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Grupo Español de Tumores Neuroendocrinos

A PHASE II STUDY OF DURVALUMAB (MEDI4736) PLUS TREMELIMUMAB FOR THE TREATMENT OF PATIENTS WITH ADVANCED NEUROENDOCRINE NEOPLASMS OF GASTROENTEROPANCREATIC OR LUNG ORIGIN (THE DUNE TRIAL)

STATISTICAL ANALYSIS PLAN (SAP)

TRIAL FULL TITLE	**A PHASE II STUDY OF DURVALUMAB (MEDI4736) PLUS TREMELIMUMAB FOR THE TREATMENT OF PATIENTS WITH ADVANCED NEUROENDOCRINE NEOPLASMS OF GASTROENTEROPANCREATIC OR LUNG ORIGIN (THE DUNE TRIAL)**
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1 GENERAL INFORMATION

TITLE

A phase II study of durvalumab (MEDI4736) plus tremelimumab for the treatment of patients with advanced neuroendocrine neoplasms of gastroenteropancreatic or lung origin (the DUNE trial).

STUDY DESIGN

Prospective, multi-center, open label, stratified, exploratory phase II study evaluating the efficacy and safety of durvalumab plus tremelimumab in different cohorts of patients with neuroendocrine neoplasms.

The study will include patients in four different cohorts:

- **Cohort 1**: Well-moderately differentiated lung neuroendocrine tumors (classically known as typical and atypical carcinoids) after progression to somatostatin analogs and one prior targeted therapy or chemotherapy.

- **Cohort 2**: G1/G2 (WHO grade 1 and 2) gastrointestinal neuroendocrine tumors after progression to somatostatin analogs and one prior targeted therapy.

- **Cohort 3**: G1/G2 (WHO grade 1 and 2) pancreatic neuroendocrine tumors after progression to standard therapies (chemotherapy, somatostatin analogs and target therapy), who have received between two and four prior lines of treatment.

- **Cohort 4**: Neuroendocrine neoplasms (WHO grade 3) of gastroenteropancreatic origin of unknown primary site (excluding lung primary tumors) after progression to first-line chemotherapy with a platinum based regimen.

TREATMENT

The treatment phase will include two stages for each cohort. The first stage will dose the first patient in each cohort in a safety run period for one cycle (4 weeks). If no unexpected side effects are observed in the first patient treated in each cohort during the safety run period, recruitment will continue up to 31 patients for cohorts 1 to 3, and 33 for cohort 4.

Subjects will be allocated in each primary tumour cohort to receive durvalumab 1500 mg Q4W for 12 months in patients plus tremelimumab 75 mg Q4W for up to 4 doses during the first 4 cycles of combined therapy. Cycles are defined by 4 weeks or 28 days. Subjects will undergo safety and efficacy assessment as defined per protocol.

SPONSOR

GETNE (Spanish Group of Neuroendocrine Tumors)

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MONITORING ORGANISATION (CRO)

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1 ABBREVIATIONS AND DEFINITIONS

Abbreviation	Explanation or special term
AchE	Acetylcholine esterase
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC0-28day	Area under the plasma drug concentration-time curve from time zero to Day 28 post-dose
AUCss	Area under the plasma drug concentration-time curve at steady state
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EdoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure

ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
OSR	Overall Survival Rate
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
Pdx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
Pgx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QtcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid

RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
UNK	Unknown
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

2 INTRODUCTION

2.1 PREFACE

Neuroendocrine neoplasms constitute a heterogenic group of tumors derived from the Kultchitzky cells of the diffuse neuroendocrine system located in the gastrointestinal tract (origin of classical carcinoid tumors), pancreatic islet cells (origin of pancreatic endocrine tumors) and lung (origin of typical and atypical carcinoids). Advanced disease is common at diagnosis leading to limited options of curative strategies, so general prognosis is poor. Neuroendocrine neoplasms are considered rare diseases, however, taken all together into account and the natural history of well-differentiated tumors, their prevalence is increasing. Systemic treatment options have been limited for several years. However, in the last decade, the better knowledge of molecular biology of neuroendocrine neoplasms has increased the interest to develop targeted agents in this field, changing the scenario of possible therapies for advanced disease. Even though, treatment options are still limited.

