study.								

a) Every effort should be made to minimise the time between inclusion and start of treatment. (i.e. within 1 day of inclusion)
b) Informed consent of study procedures may be obtained prior to the 28-day screening window. If laboratory or imaging procedures were performed for different reasons prior to signing consent, these can be used for the screening purposes with the consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of inclusion.
c) Body weight is to be recorded at each visit along with vital signs.
d) Any clinically significant abnormalities detected require triplicate ECG results.
e) Complete blood count that includes total white blood cell count with leukocyte formula, haemoglobin, 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. 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 function 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.
f) If clinical chemistry screening 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.
g) If TSH is measured within 14 days prior to C1D1 (first infusion day), it does not need to be repeated at day 1.
h) Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
i) Serology including HIV, hepatitis B (HBsAg and anti-HBc), and hepatitis C virus (HCV).
j) Women of childbearing potential are required to have a pregnancy test within 72 hours prior to the first dose of the study drug, and every 3 cycles (9 weeks) thereafter (if clinically indicated). Latest pregnancy results (maximum 9 weeks old) must be available and reviewed by the treating physician or investigator prior to commencing a new cycle of infusion. A urine or serum pregnancy test is acceptable.
k) For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed.
l) Post-treatment follow up: all patients will be followed up according to RECIST 1.1 every

12 weeks (+/-7 days) up to disease progression or death (whichever occurs first), regardless of the reason for ending the treatment. Neuroendocrine markers are to be analysed according to local practice. The follow-up period according to the protocol is 12 months considering last patient inclusion. Information on subsequent treatments should include the list of post-treatment therapies, the drugs administered, and the date of initiation and discontinuation of each drug. All the data will be recorded in the medical record and in the eCRF.

m) The initial dose of atezolizumab will be administered before cabozantinib and must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. For the rest of the cycles, cabozantinib will be self-administered by the patients daily and as per principal investigator indications. 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.

n) Biomarker study: Collection of the most recent archived tumour-biopsy sections. Processed blood samples at baseline, day 1 of cycle 2 (D1C2), 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).

o) CT Scan or MRI is to be performed at baseline and q12w ± 1w until the confirmation of objective disease progression or death (whichever comes first). The schedule of q12w ± 1 week 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. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. 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. 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.

1.4. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

1.4.1. DETERMINATION OF SAMPLE SIZE

Simon-II optimal two-stage design was applied for sample size estimation. We hypothesise that the experimental therapy will improve the probability of expected objective response rate in refractory settings, from less than 5 % in previous reports, to 20 % in the current study. With 80 % of power (0.2) and unilateral alpha (0.1), 24 patients per cohort are needed to demonstrate the primary hypothesis. The Simon-II design suggested the observation of ≥ 1 patient with objective response within the first nine patients included in the first stage. If ≥ 1 out of nine patients in each cohort achieve an objective radiological response in the first stage, the study will continue to recruit 15 additional patients up to 24 patients per cohort. If ≥ 3 out of a total of 24 patients achieve a radiological objective response at the final analysis, the study should be declared positive. If stage I is reached only in one cohort, recruitment will continue in the successful cohort and stopped in the non-effective cohorts.

1.4.2. GENERAL CONSIDERATIONS

'Last patient last visit', as defined in the protocol, is 12 months after the enrolment of last patient. Subjects may continue to receive IMPs after the cut-off because treatment cannot be discontinued for ethical reasons, but in such cases, Sponsor agrees to continue with cabozantinib supply to sites to cover patient treatment until it's finalisation and atezolizumab for a maximum of 6 months after the end of the study (LPLV). For these 6 additional months (since LPLV), the principal investigators must inform on any suspicion on adverse events/special situations in patients receiving atezolizumab's, to the marketing authorisation holder.

1.4.3. DESCRIPTION OF ANALYSIS SETS

Data will be analysed in the following populations:

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

1.4.4. MISSING DATA

The missing data will not be inputed and will be left as lost (missing value), however it will be presented. Missing data for drop-outs are not replaced by methods like LOCF (last option carried forward).

1.4.5. INTERIM ANALYSES AND DATA MONITORING

Interim analysis may be performed when analysing other primary endpoints.

1.5. SUMMARY OF STUDY DATA

For each categorical variable, the results will be summarised by frequencies and percentages. For each continuous variable, the results will be summarised by descriptive statistics such as median, range, and interquartile range or by means, standard deviations, and 95 % confidence intervals (CIs). For proportions, point estimates and exact 95 % confidence intervals will be calculated. 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. Laboratory values will be expressed as absolute values and in grades (ordinal categorical variables) according to NCI CTCAE v 5.0.

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

Continuous data will be presented with the number of observations, mean value, standard deviation, minimum, maximum, and median. Categorical data will be presented as counts and percentages. Individual subject data will be listed.

Vital signs, ECG parameters, clinical laboratory data (haematology, serum biochemistry, and urinalysis) will be presented in tabular form. Values outside the reference range will be flagged, and the clinically significantly abnormal values will be listed in tabular form. Adverse events will be tabulated by system organ class and preferred term after medical coding using the according to NCI CTCAE v 5.0.

1.5.1. PROTOCOL DEVIATIONS

Compliance with the IMP schema is critical for patients and trial outcomes, and any deviation from the IMP schema may jeopardise trial results or may affect patient safety; for these reasons, non-compliance may be considered a protocol deviation. When an investigational product is dispensed in a clinical trial, the investigator or a person designated by the investigator will ensure high level of compliance with the investigational product administration procedures.

1.6. REPORTING CONVENTIONS

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as “<0.001”. The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data.

1.7. TECHNICAL DETAILS

All analysis, tables, listing and figures will be produced with R (3.6.3), RStudio 1.3.1093 y SPSS (26.0).

2. RESULTS

2.1. STUDY POPULATION

2.1.1. RECRUITED PATIENTS (CENTRES/INVESTIGATORS)

Initially **XXX patients** were recruited in XXX Spanish sites. The recruited period lasted from **xxxxxx 20xx** until **xxxxxx 20xx**. The distribution of patients by centres will be shown in the following table:

Table 1. Recruited patients by site

Centre	Investigator	Patients
		N (%)
Total		xx (100.0)

2.1.2. EVALUABLE PATIENTS

Following protocol indications, it was analysed which patients could be included in the analysis: General inclusion criteria (see section **¡Error! No se encuentra el origen de la referencia.**.1 for detailed list of inclusion criteria).

In the following table the number of non evaluable patients along with the reason why, will be reported.

Table 2. Non evaluable patients

No.	ID patient	Cohort	Hospital	Reason

The evaluable population by sites will be described in ¡Error! No se encuentra el origen de la referencia.:

Table 3. Patients evaluable by Site

	Total
	N (%)
Hospital 1	
Hospital 2	
…	

Total	xx (100.0)

In this report, data from **xxx patients from xx** Spanish sites will be analysed. A database cut-off was made in **xxxxxx 20XX** for this analysis.

Table 4. Evaluable patients and Analysis sets

		n	%[1]
Total number of recruited patients			**100,0**
Total number of non recruited patients			
- *Reason of exclusion*			
Intent-To-Treat (ITT): All patients that has been enrolled in the trial.	**Yes**		
	No		
Evaluable population per protocol (PP): All patients fulfilling all eligibility criteria without any protocol deviation that makes patient invalid for the primary endpoint evaluation.	**Yes**		
	No		
Safety population: All patients receiving at least one dose of treatment.	**Yes**		
	No		

[1] Calculated percentage from the total of patients with available data

Table 5. Patients allocated in each cohort by hospital

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	Total
Hospital	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hospital 1							n (100%)
Hospital 2							n (100%)
Hospital 3							n (100%)
Hospital 4							n (100%)
Hospital 5							n (100%)
Hospital 6							n (100%)
…							n (100%)
Total							n (100%)

2.2. BASELINE PATIENT CHARACTERISTICS

For the descriptive analysis of the patients, the evaluable population will be used.

The mean age of the patients included in the study was **XXXX** years.

Table 6. Baseline patient characteristics

Sociodemographic		**N**	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Age				
				N (%, CI95%)
Gender	**Male**			
	Female			
Race	**Caucasian**			
	Latin			
	Asian			
	African			
	UK			
	Other			
Vital signs		**N**	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Body weight (kg)				
Height (cm)				
BMI				
Blood pressure (mmHg)				
Pulse rate (bpm)				
Respiration rate (breaths/minute)				
Temperature (ºC)				
Physical examination				**N (%, CI95%)**
Normal				
Abnormal				
Functional status				**N (%, CI95%)**
ECOG	**0**			
	1			
	2			
	3			
	4			
	5			

Tobacco smoking history			N (%, CI95%)
Usage	Never smoker (<=100 cigarrettes/life time)		
	Former smoker (>=1 year)		
	Smoker		
	Unknown		
	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Time smoking (years)			
	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Pack/year			

Table 7. Haematology and Coagulation

Haematology and Coagulation	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Hematocrit			
Hemoglobin			
Platelets			
Red blood cells			
White blood cells			
Neutrophils			
Lymphocytes			
Basophils			
Eosinophils			
Monocytes			

Table 8. Biochemistry

Biochemical	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Creatinine			
Albumin			
Direct Bilirrubin			
Indirect Bilirrubi			
Total Bilirrubin			
AST			
ALT			
Alcaline P.			
GGT			
Urea			
BUN			

Uric Acid
LDH
Calcium
Magnesium
Potassium
Sodium
Phosphorus
Glucose
Amylase
Lipase
Total Protein
Creatine kinase

Table 9. Tumor Markers

Tumor Markers	N	Mean, SD (CI95%)	Median (CI95%) [Range]
5-HIAA			
NSE			
CEA			
CGA			
Cortisol			
Methanephrines			
Adrenalin			
Norepinephrine			

Table 10. Serology

	N (%, CI95%)
HC	
Positive	
Negative	
HB	
Positive	
Negative	
HIV	
Positive	
Negative	

[1] Calculated percentage from the total of patients with available data

Table 11. Baseline TSH, fT3 and fT4 in overall (Thyroid Funciton)

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
TSH			
Free T3			
Free T4			

2.2.1. TUMOR DATA AND PRIOR TREATMENTS

Baseline cancer characteristics will be reported in this section.

Table 12. Cancer History

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Time since diagnosis until Inclusion date (months)			
Time since progression disease date until Inclusion date (months)			
Time since diagnosis until progression disease date (months)			
			N (%, CI95%)
Histological type			
Well and poorly-differentiated neuroendocrine tumours of lung origin			
Anaplastic thyroiid cancer			
Adenocortical carcinoma			
Pheochromocytima and paraganglioma			
Well-differentiated neuroendocrine tumours of gastroeropancreatic origin			
Poorly differentiated neuroendocrine tumors			
TNM			
T stage			
N stage			
M stage			
Stage			
I			
II			
III			
IV			
Histological grade			
Well differentiated			
Moderately differentiated			
Poorly differentiated			
Grade			
1			

2				
3				
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
	Ki-67 Index			
	Mitotic rate			
	Functional status			
Functioning				
Non-Functioning				
			N (%, CI95%)	
	Metastasis			
Yes				
No				
	Metastasis location			
Anus				
Ascites				
…				
	Study done with			
Octreoscan				
FDG-PET				

[1] Calculated percentage from the total of patients with available data

Details of previous surgery will be shown below:

Table 13. Baseline surgery

				N (%, CI95%)
Surgery	**Yes**			
	No			
On primary tumor	**Yes**			
	No			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Time since surgery date until Inclusion date (months)				

Time since diagnosis until surgery date (months)			

Details of previous radiotherapy will be shown below:

Table 14. Baseline Radiotherapy

			N (%, CI95%)
Radiotherapy	**Yes**		
	No		
Cyles of Radiotherapy	**1**		
	…		
Compulative dose	**…**		
	…		
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Time since Last cycle date until Inclusion date (months)			

Table 15. Previous treatments

			N (%, CI95%)
Treatment type	**Neoadjuvant**		
		Chemotherapy	
		Radiotherapy	
		Somatostatin analogs	
		Antineoplastic target therapies	
		Mitotane	
		Other	
	Adjuvant		
		Chemotherapy	
		Radiotherapy	
		Somatostatin analogs	
		Antineoplastic target therapies	
		Mitotane	
		Other	
	Line		
	1st Line		
		Chemotherapy	
		Radiotherapy	
		Somatostatin analogs	
		Antineoplastic target therapies	

		Mitotane
		Other
	2nd Line	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other
	3rd Line	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other
	Maintenance	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other

Table 16. Other cancer history

		N (%, CI95%)
Other cancer history type	**Type**	

2.2.2. PREVIOUS MEDICAL HISTORY

In this section previous relevant comorbidities will be shown.

Table 17. Relevant Comorbidiities

		N (%, CI95%)
Previous relevant illness (pathologies)	**No**	
	Yes	
Previous relevant illnesses (pathologies)	**Relevant illness 1**	
	Relevant illness 2	
	Relevant illness 3	
	…	

In this section concomitant medications will be shown.

Table 18. Prior Concomitant medication

		N (%, CI95%)
Prior Concomitant Medicantion	**Yes**	
	No	
Medication	**Acaclofenac**	
	…	

In this section other determinations will be shown:

Table 19. Urinalysis

		N (%, CI95%)
Result	**Negative**	
	Traces	
	1	
	2	
	3	
	4	
Bilirubin		
Color/apparence		
Leukocytes		
Urobilinogen		
Blood		
Glucose		
Nitrite		

Ketones			
Protein			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
pH			
Specific gravity			

Table 20. Pregnancy test

	N (%, CI95%)
Positive	
Negative	
NA	

Table 21. Electrocardiogram

			N (%, CI95%)	
Result	**Normal**			
	Abnormal			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
QTc				

2.2.3. BASELINE PATIENT CHARACTERISTICS IN COHORT 1

Baseline patient characteristics in cohort 1 is shown in this section. Cohort 1 tumor type is the Well-differentiated neuroendocrine tumors of lung origin or thymus (WHO grade 1 and 2, typical and atypical carcinoids)

The mean age of the patients included in the study was **XXXX** years.

Table 22. Baseline patient characteristics in cohort 1

Sociodemographic		**N**	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Age				
				N (%, CI95%)
Gender	**Male**			
	Female			

Race	**Caucasian**			
	Latin			
	Asian			
	African			
	UK			
	Other			
Vital signs		**N**	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Body weight (kg)				
Height (cm)				
BMI				
Blood pressure (mmHg)				
Pulse rate (bpm)				
Respiration rate (breaths/minute)				
Temperature (ºC)				
Physical examination				**N (%, CI95%)**
Normal				
Abnormal				
Functional status				**N (%, CI95%)**
ECOG	**0**			
	1			
	2			
	3			
	4			
	5			
Tobacco smoking history				**N (%, CI95%)**
Usage	**Never smoker (<=100 cigarrettes/life time)**			
	Former smoker (>=1 year)			
	Smoker			
	Unknown			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Time smoking (years)				
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Pack/year				

Table 23. Haematology and Coagulation in cohort 1

Haematology and Coagulation	N	Mean, SD (CI95%)	Median (CI95%) [Range]

Hematocrit
Hemoglobin
Platelets
Red blood cells
White blood cells
Neutrophils
Lymphocytes
Basophils
Eosinophils
Monocytes

Table 24. Biochemistry in cohort 1

Biochemical	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Creatinine			
Albumin			
Direct Bilirrubin			
Indirect Bilirrubi			
Total Bilirrubin			
AST			
ALT			
Alcaline P.			
GGT			
Urea			
BUN			
Uric Acid			
LDH			
Calcium			
Magnesium			
Potassium			
Sodium			
Phosphorus			
Glucose			
Amylase			
Lipase			
Total Protein			
Creatine kinase			

Table 25. Tumor Markers in cohort 1

Tumor Markers	N	Mean, SD (CI95%)	Median (CI95%) [Range]
5-HIAA			
NSE			
CEA			
CGA			
Cortisol			
Methanephrines			
Adrenalin			
Norepinephrine			

Table 26. Serology in cohort 1

	N (%, CI95%)
HC	
Positive	
Negative	
HB	
Positive	
Negative	
HIV	
Positive	
Negative	

[1] Calculated percentage from the total of patients with available data

Table 27. Baseline TSH, fT3 and fT4 in overall (Thyroid Funciton) in cohort 1

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
TSH			
Free T3			
Free T4			

2.2.3.1 TUMOR DATA AND PRIOR TREATMENTS IN COHORT 1

Baseline cancer characteristics in cohort 1 will be reported in this section.

Baseline cancer characteristics in cohort 1 will be reported in this section.

Table 28. Cancer History in cohort 1

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Time since diagnosis until Inclusion date (months)			
Time since progression disease date until Inclusion date (months)			
Time since diagnosis until progression disease date (months)			
		N (%, CI95%)	
Histological type			
Well and poorly-differentiated neuroendocrine tumours of lung origin			
Anaplastic thyroiid cancer			
Adenocortical carcinoma			
Pheochromocytima and paraganglioma			
Well-differentiated neuroendocrine tumours of gastroeropancreatic origin			
Poorly differentiated neuroendocrine tumors			
TNM			
T stage			
N stage			
M stage			
Stage			
I			
II			
III			
IV			
Histological grade			
Well differentiated			
Moderately differentiated			

Poorly differentiated				
Grade				
1				
2				
3				
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Ki-67 Index				
Mitotic rate				
Functional status				
Functioning				
Non Functioning				
			N (%, CI95%)	
Metastasis				
Yes				
No				
Metastasis location				
Anus				
Ascites				
…				
Study done with				
Octreoscan				
FDG-PET				

[1] Calculated percentage from the total of patients with available data

Details of previous surgery will be shown below:

Table 29. Baseline surgery in cohort 1

			N (%, CI95%)	
Surgery	**Yes**			
	No			
On primary tumor	**Yes**			
	No			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**	

Time since surgery date until Inclusion date (months)			
Time since diagnosis until surgery date (months)			

Details of previous radiotherapy will be shown below:

Table 30. Baseline Radiotherapy in cohort 1

			N (%, CI95%)
Radiotherapy	**Yes**		
	No		
Cyles of Radiotherapy	**1**		
	…		
Compulative dose	**…**		
	…		
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Time since Last cycle date until Inclusion date (months)			

Table 31. Previous treatments in cohort 1

			N (%, CI95%)
Treatment type	**Neoadjuvant**		
		Chemotherapy	
		Radiotherapy	
		Somatostatin analogs	
		Antineoplastic target therapies	
		Mitotane	
		Other	
	Adjuvant		
		Chemotherapy	
		Radiotherapy	
		Somatostatin analogs	
		Antineoplastic target therapies	
		Mitotane	
		Other	
	Line		
	1st Line		
		Chemotherapy	
		Radiotherapy	

		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other
	2nd Line	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other
	3rd Line	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other
	Maintenance	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other

Table 32. Other cancer history

		N (%, CI95%)
Other cancer history type	**Type**	

2.2.3.2 PREVIOUS MEDICAL HISTORY IN COHORT 1

In this section previous relevant comorbidities in cohort 1 will be shown.

Table 33. Relevant Comorbidiities in cohort 1

		N (%, CI95%)
Previous relevant illness (pathologies)	**No**	
	Yes	
Previous relevant illnesses (pathologies)	**Relevant illness 1**	
	Relevant illness 2	
	Relevant illness 3	
	…	

In this section concomitant medications will be shown.

Table 34. Prior Concomitant medication in cohort 1

		N (%, CI95%)
Prior Concomitant Medicantion	**Yes**	
	No	
Medication	**Acaclofenac**	
	…	

In this section other determinations will be shown:

Table 35. Urinalysis in cohort 1

				N (%, CI95%)
Result	**Negative**			
	Traces			
	1			
	2			
	3			
	4			
Bilirubin				
Color/apparence				
Leukocytes				
Urobilinogen				
Blood				
Glucose				
Nitrite				
Ketones				
Protein				
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
pH				
Specific gravity				

Table 36. Pregnancy test in cohort 1

	N (%, CI95%)
Positive	

Negative	
NA	

Table 37. Electrocardiogram in cohort 1

			N (%, CI95%)	
Result	**Normal**			
	Abnormal			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
QTc				

2.2.4. BASELINE PATIENT CHARACTERISTICS IN COHORT 2

Baseline patient characteristics in cohort 2 is shown in this section. Cohort 2 tumor type is the Anaplastic thyroid cáncer.

The mean age of the patients included in the study was **XXXX** years.

Table 38. Baseline patient characteristics in cohort 2

Sociodemographic		**N**	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Age				
				N (%, CI95%)
Gender	**Male**			
	Female			
Race	**Caucasian**			
	Latin			
	Asian			
	African			
	UK			
	Other			
Vital signs		**N**	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Body weight (kg)				
Height (cm)				
BMI				
Blood pressure (mmHg)				
Pulse rate (bpm)				

Respiration rate (breaths/minute)				
Temperature (ºC)				
Physical examination				**N (%, CI95%)**
Normal				
Abnormal				
Functional status				**N (%, CI95%)**
ECOG	**0**			
	1			
	2			
	3			
	4			
	5			
Tobacco smoking history				**N (%, CI95%)**
Usage	**Never smoker (<=100 cigarettes/life time)**			
	Former smoker (>=1 year)			
	Smoker			
	Unknown			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Time smoking (years)				
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Pack/year				

Table 39. Haematology and Coagulation in cohort 2

Haematology and Coagulation	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Hematocrit			
Hemoglobin			
Platelets			
Red blood cells			
White blood cells			
Neutrophils			
Lymphocytes			
Basophils			
Eosinophils			
Monocytes			

Table 40. Biochemistry in cohort 2

Biochemical	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Creatinine			
Albumin			
Direct Bilirrubin			
Indirect Bilirrubi			
Total Bilirrubin			
AST			
ALT			
Alcaline P.			
GGT			
Urea			
BUN			
Uric Acid			
LDH			
Calcium			
Magnesium			
Potassium			
Sodium			
Phosphorus			
Glucose			
Amylase			
Lipase			
Total Protein			
Creatine kinase			

Table 41. Tumor Markers in cohort 2

Tumor Markers	N	Mean, SD (CI95%)	Median (CI95%) [Range]
5-HIAA			
NSE			
CEA			
CGA			
Cortisol			
Methanephrines			
Adrenalin			
Norepinephrine			

Table 42. Serology in cohort 2

		N (%, CI95%)
HC		
	Positive	
	Negative	
HB		
	Positive	
	Negative	
HIV		
	Positive	
	Negative	

[1] Calculated percentage from the total of patients with available data

Table 43. Baseline TSH, fT3 and fT4 in overall (Thyroid Funciton) in cohort 2

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
TSH			
Free T3			
Free T4			

2.2.4.1 TUMOR DATA AND PRIOR TREATMENTS IN COHORT 2

Baseline cancer characteristics in cohort 2 will be reported in this section.

Table 44. Cancer History in cohort 2

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Time since diagnosis until Inclusion date (months)			
Time since progression disease date until Inclusion date (months)			
Time since diagnosis until progression disease date (months)			
			N (%, CI95%)
Histological type			

Well and poorly-differentiated neuroendocrine tumours of lung origin			
Anaplastic thyroiid cancer			
Adenocortical carcinoma			
Pheochromocytima and paraganglioma			
Well-differentiated neuroendocrine tumours of gastroeropancreatic origin			
Poorly differentiated neuroendocrine tumors			
TNM			
T stage			
N stage			
M stage			
Stage			
I			
II			
III			
IV			
Histological grade			
Well differentiated			
Moderately differentiated			
Poorly differentiated			
Grade			
1			
2			
3			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Ki-67 Index			
Mitotic rate			
Functional status			
Functioning			
Non Functioning			
		N (%, CI95%)	
Metastasis			
Yes			

No	
Metastasis location	
Anus	
Ascites	
…	
Study done with	
Octreoscan	
FDG-PET	

[1] Calculated percentage from the total of patients with available data

Details of previous surgery will be shown below:

Table 45. Baseline surgery in cohort 2

				N (%, CI95%)
Surgery	**Yes**			
	No			
On primary tumor	**Yes**			
	No			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Time since surgery date until Inclusion date (months)				
Time since diagnosis until surgery date (months)				

Details of previous radiotherapy will be shown below:

Table 46. Baseline Radiotherapy in cohort 2

		N (%, CI95%)
Radiotherapy	**Yes**	
	No	
Cyles of Radiotherapy	**1**	
	…	
Compulative dose	**…**	
	…	

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Time since Last cycle date until Inclusion date (months)			

Table 47. Previous treatments in cohort 2

		N (%, CI95%)
Treatment type	**Neoadjuvant**	
	Chemotherapy	
	Radiotherapy	
	Somatostatin analogs	
	Antineoplastic target therapies	
	Mitotane	
	Other	
	Adjuvant	
	Chemotherapy	
	Radiotherapy	
	Somatostatin analogs	
	Antineoplastic target therapies	
	Mitotane	
	Other	
	Line	
	1st Line	
	Chemotherapy	
	Radiotherapy	
	Somatostatin analogs	
	Antineoplastic target therapies	
	Mitotane	
	Other	
	2nd Line	
	Chemotherapy	
	Radiotherapy	
	Somatostatin analogs	
	Antineoplastic target therapies	
	Mitotane	
	Other	
	3rd Line	
	Chemotherapy	
	Radiotherapy	
	Somatostatin analogs	
	Antineoplastic target therapies	
	Mitotane	
	Other	
	Maintenance	
	Chemotherapy	
	Radiotherapy	
	Somatostatin analogs	
	Antineoplastic target therapies	
	Mitotane	

Other

Table 48. Other cancer history

		N (%, CI95%)
Other cancer history type	Type	

2.2.4.2 PREVIOUS MEDICAL HISTORY IN COHORT 2

In this section previous relevant comorbidities in cohort 2 will be shown.

Table 49. Relevant Comorbidiities in cohort 2

		N (%, CI95%)
Previous relevant illness (pathologies)	No	
	Yes	
Previous relevant illnesses (pathologies)	Relevant illness 1	
	Relevant illness 2	
	Relevant illness 3	
	…	

In this section concomitant medications will be shown.

Table 50. Prior Concomitant medication in cohort 2

		N (%, CI95%)
Prior Concomitant Medicantion	Yes	
	No	
Medication	Acaclofenac	
	…	

In this section other determinations will be shown:

Table 51. Urinalysis in cohort 2

		N (%, CI95%)
Result	Negative	
	Traces	
	1	

	2			
	3			
	4			
Bilirubin				
Color/apparence				
Leukocytes				
Urobilinogen				
Blood				
Glucose				
Nitrite				
Ketones				
Protein				
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
pH				
Specific gravity				

Table 52. Pregnancy test in cohort 2

	N (%, CI95%)
Positive	
Negative	
NA	

Table 53. Electrocardiogram in cohort 2

				N (%, CI95%)
	Normal			
Result	**Abnormal**			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
QTc				

2.2.5. BASELINE PATIENT CHARACTERISTICS IN COHORT 3

Baseline patient characteristics in cohort 3 is shown in this section. Cohort 3 tumor type is the Adrenocortical carcinoma.

The mean age of the patients included in the study was **XXXX** years.