Immune balance has always been related with neuroendocrine neoplasms. Prolonged stabilizations have often been described without treatment and initial immune modulators, such as interferon, have demonstrated antitumoral effects in these tumors. Recent advances in immunotherapy have permitted the development of new targeted agents with higher efficacy and lower toxicity that opens a new treatment option for patients with advanced neuroendocrine tumors.

2.2 PURPOSE OF THE ANALYSES

These analyses will assess the efficacy and safety of durvalumab plus tremelimumab in different cohorts of patients with neuroendocrine neoplasms.

3 RESEARCH METHODS

3.1 STUDY DESIGN

Prospective, multi-center, open label, stratified, exploratory phase II study evaluating the efficacy and safety of durvalumab plus tremelimumab in different cohorts of patients with neuroendocrine neoplasms.

The study will include patients in four different cohorts:

- **Cohort 1**: Well-moderately differentiated lung neuroendocrine tumors (classically known as typical and atypical carcinoids) after progression to somatostatin analogs and one prior targeted therapy or chemotherapy.

- **Cohort 2**: G1/G2 (WHO grade 1 and 2) gastrointestinal neuroendocrine tumors after progression to somatostatin analogs and one prior targeted therapy.

- **Cohort 3**: G1/G2 (WHO grade 1 and 2) pancreatic neuroendocrine tumors after progression to standard therapies (chemotherapy, somatostatin analogs and target therapy), who have received between two and four prior lines of treatment.

- **Cohort 4**: Neuroendocrine neoplasms (WHO grade 3) of gastroenteropancreatic origin of unknown primary site (excluding lung primary tumors) after progression to first-line chemotherapy with a platinum based regimen.

3.2 STUDY OBJECTIVES

Primary Objectives:

Primary endpoint for cohorts 1, 2 and 3: 9-months clinical benefit rate (CBR) by Response Evaluation Criteria In Solid Tumors (RECIST version 1.1).

Primary endpoint for cohort 4: 9-months overall survival rate.

Secondary Objective(s):

- Overall response rate (ORR) by irRECIST.

- To assess the duration of response according to irRECIST.

- To assess the median progression-free survival time (PFS) according to irRECIST.

- To assess the safety profile of durvalumab and tremelimumab in subjects with advanced neuroendocrine neoplasms.

- To assess the median overall survival (OS) time.

- To assess response status according to irRECIST at 6 and 12 months after start of study treatment.

Exploratory Objective(s):

- To evaluate biochemical response (changes in CgA and NSE levels) and its association with

response rate and progression-free survival.

- To assess whether baseline tumor and blood biomarkers may be predictive of response to durvalumab and tremelimumab therapy.

- To explore additional hypotheses related to biomarkers and relationship to durvalumab and tremelimumab efficacy and/or toxicity and neuroendocrine tumors evolution that may arise from internal or external research activities.

3.3 STUDY POPULATION

Patients with advanced/metastatic, histologically confirmed, grade 1/2 (G1/G2) of the 2010 WHO classification neuroendocrine tumors of the pancreas, gastrointestinal tract and lung origins and grade 3 (G3) of gastroenteropancreactic system or unknown primary site (excluding lung primaries) after progression to previous therapies.

3.3.1 Sites

The selected study oncology sites in Spain were:
Hospital de Vall d'Hebron
Hospital
Hospital
Hospital
Hospital
Hospital
Hospital
Hospital

3.3.2 Inclusion criteria

For inclusion in the study, patients should fulfill the following criteria:

1. Written informed consent obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
2. Age >18 years at time of study entry.
3. Subjects must have histologically confirmed diagnosis of one of the following advanced/metastatic neuroendocrine tumor types:

a) **Cohort 1**: Well-moderately differentiated neuroendocrine tumors of the lung (Ki67<20% and mitotic count ≤20 mitoses x 10 HPF), also known as typical and atypical lung carcinoids, that have progressed to prior somatostatin analog therapy and/or one prior targeted therapy or chemotherapy (only one prior systemic therapy, with the exception of patients that have been treated with somatostatin analogues and other systemic treatment, when two prior treatments are allowed).

b) **Cohort 2**: Well-moderately differentiated G1/G2 (WHO grade 1 and 2) gastrointestinal neuroendocrine tumors after progression to somatostatin analogs and one targeted therapy (prior targeted therapy could be everolimus or a multikinase inhibitor). Prior therapies with interferon alpha-2b or radionucleotide therapy are allowed.

c) **Cohort 3**: Well-moderately differentiated neuroendocrine tumors G1/G2 (WHO grade 1 and 2) from pancreatic origin after progression to standard therapies (chemotherapy, somatostatin

analogs and target therapy); patients must be treated with at least two prior systemic treatment lines and a maximum of four previous treatment lines.

d) **Cohort 4:** Neuroendocrine neoplasms (WHO grade 3) of gastroenteropancreatic origin of unknown primary site (excluding lung primary tumors) after progression to first-line chemotherapy with a platinum based regimen.

4. For patients included in cohorts 1, 2 and 3: WHO Classification G1/G2 (Ki67<20% and mitotic count ≤20 mitoses x 10 HPF) lung typical and atypical carcinoids for cohort 1, gastrointestinal for cohort 2 (including stomach, small intestine and colorectal origins), pancreatic for cohort 3.

5. For patients included in cohort 4: WHO classification G3 (Ki67≥20% or mitotic count >20 mitoses x 10 HPF) gastroenteropancreatic neuroendocrine carcinomas (NEC) or liver metastases of G3 NEC of unknown primary site.

6. Subjects must have evidence of measurable disease meeting the following criteria:

a) At least 1 lesion of ≥ 1.0 cm in the longest diameter for a non lymph node, or ≥ 1.5 cm in the short-axis diameter for a lymph node, which is serially measurable according to RECIST 1.1 (Appendix I) using computerized tomography/magnetic resonance imaging (CT/MRI). If there is only one target lesion and it is a non-lymph node, it should have a longest diameter of ≥ 1.5 cm.

b) Lesions that have had external beam radiotherapy (EBRT) or loco-regional therapies such as radiofrequency (RF) ablation or liver embolization must show evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion.

c) Subjects must show evidence of disease progression by radiologic image techniques within 12 months (an additional month will be allowed to accommodate actual dates of performance of scans, i.e., within ≤ 13 months) prior to signing informed consent, according to RECIST 1.1 (Appendix I).

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

8. Life expectancy of at least 12 weeks.

9. Adequate normal organ and marrow function as defined below:

- Haemoglobin ≥ 9.0 g/dL.
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (> 1500 per mm^3).
- Platelet count ≥ 100 x 10^9/L (>100,000 per mm^3).

1. Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.

2. AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN.

3. Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for 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:

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

4. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or

must have a negative serum pregnancy test upon study entry.

5. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

3.3.3 Exclusion criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Involvement in the planning and/or conduct of the study.
2. Participation in another clinical study with an investigational product during the last 4 weeks.
3. WHO Classification G3 neuroendocrine neoplasms of lung origin (oat cell/large cell lung cancer).
4. Prior treatment with anti-PDL-1/anti-PD-1 or anti-CTL-4 therapy.
5. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B (e.g., HBsAg reactive), hepatitis C (e.g., HCV RNA [qualitative] is detected) or known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.
6. Known history of previous clinical diagnosis of tuberculosis.
7. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab or tremelimumab, 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.
8. 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.
9. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).
10. History of allogeneic organ transplant.
11. History of hypersensitivity to durvalumab, tremelimumab or any excipient.
12. 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.
13. Knowledge of active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they have stable brain metastases [without evidence of progression by imaging confirmed [by magnetic resonance imaging (MRI) if MRI was used at prior imaging, or confirmed by computed tomography (CT) imaging if CT used at prior imaging] for at least four weeks prior to the first dose of trial treatment; also, any neurologic symptoms must have returned to baseline], have no evidence of new or enlarging brain metastases,and have not used steroids for brain metastases for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.
14. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab or tremelimumab. Note: The killed virus vaccines used for seasonal influenza vaccines for injection are allowed; however intranasal influenza vaccines (e.g., FluMist®)

are live attenuated vaccines, and are not allowed.