Table 54. Baseline patient characteristics in cohort 3

Sociodemographic		**N**	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Age				
				N (%, CI95%)
Gender	**Male**			
	Female			
Race	**Caucasian**			
	Latin			
	Asian			
	African			
	UK			
	Other			
Vital signs		**N**	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Body weight (kg)				
Height (cm)				
BMI				
Blood pressure (mmHg)				
Pulse rate (bpm)				
Respiration rate (breaths/minute)				
Temperature (ºC)				
Physical examination				**N (%, CI95%)**
Normal				
Abnormal				
Functional status				**N (%, CI95%)**
ECOG	**0**			
	1			
	2			
	3			
	4			
	5			
Tobacco smoking history				**N (%, CI95%)**
Usage	**Never smoker (<=100 cigarettes/life time)**			
	Former smoker (>=1 year)			
	Smoker			
	Unknown			

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Time smoking (years)			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Pack/year			

Table 55. Haematology and Coagulation in cohort 3

Haematology and Coagulation	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Hematocrit			
Hemoglobin			
Platelets			
Red blood cells			
White blood cells			
Neutrophils			
Lymphocytes			
Basophils			
Eosinophils			
Monocytes			

Table 56. Biochemistry in cohort 3

Biochemical	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Creatinine			
Albumin			
Direct Bilirrubin			
Indirect Bilirrubi			
Total Bilirrubin			
AST			
ALT			
Alcaline P.			
GGT			
Urea			
BUN			
Uric Acid			
LDH			
Calcium			
Magnesium			
Potassium			

Sodium
Phosphorus
Glucose
Amylase
Lipase
Total Protein
Creatine kinase

Table 57. Tumor Markers in cohort 3

Tumor Markers	N	Mean, SD (CI95%)	Median (CI95%) [Range]
5-HIAA			
NSE			
CEA			
CGA			
Cortisol			
Methanephrines			
Adrenalin			
Norepinephrine			

Table 58. Serology in cohort 3

	N (%, CI95%)
HC	
Positive	
Negative	
HB	
Positive	
Negative	
HIV	
Positive	
Negative	

[1] Calculated percentage from the total of patients with available data

Table 59. Baseline TSH, fT3 and fT4 in overall (Thyroid Funciton) in cohort 3

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
TSH			
Free T3			
Free T4			

2.2.5.1 TUMOR DATA AND PRIOR TREATMENTS IN COHORT 3

Baseline cancer characteristics in cohort 3 will be reported in this section.

Table 60. Cancer History in cohort 3

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Time since diagnosis until Inclusion date (months)			
Time since progression disease date until Inclusion date (months)			
Time since diagnosis until progression disease date (months)			
			N (%, CI95%)
Histological type			
Well and poorly-differentiated neuroendocrine tumours of lung origin			
Anaplastic thyroiid cancer			
Adenocortical carcinoma			
Pheochromocytima and paraganglioma			
Well-differentiated neuroendocrine tumours of gastroeropancreatic origin			
Poorly differentiated neuroendocrine tumors			
TNM			
T stage			
N stage			
M stage			
Stage			
I			
II			

III			
IV			
Histological grade			
Well differentiated			
Moderately differentiated			
Poorly differentiated			
Grade			
1			
2			
3			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Ki-67 Index			
Mitotic rate			
Functional status			
Functioning			
Non Functioning			
		N (%, CI95%)	
Metastasis			
Yes			
No			
Metastasis location			
Anus			
Ascites			
…			
Study done with			
Octreoscan			
FDG-PET			

[1] Calculated percentage from the total of patients with available data

Details of previous surgery will be shown below:

Table 61. Baseline surgery in cohort 3

		N (%, CI95%)
Surgery	**Yes**	

	No			
On primary tumor	**Yes**			
	No			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**	
Time since surgery date until Inclusion date (months)				
Time since diagnosis until surgery date (months)				

Details of previous radiotherapy will be shown below:

Table 62. Baseline Radiotherapy in cohort 3

			N (%, CI95%)	
Radiotherapy	**Yes**			
	No			
Cyles of Radiotherapy	**1**			
	…			
Compulative dose	**…**			
	…			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**	
Time since Last cycle date until Inclusion date (months)				

Table 63. Previous treatments in cohort 3

			N (%, CI95%)
Treatment type	**Neoadjuvant**		
		Chemotherapy	
		Radiotherapy	
		Somatostatin analogs	
		Antineoplastic target therapies	
		Mitotane	
		Other	
	Adjuvant		
		Chemotherapy	
		Radiotherapy	
		Somatostatin analogs	
		Antineoplastic target therapies	
		Mitotane	

		Other
	Line	
	1st Line	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other
	2nd Line	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other
	3rd Line	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other
	Maintenance	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other

Table 64. Other cancer history

		N (%, CI95%)
Other cancer history type	**Type**	

2.2.5.2 PREVIOUS MEDICAL HISTORY IN COHORT 3

In this section previous relevant comorbidities in cohort 3 will be shown.

Table 65. Relevant Comorbidiities in cohort 3

		N (%, CI95%)
Previous relevant illness (pathologies)	**No**	
	Yes	
Previous relevant illnesses (pathologies)	**Relevant illness 1**	
	Relevant illness 2	
	Relevant illness 3	
	…	

In this section concomitant medications will be shown.

Table 66. Prior Concomitant medication in cohort 3

		N (%, CI95%)
Prior Concomitant Medicantion	**Yes**	
	No	
Medication	**Acaclofenac**	
	…	

In this section other determinations will be shown:

Table 67. Urinalysis in cohort 3

		N (%, CI95%)
Result	**Negative**	
	Traces	
	1	
	2	
	3	
	4	
Bilirubin		
Color/apparence		
Leukocytes		
Urobilinogen		
Blood		
Glucose		

Nitrite			
Ketones			
Protein			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
pH			
Specific gravity			

Table 68. Pregnancy test in cohort 3

	N (%, CI95%)
Positive	
Negative	
NA	

Table 69. Electrocardiogram in cohort 3

			N (%, CI95%)	
Result	**Normal**			
	Abnormal			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
QTc				

2.2.6. BASELINE PATIENT CHARACTERISTICS IN COHORT 4

Baseline patient characteristics in cohort 4 is shown in this section. Cohort 4 tumor type is the Pheochromocytoma and paraganglioma.

The mean age of the patients included in the study was **XXXX** years.

Table 70. Baseline patient characteristics in cohort 4

Sociodemographic		**N**	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Age				
				N (%, CI95%)
Gender	**Male**			
	Female			
Race	**Caucasian**			

	Latin			
	Asian			
	African			
	UK			
	Other			
Vital signs		**N**	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Body weight (kg)				
Height (cm)				
BMI				
Blood pressure (mmHg)				
Pulse rate (bpm)				
Respiration rate (breaths/minute)				
Temperature (ºC)				
Physical examination				**N (%, CI95%)**
Normal				
Abnormal				
Functional status				**N (%, CI95%)**
ECOG	**0**			
	1			
	2			
	3			
	4			
	5			
Tobacco smoking history				**N (%, CI95%)**
Usage	**Never smoker (<=100 cigarettes/life time)**			
	Former smoker (>=1 year)			
	Smoker			
	Unknown			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Time smoking (years)				
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Pack/year				

Table 71. Haematology and Coagulation in cohort 4

Haematology and Coagulation	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Hematocrit			

Hemoglobin
Platelets
Red blood cells
White blood cells
Neutrophils
Lymphocytes
Basophils
Eosinophils
Monocytes

Table 72. Biochemistry in cohort 4

Biochemical	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Creatinine			
Albumin			
Direct Bilirrubin			
Indirect Bilirrubi			
Total Bilirrubin			
AST			
ALT			
Alcaline P.			
GGT			
Urea			
BUN			
Uric Acid			
LDH			
Calcium			
Magnesium			
Potassium			
Sodium			
Phosphorus			
Glucose			
Amylase			
Lipase			
Total Protein			
Creatine kinase			

Table 73. Tumor Markers in cohort 4

Tumor Markers	N	Mean, SD (CI95%)	Median (CI95%) [Range]
5-HIAA			
NSE			
CEA			
CGA			
Cortisol			
Methanephrines			
Adrenalin			
Norepinephrine			

Table 74. Serology in cohort 4

	N (%, CI95%)
HC	
Positive	
Negative	
HB	
Positive	
Negative	
HIV	
Positive	
Negative	

[1] Calculated percentage from the total of patients with available data

Table 75. Baseline TSH, fT3 and fT4 in overall (Thyroid Funciton) in cohort 4

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
TSH			
Free T3			
Free T4			

2.2.6.1 TUMOR DATA AND PRIOR TREATMENTS IN COHORT 4

Baseline cancer characteristics in cohort 4 will be reported in this section.

Table 76. Cancer History in cohort 4

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Time since diagnosis until Inclusion date (months)			
Time since progression disease date until Inclusion date (months)			
Time since diagnosis until progression disease date (months)			
			N (%, CI95%)
Histological type			
Well and poorly-differentiated neuroendocrine tumours of lung origin			
Anaplastic thyroiid cancer			
Adenocortical carcinoma			
Pheochromocytima and paraganglioma			
Well-differentiated neuroendocrine tumours of gastroeropancreatic origin			
Poorly differentiated neuroendocrine tumors			
TNM			
T stage			
N stage			
M stage			
Stage			
I			
II			
III			
IV			
Histological grade			
Well differentiated			
Moderately differentiated			
Poorly differentiated			
Grade			

1				
2				
3				
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
	Ki-67 Index			
	Mitotic rate			
	Functional status			
Functioning				
Non Functioning				
				N (%, CI95%)
	Metastasis			
Yes				
No				
	Metastasis location			
Anus				
Ascites				
…				
	Study done with			
Octreoscan				
FDG-PET				

[1] Calculated percentage from the total of patients with available data

Details of previous surgery will be shown below:

Table 77. Baseline surgery in cohort 4

				N (%, CI95%)
Surgery	**Yes**			
	No			
On primary tumor	**Yes**			
	No			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Time since surgery date until Inclusion date (months)				
Time since diagnosis until surgery date (months)				

Details of previous radiotherapy will be shown below:

Table 78. Baseline Radiotherapy in cohort 4

				N (%, CI95%)
Radiotherapy	**Yes**			
	No			
Cyles of Radiotherapy	**1**			
	…			
Compulative dose	**…**			
	…			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Time since Last cycle date until Inclusion date (months)				

Table 79. Previous treatments in cohort 4

			N (%, CI95%)
Treatment type	**Neoadjuvant**		
		Chemotherapy	
		Radiotherapy	
		Somatostatin analogs	
		Antineoplastic target therapies	
		Mitotane	
		Other	
	Adjuvant		
		Chemotherapy	
		Radiotherapy	
		Somatostatin analogs	
		Antineoplastic target therapies	
		Mitotane	
		Other	
	Line		
	1st Line		
		Chemotherapy	
		Radiotherapy	
		Somatostatin analogs	
		Antineoplastic target therapies	
		Mitotane	
		Other	
	2nd Line		

		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other
	3rd Line	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other
	Maintenance	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other

Table 80. Other cancer history

		N (%, CI95%)
Other cancer history type	**Type**	

2.2.6.2 PREVIOUS MEDICAL HISTORY IN COHORT 4

In this section previous relevant comorbidities in cohort 4 will be shown.

Table 81. Relevant Comorbidiities in cohort 4

		N (%, CI95%)
Previous relevant illness (pathologies)	**No**	
	Yes	
Previous relevant illnesses (pathologies)	**Relevant illness 1**	
	Relevant illness 2	
	Relevant illness 3	
	…	

In this section concomitant medications will be shown.

Table 82. Prior Concomitant medication in cohort 4

		N (%, CI95%)
Prior Concomitant Medicantion	**Yes**	
	No	
Medication	**Acaclofenac**	
	…	

In this section other determinations will be shown:

Table 83. Urinalysis in cohort 4

			N (%, CI95%)	
Result	**Negative**			
	Traces			
	1			
	2			
	3			
	4			
Bilirubin				
Color/apparence				
Leukocytes				
Urobilinogen				
Blood				
Glucose				
Nitrite				
Ketones				
Protein				
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
pH				
Specific gravity				

Table 84. Pregnancy test in cohort 4

	N (%, CI95%)
Positive	
Negative	
NA	

Table 85. Electrocardiogram in cohort 4

			N (%, CI95%)	
Result	Normal			
	Abnormal			
		N	Mean, SD (CI95%)	Median (CI95%) [Range]
QTc				

2.2.7. BASELINE PATIENT CHARACTERISTICS IN COHORT 5

Baseline patient characteristics in cohort 5 is shown in this section. Cohort 5 tumor type is the Well-differentiated neuroendocrine tumors of gastroenteropancreatic origin (WHO grade 1 and 2).

The mean age of the patients included in the study was **XXXX** years.

Table 86. Baseline patient characteristics in cohort 5

Sociodemographic		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Age				
				N (%, CI95%)
Gender	Male			
	Female			
Race	Caucasian			
	Latin			
	Asian			
	African			
	UK			
	Other			
Vital signs		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Body weight (kg)				
Height (cm)				
BMI				
Blood pressure (mmHg)				
Pulse rate (bpm)				
Respiration rate (breaths/minute)				
Temperature (ºC)				

Physical examination				N (%, CI95%)
Normal				
Abnormal				
Functional status				N (%, CI95%)
ECOG	0			
	1			
	2			
	3			
	4			
	5			
Tobacco smoking history				N (%, CI95%)
Usage	Never smoker (<=100 cigarettes/life time)			
	Former smoker (>=1 year)			
	Smoker			
	Unknown			
		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Time smoking (years)				
		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Pack/year				

Table 87. Haematology and Coagulation in cohort 5

Haematology and Coagulation	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Hematocrit			
Hemoglobin			
Platelets			
Red blood cells			
White blood cells			
Neutrophils			
Lymphocytes			
Basophils			
Eosinophils			
Monocytes			

Table 88. Biochemistry in cohort 5

Biochemical	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Creatinine			

Albumin
Direct Bilirrubin
Indirect Bilirrubi
Total Bilirrubin
AST
ALT
Alcaline P.
GGT
Urea
BUN
Uric Acid
LDH
Calcium
Magnesium
Potassium
Sodium
Phosphorus
Glucose
Amylase
Lipase
Total Protein
Creatine kinase

Table 89. Tumor Markers in cohort 5

Tumor Markers	N	Mean, SD (CI95%)	Median (CI95%) [Range]
5-HIAA			
NSE			
CEA			
CGA			
Cortisol			
Methanephrines			
Adrenalin			
Norepinephrine			

Table 90. Serology in cohort 5

	N (%, CI95%)
HC	
Positive	
Negative	
HB	
Positive	
Negative	
HIV	
Positive	
Negative	

[1] Calculated percentage from the total of patients with available data

Table 91. Baseline TSH, fT3 and fT4 in overall (Thyroid Funciton) in cohort 5

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
TSH			
Free T3			
Free T4			

2.2.7.1 TUMOR DATA AND PRIOR TREATMENTS IN COHORT 5

Baseline cancer characteristics in cohort 5 will be reported in this section.