15. Subjects having known history of, or any evidence of interstitial lung disease or active, noninfectious pneumonitis.
16. Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1.
17. Subjects who have received any anti-cancer treatment within 21 days or any investigational agent within 30 days prior to the first dose of study drug and should have recovered from any toxicity related to previous anti-cancer treatment. This does not apply to the use of somatostatin analogues for symptomatic therapy.
18. Major surgery within 3 weeks prior to the first dose of study drug.
19. Subjects having > 1+ proteinuria on urine dipstick testing will undergo 24h urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥ 1 g/24h will be ineligible.
20. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina; myocardial infarction or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment.
21. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction.
22. Bleeding or thrombotic disorders or use of anticoagulants, such as warfarin, or similar agents requiring therapeutic international normalized ration (INR)monitoring. Treatment with low molecular weight heparin (LMWH) is allowed.
23. Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug.
24. Active infection (any infection requiring treatment).
25. Active malignancy (except for differentiated thyroid carcinoma, or definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 24 months.
26. Known intolerance to any of the study drugs (or any of the excipients).
27. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ highly effective birth control from screening to 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.
28. Documented active alcohol or drug abuse.
29. Patients with a prior history of non-compliance with medical regimens.
30. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

3.3.4 Procedures for handling subjects incorrectly enrolled

Patients incorrectly enrolled in the trial will be considered as protocol desviations. If investigador considerer that the patient is obtaining benefit of the investigational treatment, patients could continue on therapy. They will not be considered for the primary endpoint of the trial, neither for efficacy nor biomarker secondary and exploratory analyses.

3.4 SCHEDULE OF STUDY PROCEDURES

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and

laboratory studies may be repeated more frequently if clinically indicated.

Screening phase

Screening will occur between Day -28 and Day -1. The purpose of the screening period is to establish protocol eligibility. Informed consent will be obtained up to 4 weeks prior to Cycle 1 Day 1 and after the study has been fully explained to each subject and prior to the conduct of any screening procedures or assessments. The purpose of the baseline visit is to establish disease characteristics prior to allocation and treatment and to confirm protocol eligibility as specified in the inclusion/exclusion criteria. Results of baseline assessments must be obtained prior to the first dose of study drug (Cycle 1/Day 1). Baseline assessments may be performed on Day -1 or on Cycle 1/Day 1 prior to dosing. Clinical laboratory tests including pregnancy test (where applicable) can be performed within 72 hours of the first dose of study drug. Subjects who complete the baseline visit and continue to meet the criteria for inclusion/exclusion will begin the treatment phase of this study.

Treatment phase

The treatment phase will begin at the time of allocation of the first patient and will consist of the study treatment cycles. The treatment phase will end when the last patient discontinue the study drug. The treatment phase will include two stages for each cohort. The first stage will dose the first patient in each cohort in a safety run period for one cycle (4 weeks). If no unexpected side effects are observed in the first patient treated in each cohort during the safety run period, recruitment will continue up to 31 patients for cohorts 1 to 3, and 33 for cohort 4. Subjects will be allocated in each primary tumor cohort to receive durvalumab 1500 mg Q4W for 12 months in patients plus tremelimumab 75 mg Q4W for up to 4 doses during the first 4 cycles of combined therapy. Cycles are defined by 4 weeks or 28 days. Subjects will undergo safety and efficacy assessment as defined per protocol.

Follow-up phase

Patients will finish the treatment phase after the administration of 12 cycles of durvalumab or after disease progression during the treatment phase. For patients that complete all scheduled treatment, the follow-up phase will begin to determine survival endpoints. Tumor assessments will continue every 12 weeks and clinical appointments will start monthly during the first 3 months of follow-up and continue every 12 weeks until disease progression.

End of Treatment

End of treatment is defined as the last planned dosing visit within the 12-month dosing period.

For subjects who discontinue durvalumab or tremelimumab prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit. Blood samples for biomarker analysis are collected. Assessments for subjects who have completed durvalumab and tremelimumab treatment and achieved disease control, or have discontinued durvalumab or tremelimumab due to toxicity in the absence of confirmed progressive disease are provided in APPENDIX 2 of the protocol.