Table 92. Cancer History in cohort 5

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Time since diagnosis until Inclusion date (months)			
Time since progression disease date until Inclusion date (months)			
Time since diagnosis until progression disease date (months)			

				N (%, CI95%)
Histological type				
Well and poorly-differentiated neuroendocrine tumours of lung origin				
Anaplastic thyroiid cancer				
Adenocortical carcinoma				
Pheochromocytima and paraganglioma				
Well-differentiated neuroendocrine tumours of gastroeropancreatic origin				
Poorly differentiated neuroendocrine tumors				
TNM				
T stage				
N stage				
M stage				
Stage				
I				
II				
III				
IV				
Histological grade				
Well differentiated				
Moderately differentiated				
Poorly differentiated				
Grade				
1				
2				
3				
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Ki-67 Index				
Mitotic rate				
Functional status				
Functioning				
Non Functioning				
				N (%, CI95%)

Metastasis	
Yes	
No	
Metastasis location	
Anus	
Ascites	
…	
Study done with	
Octreoscan	
FDG-PET	

[1] Calculated percentage from the total of patients with available data

Details of previous surgery will be shown below:

Table 93. Baseline surgery in cohort 5

				N (%, CI95%)
Surgery	**Yes**			
	No			
On primary tumor	**Yes**			
	No			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Time since surgery date until Inclusion date (months)				
Time since diagnosis until surgery date (months)				

Details of previous radiotherapy will be shown below:

Table 94. Baseline Radiotherapy in cohort 5

		N (%, CI95%)
Radiotherapy	**Yes**	
	No	
Cyles of Radiotherapy	**1**	
	…	

Compulative dose	**…**		
	…		
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Time since Last cycle date until Inclusion date (months)			

Table 95. Previous treatments in cohort 5

						N (%, CI95%)
Treatment type	**Neoadjuvant**					
		Chemotherapy				
		Radiotherapy				
		Somatostatin analogs				
		Antineoplastic target therapies				
		Mitotane				
		Other				
	Adjuvant					
		Chemotherapy				
		Radiotherapy				
		Somatostatin analogs				
		Antineoplastic target therapies				
		Mitotane				
		Other				
	Line					
		1st Line				
		Chemotherapy				
		Radiotherapy				
		Somatostatin analogs				
		Antineoplastic target therapies				
		Mitotane				
		Other				
		2nd Line				
		Chemotherapy				
		Radiotherapy				
		Somatostatin analogs				
		Antineoplastic target therapies				
		Mitotane				
		Other				
		3rd Line				
		Chemotherapy				
		Radiotherapy				
		Somatostatin analogs				
		Antineoplastic target therapies				
		Mitotane				
		Other				
	Maintenance					
		Chemotherapy				
		Radiotherapy				

	Somatostatin analogs
	Antineoplastic target therapies
	Mitotane
	Other

Table 96. Other cancer history

		N (%, CI95%)
Other cancer history type	**Type**	

2.2.7.2 PREVIOUS MEDICAL HISTORY IN COHORT 5

In this section previous relevant comorbidities in cohort 5 will be shown.

Table 97. Relevant Comorbidiities in cohort 5

		N (%, CI95%)
Previous relevant illness (pathologies)	**No**	
	Yes	
Previous relevant illnesses (pathologies)	**Relevant illness 1**	
	Relevant illness 2	
	Relevant illness 3	
	…	

In this section concomitant medications will be shown.

Table 98. Prior Concomitant medication in cohort 5

		N (%, CI95%)
Prior Concomitant Medicantion	**Yes**	
	No	
Medication	**Acaclofenac**	
	…	

In this section other determinations will be shown:

Table 99. Urinalysis in cohort 5

		N (%, CI95%)
Result	**Negative**	

	Traces			
	1			
	2			
	3			
	4			
Bilirubin				
Color/apparence				
Leukocytes				
Urobilinogen				
Blood				
Glucose				
Nitrite				
Ketones				
Protein				
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
pH				
Specific gravity				

Table 100. Pregnancy test in cohort 5

	N (%, CI95%)
Positive	
Negative	
NA	

Table 101. Electrocardiogram in cohort 5

		N (%, CI95%)		
	Normal			
Result	**Abnormal**			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
QTc				

2.2.8. BASELINE PATIENT CHARACTERISTICS IN COHORT 6

Baseline patient characteristics in cohort 6 is shown in this section. Cohort 6 tumor type is the Poorly differentiated neuroendocrine tumors (WHO grade 3), excluding small cell lung cancer.

The mean age of the patients included in the study was **XXXX** years.

Table 102. Baseline patient characteristics in cohort 6

Sociodemographic		**N**	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Age				
				N (%, CI95%)
Gender	**Male**			
	Female			
Race	**Caucasian**			
	Latin			
	Asian			
	African			
	UK			
	Other			
Vital signs		**N**	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Body weight (kg)				
Height (cm)				
BMI				
Blood pressure (mmHg)				
Pulse rate (bpm)				
Respiration rate (breaths/minute)				
Temperature (ºC)				
Physical examination				**N (%, CI95%)**
Normal				
Abnormal				
Functional status				**N (%, CI95%)**
ECOG	**0**			
	1			
	2			
	3			
	4			
	5			
Tobacco smoking history				**N (%, CI95%)**
Usage	**Never smoker (<=100 cigarettes/life time)**			

Former smoker (>=1 year)			
Smoker			
Unknown			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Time smoking (years)			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Pack/year			

Table 103. Haematology and Coagulation in cohort 6

Haematology and Coagulation	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Hematocrit			
Hemoglobin			
Platelets			
Red blood cells			
White blood cells			
Neutrophils			
Lymphocytes			
Basophils			
Eosinophils			
Monocytes			

Table 104. Biochemistry in cohort 6

Biochemical	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Creatinine			
Albumin			
Direct Bilirrubin			
Indirect Bilirrubi			
Total Bilirrubin			
AST			
ALT			
Alcaline P.			
GGT			
Urea			
BUN			
Uric Acid			
LDH			

Calcium
Magnesium
Potassium
Sodium
Phosphorus
Glucose
Amylase
Lipase
Total Protein
Creatine kinase

Table 105. Tumor Markers in cohort 6

Tumor Markers	N	Mean, SD (CI95%)	Median (CI95%) [Range]
5-HIAA			
NSE			
CEA			
CGA			
Cortisol			
Methanephrines			
Adrenalin			
Norepinephrine			

Table 106. Serology in cohort 6

	N (%, CI95%)
HC	
Positive	
Negative	
HB	
Positive	
Negative	
HIV	
Positive	
Negative	

[1] Calculated percentage from the total of patients with available data

Table 107. Baseline TSH, fT3 and fT4 in overall (Thyroid Funciton) in cohort 6

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
TSH			
Free T3			
Free T4			

2.2.8.1 TUMOR DATA AND PRIOR TREATMENTS IN COHORT 6

Baseline cancer characteristics in cohort 6 will be reported in this section.

Table 108. Cancer History in cohort 6

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Time since diagnosis until Inclusion date (months)			
Time since progression disease date until Inclusion date (months)			
Time since diagnosis until progression disease date (months)			
			N (%, CI95%)
Histological type			
Well and poorly-differentiated neuroendocrine tumours of lung origin			
Anaplastic thyroiid cancer			
Adenocortical carcinoma			
Pheochromocytima and paraganglioma			
Well-differentiated neuroendocrine tumours of gastroeropancreatic origin			
Poorly differentiated neuroendocrine tumors			
TNM			
T stage			
N stage			

M stage			
Stage			
I			
II			
III			
IV			
Histological grade			
Well differentiated			
Moderately differentiated			
Poorly differentiated			
Grade			
1			
2			
3			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Ki-67 Index			
Mitotic rate			
Functional status			
Functioning			
Non Functioning			
		N (%, CI95%)	
Metastasis			
Yes			
No			
Metastasis location			
Anus			
Ascites			
…			
Study done with			
Octreoscan			
FDG-PET			

[1] Calculated percentage from the total of patients with available data

Details of previous surgery will be shown below:

Table 109. Baseline surgery in cohort 6

				N (%, CI95%)
Surgery	**Yes**			
	No			
On primary tumor	**Yes**			
	No			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Time since surgery date until Inclusion date (months)				
Time since diagnosis until surgery date (months)				

Details of previous radiotherapy will be shown below:

Table 110. Baseline Radiotherapy in cohort 6

				N (%, CI95%)
Radiotherapy	**Yes**			
	No			
Cyles of Radiotherapy	**1**			
	…			
Compulative dose	**…**			
	…			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Time since Last cycle date until Inclusion date (months)				

Table 111. Previous treatments in cohort 6

		N (%, CI95%)
Treatment type	**Neoadjuvant**	
	Chemotherapy	
	Radiotherapy	
	Somatostatin analogs	
	Antineoplastic target therapies	
	Mitotane	

		Other
	Adjuvant	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other
	Line	
	1st Line	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other
	2nd Line	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other
	3rd Line	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other
	Maintenance	
		Chemotherapy
		Radiotherapy
		Somatostatin analogs
		Antineoplastic target therapies
		Mitotane
		Other

Table 112. Other cancer history

		N (%, CI95%)
Other cancer history type	**Type**	

2.2.8.2 PREVIOUS MEDICAL HISTORY IN COHORT 6

In this section previous relevant comorbidities in cohort 6 will be shown.

Table 113. Relevant Comorbidiities in cohort 6

		N (%, CI95%)
Previous relevant illness (pathologies)	**No**	
	Yes	
Previous relevant illnesses (pathologies)	**Relevant illness 1**	
	Relevant illness 2	
	Relevant illness 3	
	…	

In this section concomitant medications will be shown.

Table 114. Prior Concomitant medication in cohort 6

		N (%, CI95%)
Prior Concomitant Medicantion	**Yes**	
	No	
Medication	**Acaclofenac**	
	…	

In this section other determinations will be shown:

Table 115. Urinalysis in cohort 6

		N (%, CI95%)
Result	**Negative**	
	Traces	
	1	
	2	
	3	
	4	
Bilirubin		
Color/apparence		
Leukocytes		
Urobilinogen		
Blood		
Glucose		
Nitrite		
Ketones		

Protein			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
pH			
Specific gravity			

Table 116. Pregnancy test in cohort 6

	N (%, CI95%)
Positive	
Negative	
NA	

Table 117. Electrocardiogram in cohort 6

		N (%, CI95%)		
Result	**Normal**			
	Abnormal			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
QTc				

2.3. TREATMENT EXPOSURE

All the subjects will be treated with the combination until disease progression, unacceptable toxicity, or patient consent withdrawal (whichever occurs first) according to section 7 of the protocol.

- Cabozantinib 40 mg or 20 mg tablets, oral administration once daily continuously.
- Atezolizumab 1200 mg administered intravenously (IV) every three weeks (cycle).

Dosing scheme:

- Level 0 (starting dose): cabozantinib 40 mg qd + atezolizumab 1200 mg iv every 21 days (one cycle).
- Level -1: cabozantinib 20 mg qd + atezolizumab 1200 mg iv every 21 days (one cycle).

Details of treatment compliance will be shown in the following table:

Table 118. Cabozantinib compliance

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Number of Cabozantinb cycles			
			N (%, CI95%)
Total number of cycles with Cabozantinb	**1 cycle**		
	2 cycles		
	3 cycles		
	4 cycles		
	…		
	20 cycles		
Patients with reductions	**No**		
	Yes (at least 1 reduction)		
Total number of dose reductions	**1 reduction**		
	2 reductions		
	3 reductions		
	4 reductions		
	5 reductions		
	6 reductions		
Reason for reductions	**Reason 1**		
	Reason 2		
	Reason 3		
	…		
Patients with interruptions	**No**		
	Yes (at least 1 interruption)		
Total number of treatment interruption	**1 interruption**		
	…		
Reason for treatment interruption	**Reason 1**		
	Reason 2		
	Reason 3		
	…		
Interruption	**Temporary**		
	Permanent		
Total number of treatment omissions	**1 intake**		
	…		

		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Length of temporary interruption (weeks)				
				N (%, CI95%)
Medicine bottle NOT delivered	**In 1 cycle**			
	In 2 cycle			
	…			
Reason for medicine bottle NOT delivered	**Reason 1**			
	Reason 2			
	Reason 3			

If any patient did not receive Cabozantinib it will be listed below along with his/her details.

Table 119. List of patients that did not receive Cabozantinib

Patient ID code	Total number of cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle …
	0						

Details of Atezolizumab compliance will be shown in the following table:

Table 120. Atezolizumab compliance

		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Number of Atezolizumab cycles				
				N (%, CI95%)
Total number of cycles	**1 cycle**			
	2 cycles			
	3 cycles			
	4 cycles			
	…			
	20 cycles			
Patients with interruptions	**No**			
	Yes (at least 1 interruption)			
Medicine bottle NOT delivered	**1 interruption**			
	…			
Reason for treatment interruption	**Reason 1**			
	Reason 2			
	Reason 3			
	…			
Interruptions	**Temporary**			
	Permanent			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Length of temporary interruption (weeks)				

If any patient did not receive Atezolizumab it will be listed below along with his/her details.

Table 121. List of patients that did not receive Atezolizumab

Patient ID code	Total number of Olparaib cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle …
	0						

2.3.1. TREATMENT EXPOSURE IN COHORT 1

Details of treatment compliance in cohort 1 will be shown in the following table:

Table 122. Cabozantinib compliance in cohort 1

		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Number of Cabozantinb cycles				
				N (%, CI95%)
Total number of cycles with Cabozantinb	**1 cycle**			
	2 cycles			
	3 cycles			
	4 cycles			
	…			
	20 cycles			
Patients with reductions	**No**			
	Yes (at least 1 reduction)			
Total number of dose reductions	**1 reduction**			
	2 reductions			
	3 reductions			
	4 reductions			
	5 reductions			
	6 reductions			
Reason for reductions	**Reason 1**			
	Reason 2			
	Reason 3			
	…			
Patients with interruptions	**No**			
	Yes (at least 1 interruption)			
Total number of treatment interruption	**1 interruption**			
	…			
Reason for treatment interruption	**Reason 1**			
	Reason 2			
	Reason 3			
	…			
Interruption	**Temporary**			
	Permanent			
Total number of treatment omissions	**1 intake**			
	…			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Length of temporary interruption (weeks)				
				N (%, CI95%)
Medicine bottle NOT delivered	**In 1 cycle**			
	In 2 cycle			
	…			
Reason for medicine bottle NOT delivered	**Reason 1**			
	Reason 2			
	Reason 3			

If any patient did not receive Cabozantinib it will be listed below along with his/her details.

Table 123. List of patients that did not receive Cabozantinib in cohort 1

Patient ID code	Total number of cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle …
	0						

Details of Atezolizumab compliance will be shown in the following table:

Table 124. Atezolizumab compliance in cohort 1

		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Number of Atezolizumab cycles				
				N (%, CI95%)
Total number of cycles	**1 cycle**			
	2 cycles			
	3 cycles			
	4 cycles			
	…			
	20 cycles			
Patients with interruptions	**No**			
	Yes (at least 1 interruption)			
Medicine bottle NOT delivered	**1 interruption**			
	…			
Reason for treatment interruption	**Reason 1**			
	Reason 2			
	Reason 3			
	…			
Interruptions	**Temporary**			
	Permanent			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Length of temporary interruption (weeks)				

If any patient did not receive Atezolizumab it will be listed below along with his/her details.

Table 125. List of patients that did not receive Atezolizumab in cohort 1

Patient ID code	Total number of Olparaib cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle …
	0						

2.3.2. TREATMENT EXPOSURE IN COHORT 2

Details of treatment compliance in cohort 2 will be shown in the following table:

Table 126. Cabozantinib compliance in cohort 2

		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Number of Cabozantinb cycles				
				N (%, CI95%)
Total number of cycles with Cabozantinb	**1 cycle**			
	2 cycles			
	3 cycles			

	4 cycles			
	…			
	20 cycles			
Patients with reductions	**No**			
	Yes (at least 1 reduction)			
Total number of dose reductions	**1 reduction**			
	2 reductions			
	3 reductions			
	4 reductions			
	5 reductions			
	6 reductions			
Reason for reductions	**Reason 1**			
	Reason 2			
	Reason 3			
	…			
Patients with interruptions	**No**			
	Yes (at least 1 interruption)			
Total number of treatment interruption	**1 interruption**			
	…			
Reason for treatment interruption	**Reason 1**			
	Reason 2			
	Reason 3			
	…			
Interruption	**Temporary**			
	Permanent			
Total number of treatment omissions	**1 intake**			
	…			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**	
Length of temporary interruption (weeks)				
				N (%, CI95%)
Medicine bottle NOT delivered	**In 1 cycle**			
	In 2 cycle			
	…			
Reason for medicine bottle NOT delivered	**Reason 1**			
	Reason 2			
	Reason 3			

If any patient did not receive Cabozantinib it will be listed below along with his/her details.

Table 127. List of patients that did not receive Cabozantinib in cohort 2

Patient ID code	Total number of cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle …
	0						

Details of Atezolizumab compliance will be shown in the following table:

Table 128. Atezolizumab compliance in cohort 2

	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**	
Number of Atezolizumab cycles				
				N (%, CI95%)
Total number of cycles	**1 cycle**			
	2 cycles			

	3 cycles			
	4 cycles			
	…			
	20 cycles			
Patients with interruptions	**No**			
	Yes (at least 1 interruption)			
Medicine bottle NOT delivered	**1 interruption**			
	…			
Reason for treatment interruption	**Reason 1**			
	Reason 2			
	Reason 3			
	…			
Interruptions	**Temporary**			
	Permanent			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**	
Length of temporary interruption (weeks)				

If any patient did not receive Atezolizumab it will be listed below along with his/her details.

Table 129. List of patients that did not receive Atezolizumab in cohort 2

Patient ID code	Total number of Olparaib cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle …
	0						

2.3.3. TREATMENT EXPOSURE IN COHORT 3

Details of treatment compliance in cohort 3 will be shown in the following table:

Table 130. Cabozantinib compliance in cohort 3

		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Number of Cabozantinb cycles				
				N (%, CI95%)
Total number of cycles with Cabozantinb	**1 cycle**			
	2 cycles			
	3 cycles			
	4 cycles			
	…			
	20 cycles			
Patients with reductions	**No**			
	Yes (at least 1 reduction)			
Total number of dose reductions	**1 reduction**			
	2 reductions			
	3 reductions			
	4 reductions			
	5 reductions			
	6 reductions			

Reason for reductions	**Reason 1**		
	Reason 2		
	Reason 3		
	…		
Patients with interruptions	**No**		
	Yes (at least 1 interruption)		
Total number of treatment interruption	**1 interruption**		
	…		
Reason for treatment interruption	**Reason 1**		
	Reason 2		
	Reason 3		
	…		
Interruption	**Temporary**		
	Permanent		
Total number of treatment omissions	**1 intake**		
	…		
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Length of temporary interruption (weeks)			
			N (%, CI95%)
Medicine bottle NOT delivered	**In 1 cycle**		
	In 2 cycle		
	…		
Reason for medicine bottle NOT delivered	**Reason 1**		
	Reason 2		
	Reason 3		

If any patient did not receive Cabozantinib it will be listed below along with his/her details.

Table 131. List of patients that did not receive Cabozantinib in cohort 3

Patient ID code	Total number of cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle …
	0						

Details of Atezolizumab compliance will be shown in the following table:

Table 132. Atezolizumab compliance in cohort 3

	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Number of Atezolizumab cycles			
			N (%, CI95%)
Total number of cycles	**1 cycle**		
	2 cycles		
	3 cycles		
	4 cycles		
	…		
	20 cycles		
Patients with interruptions	**No**		
	Yes (at least 1 interruption)		
Medicine bottle NOT delivered	**1 interruption**		
	…		
Reason for treatment interruption	**Reason 1**		
	Reason 2		
	Reason 3		

	…			
Interruptions	**Temporary**			
	Permanent			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**	
Length of temporary interruption (weeks)				

If any patient did not receive Atezolizumab it will be listed below along with his/her details.

Table 133. List of patients that did not receive Atezolizumab in cohort 3

Patient ID code	Total number of Olparaib cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle …
	0						

2.3.4. TREATMENT EXPOSURE IN COHORT 4

Details of treatment compliance in cohort 4 will be shown in the following table:

Table 134. Cabozantinib compliance in cohort 4

	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Number of Cabozantinb cycles			
			N (%, CI95%)
Total number of cycles with Cabozantinb	**1 cycle**		
	2 cycles		
	3 cycles		
	4 cycles		
	…		
	20 cycles		
Patients with reductions	**No**		
	Yes (at least 1 reduction)		
Total number of dose reductions	**1 reduction**		
	2 reductions		
	3 reductions		
	4 reductions		
	5 reductions		
	6 reductions		
Reason for reductions	**Reason 1**		
	Reason 2		
	Reason 3		
	…		
Patients with interruptions	**No**		
	Yes (at least 1 interruption)		
Total number of treatment interruption	**1 interruption**		
	…		
Reason for treatment interruption	**Reason 1**		
	Reason 2		
	Reason 3		
	…		
Interruption	**Temporary**		
	Permanent		
Total number of treatment omissions	**1 intake**		
	…		
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**

Length of temporary interruption (weeks)		
		N (%, CI95%)
Medicine bottle NOT delivered	**In 1 cycle**	
	In 2 cycle	
	…	
Reason for medicine bottle NOT delivered	**Reason 1**	
	Reason 2	
	Reason 3	

If any patient did not receive Cabozantinib it will be listed below along with his/her details.

Table 135. List of patients that did not receive Cabozantinib in cohort 4

Patient ID code	Total number of cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle …
	0						

Details of Atezolizumab compliance will be shown in the following table:

Table 136. Atezolizumab compliance in cohort 4

		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Number of Atezolizumab cycles				
				N (%, CI95%)
Total number of cycles	**1 cycle**			
	2 cycles			
	3 cycles			
	4 cycles			
	…			
	20 cycles			
Patients with interruptions	**No**			
	Yes (at least 1 interruption)			
Medicine bottle NOT delivered	**1 interruption**			
	…			
Reason for treatment interruption	**Reason 1**			
	Reason 2			
	Reason 3			
	…			
Interruptions	**Temporary**			
	Permanent			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Length of temporary interruption (weeks)				

If any patient did not receive Atezolizumab it will be listed below along with his/her details.

Table 137. List of patients that did not receive Atezolizumab in cohort 4

Patient ID code	Total number of Olparaib cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle …
	0						

2.3.5. TREATMENT EXPOSURE IN COHORT 5

Details of treatment compliance in cohort 5 will be shown in the following table:

Table 138. Cabozantinib compliance in cohort 5

		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Number of Cabozantinb cycles				
				N (%, CI95%)
Total number of cycles with Cabozantinb	**1 cycle**			
	2 cycles			
	3 cycles			
	4 cycles			
	…			
	20 cycles			
Patients with reductions	**No**			
	Yes (at least 1 reduction)			
Total number of dose reductions	**1 reduction**			
	2 reductions			
	3 reductions			
	4 reductions			
	5 reductions			
	6 reductions			
Reason for reductions	**Reason 1**			
	Reason 2			
	Reason 3			
	…			
Patients with interruptions	**No**			
	Yes (at least 1 interruption)			
Total number of treatment interruption	**1 interruption**			
	…			
Reason for treatment interruption	**Reason 1**			
	Reason 2			
	Reason 3			
	…			
Interruption	**Temporary**			
	Permanent			
Total number of treatment omissions	**1 intake**			
	…			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Length of temporary interruption (weeks)				
				N (%, CI95%)
Medicine bottle NOT delivered	**In 1 cycle**			
	In 2 cycle			
	…			
Reason for medicine bottle NOT delivered	**Reason 1**			
	Reason 2			
	Reason 3			

If any patient did not receive Cabozantinib it will be listed below along with his/her details.

Table 139. List of patients that did not receive Cabozantinib in cohort 5

Patient ID code	Total number of cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle …
	0						

Details of Atezolizumab compliance will be shown in the following table:

Table 140. Atezolizumab compliance in cohort 5

		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Number of Atezolizumab cycles				
				N (%, CI95%)
Total number of cycles	**1 cycle**			
	2 cycles			
	3 cycles			
	4 cycles			
	…			
	20 cycles			
Patients with interruptions	**No**			
	Yes (at least 1 interruption)			
Medicine bottle NOT delivered	**1 interruption**			
	…			
Reason for treatment interruption	**Reason 1**			
	Reason 2			
	Reason 3			
	…			
Interruptions	**Temporary**			
	Permanent			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Length of temporary interruption (weeks)				

If any patient did not receive Atezolizumab it will be listed below along with his/her details.

Table 141. List of patients that did not receive Atezolizumab in cohort 5

Patient ID code	Total number of Olparaib cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle …
	0						

2.3.6. TREATMENT EXPOSURE IN COHORT 6

Details of treatment compliance in cohort 6 will be shown in the following table:

Table 142. Cabozantinib compliance in cohort 6

		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Number of Cabozantinb cycles				
				N (%, CI95%)
Total number of cycles with Cabozantinb	**1 cycle**			
	2 cycles			
	3 cycles			
	4 cycles			
	…			
	20 cycles			
Patients with reductions	**No**			
	Yes (at least 1 reduction)			
Total number of dose reductions	**1 reduction**			
	2 reductions			
	3 reductions			
	4 reductions			
	5 reductions			
	6 reductions			
Reason for reductions	**Reason 1**			
	Reason 2			
	Reason 3			
	…			
Patients with interruptions	**No**			
	Yes (at least 1 interruption)			
Total number of treatment interruption	**1 interruption**			
	…			
Reason for treatment interruption	**Reason 1**			
	Reason 2			
	Reason 3			
	…			
Interruption	**Temporary**			
	Permanent			
Total number of treatment omissions	**1 intake**			
	…			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Length of temporary interruption (weeks)				
				N (%, CI95%)
Medicine bottle NOT delivered	**In 1 cycle**			
	In 2 cycle			
	…			
Reason for medicine bottle NOT delivered	**Reason 1**			
	Reason 2			
	Reason 3			

If any patient did not receive Cabozantinib it will be listed below along with his/her details.

Table 143. List of patients that did not receive Cabozantinib in cohort 6

Patient ID code	Total number of cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle …
	0						

Details of Atezolizumab compliance will be shown in the following table:

Table 144. Atezolizumab compliance in cohort 6

		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Number of Atezolizumab cycles				
				N (%, CI95%)
Total number of cycles	**1 cycle**			
	2 cycles			
	3 cycles			
	4 cycles			
	…			
	20 cycles			
Patients with interruptions	**No**			
	Yes (at least 1 interruption)			
Medicine bottle NOT delivered	**1 interruption**			
	…			
Reason for treatment interruption	**Reason 1**			
	Reason 2			
	Reason 3			
	…			
Interruptions	**Temporary**			
	Permanent			
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Length of temporary interruption (weeks)				

If any patient did not receive Atezolizumab it will be listed below along with his/her details.

Table 145. List of patients that did not receive Atezolizumab in cohort 6

Patient ID code	Total number of Olparaib cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle …
	0						

2.3.7. WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT

Patient is, at any time, free to withdraw from study (investigational product and study assessments), without prejudice to further treatment (withdrawal of consent). Subjects that choose to withdraw early from the study will be voluntarily surveyed for reasons for withdrawal, including information of possible presence of any adverse events. If possible, he/she will be seen and assessed by an investigator.

Adverse events will be followed up and all study material (if any) should be returned by the patient. 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. Withdrawn patient will not be replaced.

If any patient stopped the study treatment prematurely (before the 6 cycles), it will be listed below along with his/her details.

Table 146. Study treatment premature interruption

		N (%, CI95%)
Study treatment premature interruption	**Yes**	
	No	
Reasons for study treatment premature interruption	**Reason 1**	
	Reason 2	
	Reason 3	
	…	

Details of the end of treatment reasons will be shown in the following table.

Table 147. Reason for end of treatment for Cabozantinib

			N (%, CI95%)
Reasons for end of treatment	**Progression**		
	Unaccepted toxicity		
	Details of toxicities	**Toxicity 1**	
		Toxicity 2	
		….	
	AE not related to the treatment study		
	Investigator decision		
	Details of investigator decisions	**Investigator decision 1**	
		Investigator decision 1	
		…	
	Withdraw consent		
	Other reasons		
	Details of other reasons	**Other reasons 1**	
		Other reasons 2	
		…	
Patients with treatment completion			

Table 148. Reason for end of treatment for Atezolizumab

			N (%, CI95%)
Reasons for end of treatment	**Progression**		
	Unaccepted toxicity		
	Details of toxicities	**Toxicity 1**	
		Toxicity 2	
		….	
	AE not related to the treatment study		
	Investigator decision		
	Details of investigator decisions	**Investigator decision 1**	
		Investigator decision 1	
		…	
	Withdraw consent		
	Other reasons		
	Details of other reasons	**Other reasons 1**	
		Other reasons 2	
		…	
Patients with treatment completion			

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Induction cycles received			

The median of the study treatment was **XXX** weeks:

Table 149. Study treatment length

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Length of study treatment (months)			

2.3.7.1 WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT IN COHORT 1

Details of the withdrawal of patients in cohort 1 are shown below:

Table 150. Study treatment premature interruption in cohort 1

		N (%, CI95%)
Study treatment premature interruption	**Yes**	
	No	
Reasons for study treatment premature interruption	**Reason 1**	
	Reason 2	
	Reason 3	
	…	

Details of the end of treatment reasons will be shown in the following table.

Table 151. Reason for end of treatment for Cabozantinib in cohort 1

			N (%, CI95%)
Reasons for end of treatment	Progression		
	Unaccepted toxicity		
	Details of toxicities	Toxicity 1	
		Toxicity 2	
		….	
	AE not related to the treatment study		
	Investigator decision		
	Details of investigator decisions	Investigator decision 1	
		Investigator decision 1	
		…	
	Withdraw consent		
	Other reasons		
	Details of other reasons	Other reasons 1	
		Other reasons 2	
		…	
Patients with treatment completion			

Table 152. Reason for end of treatment for Atezolizumab in cohort 1

				N (%, CI95%)
Reasons for end of treatment	Progression			
	Unaccepted toxicity			
	Details of toxicities	Toxicity 1		
		Toxicity 2		
		….		
	AE not related to the treatment study			
	Investigator decision			
	Details of investigator decisions	Investigator decision 1		
		Investigator decision 1		
		…		
	Withdraw consent			
	Other reasons			
	Details of other reasons	Other reasons 1		
		Other reasons 2		
		…		
Patients with treatment completion				
		N	Mean, SD (CI95%)	Median (CI95%) [Range]
Induction cycles received				

The median of the study treatment was **XXX** weeks:

Table 153. Study treatment length in cohort 1

	N	Mean, SD (CI95%)	Median (CI95%) [Range]

Length of study treatment (months)

2.3.7.2 WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT IN COHORT 2

Details of the withdrawal of patients in cohort 2 are shown below:

Table 154. Study treatment premature interruption in cohort 2

		N (%, CI95%)
Study treatment premature interruption	**Yes**	
	No	
Reasons for study treatment premature interruption	**Reason 1**	
	Reason 2	
	Reason 3	
	…	

Details of the end of treatment reasons will be shown in the following table.

Table 155. Reason for end of treatment for Cabozantinib in cohort 2

			N (%, CI95%)
Reasons for end of treatment	**Progression**		
	Unaccepted toxicity		
	Details of toxicities	**Toxicity 1**	
		Toxicity 2	
		….	
	AE not related to the treatment study		
	Investigator decision		
	Details of investigator decisions	**Investigator decision 1**	
		Investigator decision 1	
		…	
	Withdraw consent		
	Other reasons		
	Details of other reasons	**Other reasons 1**	
		Other reasons 2	
		…	
Patients with treatment completion			

Table 156. Reason for end of treatment for Atezolizumab in cohort 2

			N (%, CI95%)
Reasons for end of treatment	**Progression**		
	Unaccepted toxicity		
	Details of toxicities	**Toxicity 1**	
		Toxicity 2	
		….	

	AE not related to the treatment study			
	Investigator decision			
	Details of investigator decisions	**Investigator decision 1**		
		Investigator decision 1		
		…		
	Withdraw consent			
	Other reasons			
	Details of other reasons	**Other reasons 1**		
		Other reasons 2		
		…		
Patients with treatment completion				
		N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Induction cycles received				

The median of the study treatment was **XXX** weeks:

Table 157. Study treatment length in cohort 2

	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Length of study treatment (months)			

2.3.7.3 WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT IN COHORT 3

Details of the withdrawal of patients in cohort 3 are shown below:

Table 158. Study treatment premature interruption in cohort 3

		N (%, CI95%)
Study treatment premature interruption	**Yes**	
	No	
Reasons for study treatment premature interruption	**Reason 1**	
	Reason 2	
	Reason 3	
	…	

Details of the end of treatment reasons will be shown in the following table.

Table 159. Reason for end of treatment for Cabozantinib in cohort 3

			N (%, CI95%)
Reasons for end of treatment	**Progression**		
	Unaccepted toxicity		
	Details of toxicities	**Toxicity 1**	
		Toxicity 2	

		….
	AE not related to the treatment study	
	Investigator decision	
	Details of investigator decisions	**Investigator decision 1**
		Investigator decision 1
		…
	Withdraw consent	
	Other reasons	
	Details of other reasons	**Other reasons 1**
		Other reasons 2
		…
Patients with treatment completion		

Table 160. Reason for end of treatment for Atezolizumab in cohort 3

			N (%, CI95%)
Reasons for end of treatment	**Progression**		
	Unaccepted toxicity		
	Details of toxicities	**Toxicity 1**	
		Toxicity 2	
		….	
	AE not related to the treatment study		
	Investigator decision		
	Details of investigator decisions	**Investigator decision 1**	
		Investigator decision 1	
		…	
	Withdraw consent		
	Other reasons		
	Details of other reasons	**Other reasons 1**	
		Other reasons 2	
		…	
Patients with treatment completion			
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Induction cycles received			

The median of the study treatment was **XXX** weeks:

Table 161. Study treatment length in cohort 3

	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Length of study treatment (months)			

2.3.7.4 WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT IN COHORT 4

Details of the withdrawal of patients in cohort 4 are shown below:

Table 162. Study treatment premature interruption in cohort 4

		N (%, CI95%)
Study treatment premature interruption	**Yes**	
	No	
Reasons for study treatment premature interruption	**Reason 1**	
	Reason 2	
	Reason 3	
	…	

Details of the end of treatment reasons will be shown in the following table.

Table 163. Reason for end of treatment for Cabozantinib in cohort 4

			N (%, CI95%)
Reasons for end of treatment	**Progression**		
	Unaccepted toxicity		
	Details of toxicities	**Toxicity 1**	
		Toxicity 2	
		….	
	AE not related to the treatment study		
	Investigator decision		
	Details of investigator decisions	**Investigator decision 1**	
		Investigator decision 1	
		…	
	Withdraw consent		
	Other reasons		
	Details of other reasons	**Other reasons 1**	
		Other reasons 2	
		…	
Patients with treatment completion			

Table 164. Reason for end of treatment for Atezolizumab in cohort 4

			N (%, CI95%)
Reasons for end of treatment	**Progression**		
	Unaccepted toxicity		
	Details of toxicities	**Toxicity 1**	
		Toxicity 2	
		….	
	AE not related to the treatment study		
	Investigator decision		
	Details of investigator decisions	**Investigator decision 1**	

		Investigator decision 1		
		…		
	Withdraw consent			
	Other reasons			
	Details of other reasons	**Other reasons 1**		
		Other reasons 2		
		…		
Patients with treatment completion				
	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**	
Induction cycles received				

The median of the study treatment was **XXX** weeks:

Table 165. Study treatment length in cohort 4

	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Length of study treatment (months)			

2.3.7.5 WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT IN COHORT 5

Details of the withdrawal of patients in cohort 5 are shown below:

Table 166. Study treatment premature interruption in cohort 5

		N (%, CI95%)
Study treatment premature interruption	**Yes**	
	No	
Reasons for study treatment premature interruption	**Reason 1**	
	Reason 2	
	Reason 3	
	…	

Details of the end of treatment reasons will be shown in the following table.

Table 167. Reason for end of treatment for Cabozantinib in cohort 5

			N (%, CI95%)
Reasons for end of treatment	**Progression**		
	Unaccepted toxicity		
	Details of toxicities	**Toxicity 1**	
		Toxicity 2	
		….	
	AE not related to the treatment study		
	Investigator decision		
	Details of investigator decisions	**Investigator decision 1**	

		Investigator decision 1
		…
	Withdraw consent	
	Other reasons	
	Details of other reasons	**Other reasons 1**
		Other reasons 2
		…
Patients with treatment completion		

Table 168. Reason for end of treatment for Atezolizumab in cohort 5

			N (%, CI95%)
Reasons for end of treatment	**Progression**		
	Unaccepted toxicity		
	Details of toxicities	**Toxicity 1**	
		Toxicity 2	
		….	
	AE not related to the treatment study		
	Investigator decision		
	Details of investigator decisions	**Investigator decision 1**	
		Investigator decision 1	
		…	
	Withdraw consent		
	Other reasons		
	Details of other reasons	**Other reasons 1**	
		Other reasons 2	
		…	
Patients with treatment completion			

	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Induction cycles received			

The median of the study treatment was **XXX** weeks:

Table 169. Study treatment length in cohort 5

	N	**Mean, SD (CI95%)**	**Median (CI95%) [Range]**
Length of study treatment (months)			

2.3.7.6 WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT IN COHORT 6

Details of the withdrawal of patients in cohort 6 are shown below:

Table 170. Study treatment premature interruption in cohort 6

	N (%, CI95%)
Yes	

Study treatment premature interruption	**No**
Reasons for study treatment premature interruption	**Reason 1**
	Reason 2
	Reason 3
	…

Details of the end of treatment reasons will be shown in the following table.

Table 171. Reason for end of treatment for Cabozantinib in cohort 6

			N (%, CI95%)
Reasons for end of treatment	**Progression**		
	Unaccepted toxicity		
	Details of toxicities	**Toxicity 1**	
		Toxicity 2	
		….	
	AE not related to the treatment study		
	Investigator decision		
	Details of investigator decisions	**Investigator decision 1**	
		Investigator decision 1	
		…	
	Withdraw consent		
	Other reasons		
	Details of other reasons	**Other reasons 1**	
		Other reasons 2	
		…	
Patients with treatment completion			

Table 172. Reason for end of treatment for Atezolizumab in cohort 6

			N (%, CI95%)
Reasons for end of treatment	**Progression**		
	Unaccepted toxicity		
	Details of toxicities	**Toxicity 1**	
		Toxicity 2	
		….	
	AE not related to the treatment study		
	Investigator decision		
	Details of investigator decisions	**Investigator decision 1**	
		Investigator decision 1	
		…	
	Withdraw consent		
	Other reasons		
	Details of other reasons	**Other reasons 1**	
		Other reasons 2	
		…	
Patients with treatment completion			

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Induction cycles received			

The median of the study treatment was **XXX** weeks:

Table 173. Study treatment length in cohort 6

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Length of study treatment (months)			

2.4. ANALYSIS SETS

As defined in the protocol, all efficacy analyses will be based primarily on the Intention-to treat (ITT) analysis set and secondarily on the Per Protocol (PP) analysis set, which are defined as follows:

- ITT analysis set: All patients who were enrolled (included) in the trial.
- PP analysis set: All patients fulfilling all eligibility criteria without any protocol deviation that makes patient invalid for the primary endpoint evaluation.

And the safety analysis set is defined as:

- Any patient included in the study receiving at least a single dose of study medication will be evaluable for the toxicity analysis.

Table 174. Analysis sets

		N (%)
ITT population	**Yes**	
	No	
PP population	**Yes**	
	No	
Safety population	**Yes**	
	No	

If any patient is excluded either from the ITT, PP and/or security population, it will be listed below along with the reasons why:

Table 175. List of patients that are excluded from ITT, PP and/or security population

Patient ID code	ITT population	Reason excluded form ITT population	PP population	Reason excluded form PP population	Security population	Reason excluded form security population

2.5. EFFICACY ANALYSIS

Both ITT and PP populations will be used to present the efficacy analysis.

2.5.1. PRIMARY EFFICACY ANALYSIS

Overall Response Rate (ORR): includes patients with confirmed partial (PR) and complete response (CR) as best response according to RECIST v 1.1.

The ORR is the proportion of patients with tumor size reduction (CR or PR), recorded between the date of the first dose and the last tumor evaluation before starting a subsequent treatment of each patient in the study. The proportion of response rates will be expressed with the 95% confidence interval.

The Overall response rate by RECIST in the ITT population (n=**XX**) is shown in the following table:

Table 176. ORR (ITT)

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)
ORR						
CR						
PR						
SD						
PD						
Total	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)
CR or PR						
SD or PD						
Total	n 100%)	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)

The Overall response rate by RECIST in the PP population (n=**XX**) is shown in the following table:

Table 177. ORR (PP)

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)
ORR						
CR						
PR						
SD						
PD						
Total	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)
CR or PR						
SD or PD						
Total	n 100%)	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)

2.5.2. SECONDARY EFFICACY ANALYSIS

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

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).

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

Biomarkers: To be determined according to study results and Sponsor feasibility.

2.5.2.1 DURATION OF RESPONSE

Duration of response (DOR) as per RECIST in the ITT set is shown in the following table:

Table 178. Duration of response (DOR) (ITT)

Duration of Response (months)	n	Mean (SD)	Median (IQR)	Min-Max	CI95% of the mean
Cohort1					
Cohort 2					
Cohort 3					
Cohort 4					
Cohort 5					
Cohort 6					
Total					

Duration of response (DOR) as per RECIST in the PP set is shown in the following table:

Table 179. Duration of response (DOR) (PP)

Duration of Response (months)	n	Mean (SD)	Median (IQR)	Min-Max	CI95% of the mean
Cohort1					
Cohort 2					
Cohort 3					
Cohort 4					
Cohort 5					
Cohort 6					
Total					

2.5.2.2 PROGRESSION FREE SURVIVAL

The 6 months progression-free survival rate will be estimated and plotted using the Kaplan-Meier product-limit method, along with their corresponding log-log transformed 95% confidence intervals.

2.5.2.2.1 Progression free survival ITT POPULATION

In the ITT population (n=**XX**), at 6 months the proportion of patents that survived without PD or death was **XXXX** with a CI95% **XXXX-XXXX**. The overall median of PFS was **XXX** months (CI95% **XXX-XXX**).

Table 180. Progression free survival at 6 and 12 months (ITT)

	N events	Patients at risk	% estimated cumulative survival ratio[1]	95% CI	% of PFS
at 6 months	Cohort 1				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Cohort 5				
	Cohort 6				
at 12 months	Cohort 1				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Cohort 5				
	Cohort 6				
	N	**N (%) events**	**Median (months)**	**Standard error**	**95% CI**
Estimated PFS[1]	Cohort 1				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Cohort 5				
	Cohort 6				

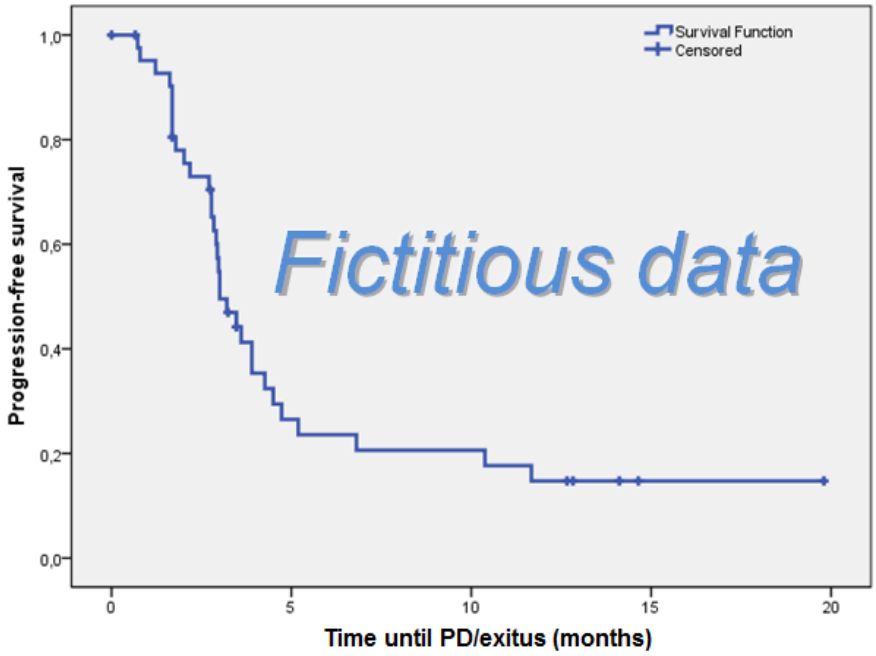
1: Estimated using Kaplan-Meier product-limit method

Table 181. Progression free survival events at 6 months (ITT)

	PFS event	N (%, CI95%)
Cohort 1	Without PD/Death	
	PD	
	Death (without previous PD)	
	Total	
Cohort 2	Without PD/Death	
	PD	
	Death (without previous PD)	
	Total	
Cohort 3	Without PD/Death	
	PD	
	Death (without previous PD)	
	Total	

	PFS event	N (%, CI95%)
Cohort 4	**Without PD/Death**	
	PD	
	Death (without previous PD)	
	Total	
Cohort 5	**Without PD/Death**	
	PD	
	Death (without previous PD)	
	Total	
Cohort 6	**Without PD/Death**	
	PD	
	Death (without previous PD)	
	Total	

Figure 1 Kaplan Meier curve: PFS (ITT)



2.5.2.2.2 Progression free survival PP POPULATION

In the PP population (n=**XX**), at 6 months the proportion of patents that survived without PD or death was **XXXX** with a CI95% **XXXX-XXXX**. The overall median of PFS was **XXX** months (CI95% **XXX-XXX**).

Table 182. Progression free survival at 6 and 12 months (PP)

	N events	Patients at risk	% estimated cumulative survival ratio[1]	95% CI	% of PFS
at 6 months	Cohort 1				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Cohort 5				
	Cohort 6				
	Total				
at 12 months	Cohort 1				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Cohort 5				
	Cohort 6				
	Total				
	N	**N (%) events**	**Median (months)**	**Standard error**	**95% CI**
Estimated PFS[1]	Cohort 1				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Cohort 5				
	Cohort 6				
	Total				

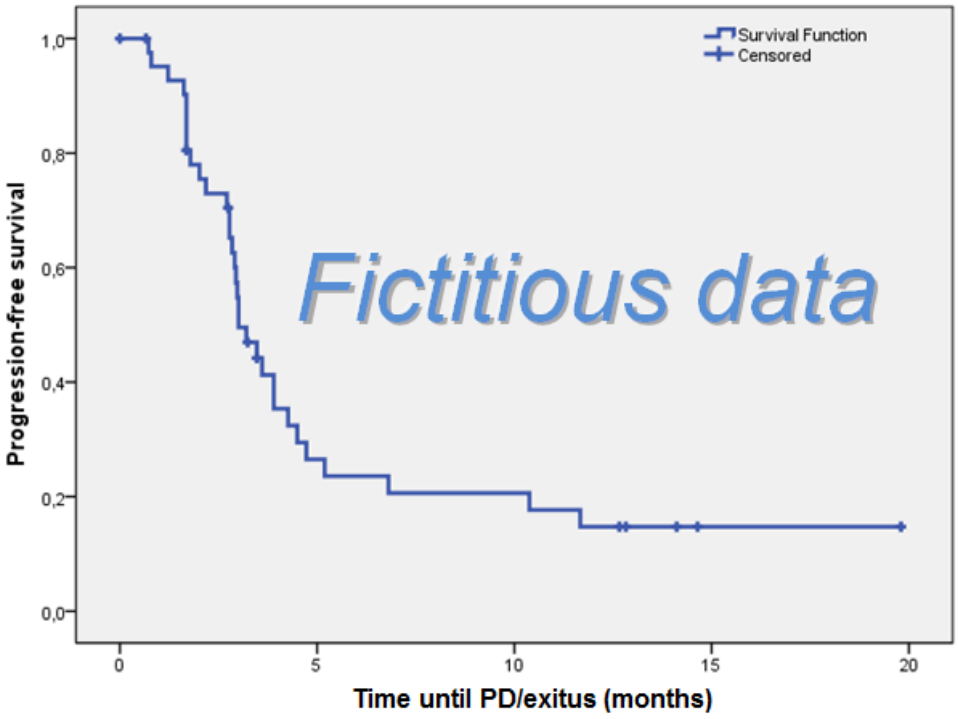
1: Estimated using Kaplan-Meier product-limit method

Table 183. Progression free survival events at 6 months (PP)

	PFS event	N (%, CI95%)
Cohort 1	Without PD/Death	
	PD	
	Death (without previous PD)	
	Total	
Cohort 2	Without PD/Death	
	PD	
	Death (without previous PD)	
	Total	
Cohort 3	Without PD/Death	
	PD	
	Death (without previous PD)	
	Total	
Cohort 4	Without PD/Death	
	PD	
	Death (without previous PD)	
	Total	

	PFS event	N (%, CI95%)
Cohort 5	**Without PD/Death**	
	PD	
	Death (without previous PD)	
	Total	
Cohort 6	**Without PD/Death**	
	PD	
	Death (without previous PD)	
	Total	
Total	**Without PD/Death**	
	PD	
	Death (without previous PD)	
	Total	

Figure 2 Kaplan Meier curve: PFS (PP)



2.5.2.3 OVERALL SURVIVAL

The overall survival rate will be estimated and plotted using the Kaplan-Meier product-limit method, along with their corresponding log-log transformed 95% confidence intervals.

2.5.2.3.1 OVERALL survival ITT POPULATION

In the ITT population (n=**XX**), at 6 months the proportion of patents that survived was **XXXX** with a CI95% **XXXX-XXXX**. The overall median of OS was **XXX** months (CI95% **XXX-XXX**).

Table 184. Overall survival at 6 and 12 months (ITT)

	N events	Patients at risk	% estimated cumulative survival ratio[1]	95% CI	% of OS
at 6 months	Cohort 1				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Cohort 5				
	Cohort 6				
	Total				
at 12 months	Cohort 1				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Cohort 5				
	Cohort 6				
	Total				
	N	**N (%) death**	**Median (months)**	**Standard error**	**95% CI**
Estimated OS[1]	Cohort 1				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Cohort 5				
	Cohort 6				
	Total				

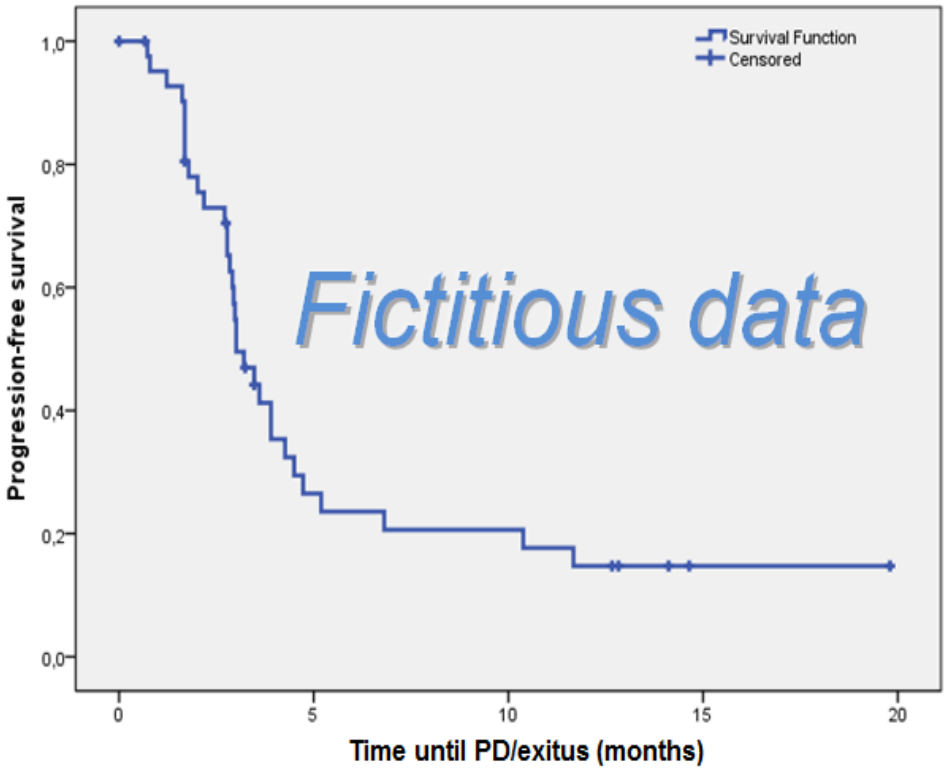
1: Estimated using Kaplan-Meier product-limit method

Table 185. Overall survival events at 6 months (ITT)

	OS event	N (%, CI95%)
Cohort 1	No death at end of follow-up	
	Death	
	Total	
Cohort 2	No death at end of follow-up	
	Death	
	Total	
Cohort 3	No death at end of follow-up	
	Death	
	Total	

Cohort 4	**No death at end of follow-up**
	Death
	Total
Cohort 5	**No death at end of follow-up**
	Death
	Total
Cohort 6	**No death at end of follow-up**
	Death
	Total
Total	**No death at end of follow-up**
	Death
	Total

Figure 3 Kaplan Meier curve: OS (ITT)



2.5.2.3.2 OVERALL survival PP POPULATION

In the PP population (n=**XX**), at 6 months the proportion of patents that survived was **XXXX** with a CI95% **XXXX-XXXX**. The overall median of OS was **XXX** months (CI95% **XXX-XXX**).

Table 186. Overall survival at 6 and 12 months (PP)

	N events	Patients at risk	% estimated cumulative survival ratio[1]	95% CI	% of OS
at 6 months	Cohort 1				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Cohort 5				
	Cohort 6				
	Total				
at 12 months	Cohort 1				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Cohort 5				
	Cohort 6				
	Total				
	N	**N (%) death**	**Median (months)**	**Standard error**	**95% CI**
Estimated OS[1]	Cohort 1				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Cohort 5				
	Cohort 6				
	Total				

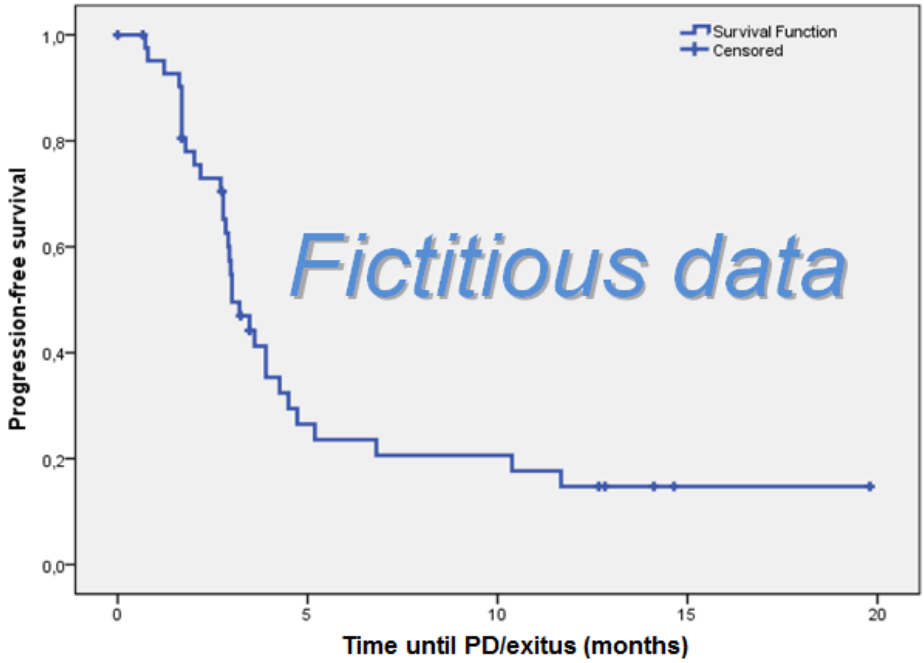
1: Estimated using Kaplan-Meier product-limit method

Table 187. Overall survival events at 6 months (PP)

	OS event	N (%, CI95%)
Cohort 1	No death at end of follow-up	
	Death	
	Total	
Cohort 2	No death at end of follow-up	
	Death	
	Total	
Cohort 3	No death at end of follow-up	
	Death	
	Total	
Cohort 4	No death at end of follow-up	
	Death	
	Total	
Cohort 5	No death at end of follow-up	
	Death	
	Total	
Cohort 6	No death at end of follow-up	
	Death	
	Total	

		No death at end of follow-up
Total		**Death**
		Total

Figure 4 Kaplan Meier curve: OS (PP)



2.5.2.4 FOLLOW UP

Mean and median for the global follow up are shown below.

Table 188. Follow up: mean and median ITT

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Follow up			

Table 189. Follow up: mean and median PP

	N	Mean, SD (CI95%)	Median (CI95%) [Range]
Follow up			

2.6. SAFETY ANALYSIS

The **safety analysis set** will be used in this section and it is defined as: Any patient included in the study receiving at least a single dose of study medication will be evaluable for the toxicity analysis.

Safety profile of cabozantinib and atezolizumab: The number of patients with AEs and SAEs, changes in laboratory values, vital signs, ECGs, and results of physician examinations graded according to the CTCAE v 5.0. This will be analysed using descriptive statistics techniques such as frequency and contingency tables. The final statistical analysis of this endpoint is expected to be performed within 6 months after database closure, which is expected at 12 months after last patient inclusion. However, interim analysis may be performed when analysing other primary endpoints. .....

2.6.1. SAFETY SUMMARY: ALL EVENTS IN OVERALL

Table 190. Safety

		N (%, CI95%)
AE related* (any)	No	
	Yes	
	Total	
AE related* Grade≥3	No	
	Yes	
	Total	
AE related* to both treatments	No	
	Yes	
	Total	
AE related* to Cabozantinib (only)	No	
	Yes	
	Total	
AE related * to Atezolizumab (only)	No	
	Yes	
	Total	
AE	No	
	Yes	
	Total	
AE Grade≥3	No	
	Yes	
	Total	
SAE	No	
	Yes	
	Total	

SAE related (any)	No	
	Yes	
	Total	

*Toxicities

2.6.2. TOXICITIES (AE RELATED TO ANY TREATMENT)

The following table shows those toxicities (AEs related to any of the study treatments) which had a frequency higher than 10% (presented in more than 2 patients).

Table 191. Most frequent toxicities (>10%, n>2)

Toxicities		N, % (CI 95%)
Toxicity 1	No	
	Yes	
	Total	
Toxicity 2	No	
	Yes	
	Total	
….	No	
	Yes	
	Total	
	No	
	Yes	
	Total	
	No	
	Yes	
	Total	
	No	
	Yes	
	Total	

Table 192. Most frequent toxicities by grade

Toxicities		No	G1	G2	G3	G4	G5	Total
		N, % (CI 95%)	N, % (CI 95%)	N, % (CI 95%)	N, % (CI 95%)	N, % (CI 95%)	N, % (CI 95%)	N, % (CI 95%)
	Toxicity 1							
	Toxicity 2							
	…							

2.6.3. TOXICITIES GRADE ≥3

Table 193. Frequency of toxicities grade ≥3

Toxicities	N, % (CI 95%)
Toxicity 1 grade ≥3	
Toxicity 2 grade ≥3	
…	

Table 194. List of toxicities grade ≥3

Patient ID	Cohort	Adverse Event (CTC)	Adverse Event (CTC specify)	AE relationship to treatment	Date AE started	Date AE ended	Dur. (days)	Continuous

2.6.4. TOXICITIES RELATED TO BOTH TREATMENTS

Table 195. Toxicities related to both treatments

Patient ID	Cohort	Adverse Event (CTC)	Adverse Event (CTC specify)	AE relationship to treatment	Date AE started	Date AE ended	Duration (days)	Continuous

2.6.5. TOXICITIES RELATED ONLY TO CABOZANTINIB

Table 196. Toxicities related only with cabozantinib

Patient ID	Cohort	Adverse Event (CTC)	Adverse Event (CTC specify)	AE relationship to treatment	Date AE started	Date AE ended	Duration (days)	Continuous

2.6.6. TOXICITIES RELATED ONLY TO ATEZOLIZUMAB

Table 197. Toxicities related only with atezolizumab

Patient ID	Cohort	Adverse Event (CTC)	Adverse Event (CTC specify)	AE relationship to treatment	Date AE started	Date AE ended	Duration (days)	Continuous

2.6.7. MOST FREQUENT AES

Table 198. Most frequent AEs (>20%, n>4)

AEs		N, % (CI 95%)
AE 1	No	
	Yes	
	Total	
AE 2	No	
	Yes	
	Total	
…	No	
	Yes	
	Total	
	No	
	Yes	
	Total	
	No	
	Yes	
	Total	
	No	
	Yes	
	Total	
	No	
	Yes	
	Total	
	No	
	Yes	
	Total	
	No	
	Yes	
	Total	
	No	
	Yes	
	Total	
	No	
	Yes	
	Total	
	No	
	Yes	
	Total	

	No
	Yes
	Total
	No
	Yes
	Total

Table 199. Most frequent AEs by grade

AEs	**No**	**G1**	**G2**	**G3**	**G4**	**G5**	**Total**
	N, % (CI 95%)	**N, % (CI 95%)**	**N, % (CI 95%)**	**N, % (CI 95%)**	**N, % (CI 95%)**	**N, % (CI 95%)**	**N, % (CI 95%)**
AE 1							
AE 2							
…							

2.6.8. AE GRADE ≥3

Table 200. Frequency of AEs grade ≥3

AEs	N (%, CI95%)
AE 1 grade ≥3	
AE 2 grade ≥3	
…	

In this table, AEs are grouped using the maximum grade reported for each patient

Table 201. List of AEs with grade ≥3

Patient ID	Cohort	Adverse Event (CTC)	Adverse Event (CTC specify)	AE relationship to treatment	Date AE started	Date AE ended

2.6.9. SAE

Table 202. SAEs

SAEs	N (%, CI95%)
SAE 1	
SAE 2	
…	

Table 203. List of all SAEs

Patient ID	Cohort	Adverse Event (CTC)	Adverse Event (CTC specify)	Intensity	AE relationship to treatment	Date AE started	Date AE ended

1: SAE reported in the period after signing the informed consent form and previous to the start of the study treatment.

2.6.10. SAE RELATED TO ANY TREATMENT

Table 204. SAEs RELATED

Relates SAEs	N (%, CI95%)
SAE 1	
SAE 2	
…	

Table 205. List of all SAEs RELATED

Patient ID	Cohort	Adverse Event (CTC)	Adverse Event (CTC specify)	Intensity	AE relationship to treatment	Date AE started	Date AE ended

2.6.11. SAFETY SUMMARY: ALL EVENTS PER COHORTS

Table 206. Safety per cohorts

		Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
		N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)
AE related* (any)	No						
	Yes						
	Total						
AE related* Grade≥3	No						
	Yes						
	Total						
AE related* to both treatments	No						
	Yes						
	Total						
AE related* to Cabozantinib (only)	No						
	Yes						
	Total						
AE related * to Atezolizumab (only)	No						
	Yes						
	Total						
AE	No						
	Yes						
	Total						
AE Grade≥3	No						
	Yes						
	Total						
SAE	No						
	Yes						
	Total						
SAE related (any)	No						
	Yes						
	Total						

*Toxicities

Sponsor: Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE)

2.6.12. TOXICITIES (AE RELATED TO ANY TREATMENT) PER COHORTS

Table 207. Most frequent toxicities (>10%, n>2) per cohorts

Toxicities		Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
		N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)
Toxicity 1	No						
	Yes						
	Total						
Toxicity 2	No						
	Yes						
	Total						
….	No						
	Yes						
	Total						
	No						
	Yes						
	Total						
	No						
	Yes						
	Total						
	No						
	Yes						
	Total						

Table 208. Most frequent toxicities by grade per cohorts

Toxicities	Cohort	No	G1	G2	G3	G4	G5	Total
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Toxicity 1	C1							
	C2							
	C3							
	C4							
	C5							
	C6							
Toxicity 2	C1							

	C2
	C3
	C4
	C5
	C6
Toxicity 3	**C1**
	C2
	C3
	C4
	C5
	C6

2.6.13. TOXICITIES GRADE ≥3 PER COHORTS

Table 209. Frequency of toxicities grade ≥3 per cohorts

Toxicities	Cohort	N (%, CI95%)
Toxicity 1	**C1**	
	C2	
	C3	
	C4	
	C5	
	C6	
Toxicity 2	**C1**	
	C2	
	C3	
	C4	
	C5	
	C6	
…	**C1**	
	C2	
	C3	
	C4	
	C5	

C6

2.6.14. MOST FREQUENT AES

Table 210. Most frequent AEs (>20%, n>4) per cohorts

AEs		Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
		N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)
AE 1	No						
	Yes						
	Total						
AE2	No						
	Yes						
	Total						
…	No						
	Yes						
	Total						
	No						
	Yes						
	Total						
	No						
	Yes						
	Total						
	No						
	Yes						
	Total						
	No						
	Yes						
	Total						
	No						
	Yes						
	Total						
	No						
	Yes						
	Total						

Table 211. Most frequent AEs by grade per cohorts

AEs	Cohort	No	G1	G2	G3	G4	G5	Total

		N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)	N (%, CI95%)
AE1	**C1**							
	C2							
	C3							
	C4							
	C5							
	C6							
AE2	**C1**							
	C2							
	C3							
	C4							
	C5							
	C6							
	C1							
	C2							
	C3							
	C4							
	C5							
	C6							

2.6.15. AE GRADE ≥3 PER COHORTS

Table 212. Frequency of AEs grade ≥3 per cohorts

AEs	Cohort	N (%, CI95%)
AE 1	**C1**	
	C2	
	C3	
	C4	
	C5	
	C6	
AE 2	**C1**	
	C2	
	C3	

	C4
	C5
	C6
AE 3	**C1**
	C2
	C3
	C4
	C5
	C6

2.6.16. SAE PER COHORTS

Table 213. SAEs per cohorts

SAEs	Cohort	N (%, CI95%)
SAE 1	C1	
	C2	
	C3	
	C4	
	C5	
	C6	
SAE 2	C1	
	C2	
	C3	
	C4	
	C5	
	C6	
SAE 3	C1	
	C2	
	C3	
	C4	
	C5	
	C6	

2.6.17. SAE RELATED TO ANY TREATMENT PER COHORTS

Table 214. SAEs RELATED per cohorts

Relates SAEs	Cohort	N (%, CI95%)
SAE 1	C1	
	C2	
	C3	
	C4	
	C5	
	C6	

SAE 2	**C1**
	C2
	C3
	C4
	C5
	C6
SAE 3	**C1**
	C2
	C3
	C4
	C5
	C6

2.7. ANNEX: LIST OF ALL TOXICITIES

Table 215. List of all toxicities

	Patient ID	Cohort	Adverse Event (CTC)	Adverse Event (CTC specify)	AE relationship to treatment	Date AE started	Date AE ended	Duration (days)	Continuous

3. CONCLUSIONS

4. ANEXES

4.1. ANEX I: DATABASE MANAGEMENT

In this section, the process of data base management and data cleaning will be described.

5. REFERENCES

Provide references for any citations in the main body of the SAP.