Assessments for subjects who have discontinued durvalumab or tremelimumab treatment due to confirmed PD are presented in APPENDIX 3 of the protocol.

All subjects will be followed for survival until the end of the study regardless of further treatments,

or until the sponsor ends the study.

3.5 STUDY VARIABLES

Screening/Baseline variables:

- Hospital
- Informed Consent
- Eligibility criteria
- Allocated cohort
- Medical history and demographics (gender, date of birth and Race/ethnicity)
- Vital signs (temperature, respiratory rate, resting blood pressure, pulse), height and weight.
- ECOG performance status
- Concomitant medications
- 12-lead ECG (in triplicate [2-5 minutes apart])
- Record any Aes or SAEs (since ICF signature)
- Imaging by CT/MRI
- Review of octreoscan/PET (up to 6 months prior inclusion)
- Biomarkers analysis
- Archival tumor block or slides
- Clinical laboratory tests for:
  - Hematology, Clinical chemistry, TSH, fT3 and fT4, Coagulation (PT, PTT, INR), Creatinine Clearance, Serum pregnancy test (for women of childbearing potential only),Hepatitis and VIH serologies, Urinalysis, Disease-specific tumor markers and Anti PNS.

Tratment phase variables:

Cycle 1/Day 1:

- Vital signs (temperature, respiratory rate, resting blood pressure, pulse) and weight.
- Administered study drug
- Concomitant medications
- Aes or SAEs

Cycle 1 to 3 /Day 15:

- Vital signs (temperature, respiratory rate, resting blood pressure, pulse) and weight.
- ECOG performance status
- Administered study drug
- Concomitant medications
- Aes or SAEs
- Biomarkers analysis
- Clinical laboratory tests for:
  - Hematology, Clinical chemistry, TSH, fT3 and fT4, Coagulation (PT, PTT, INR), Creatinine Clearance ,Serum pregnancy test (for women of childbearing potential only),Hepatitis and VIH serologies ,Urinalysis, Disease-specific tumor markers and Anti PNS.

Cycle 2 to 12 /Day 1:

- Vital signs (temperature, respiratory rate, resting blood pressure, pulse) and weight.
- ECOG performance status
- Administered study drug (from C5D1 to C12D1 tremelimumab no longer administered, only

durvalumab).

- Biomarkers analysis
- Clinical laboratory tests for:
  - Hematology, Clinical chemistry, TSH, fT3 and fT4, Coagulation (PT, PTT, INR), Creatinine Clearance ,Serum pregnancy test (for women of childbearing potential only),Hepatitis and VIH serologies ,Urinalysis, Disease-specific tumor markers and Anti PNS.
- Concomitant medications
- Aes or SAEs
- Survival Data: Date and Status (alive/exitus)

Tumor assessments (CT/MRI)[l]

- CT/MRI of chest/abdomen/pelvis and other areas of known disease at screening plus any areas of newly suspected disease should be performed every 8 weeks for the first 48 weeks and then every 12 weeks until confirmed PD (Date of assessment and status (PD or not PD)).

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3.5.1 Schedule of study assessments

Table 1 Schedule of study assessments

Phase	**Screening Phase**		**Treatment Phase**								**Follow-up**
Period	**Screening [a,b]**	**Baseline[a,b]**	**Study Treatment**								
Visit	**V1 -28 to -2**	**V2 Day -1**	**V3 C1D1**	**V4 C1D15**	**V5 C2D1 (C1D28)**	**V6 C2D15**	**V7 C3D1 (C2D28)**	**V8 C3D15**	**V9 C4D1 (C3D28)**	**V10-V16 C5D1 C12D1**	
Informed consent	X										
Inclusion/Exclusion	X	X									
Allocation		X									
Demographic Data	X										
ECOG PS[c]	X	X		X	X	X	X	X	X	X	X
Prior Therapies for neuroendocrine neoplasms	X										
Vitals signs[d]	X		X	X	X	X	X	X	X	X	X
Physical exam[f]	X	X[e]		X	X	X	X	X	X	X	X
12/lead ECG[g]	X		Only when clinically indicated								
Biochemistry and hematology[h]	X	X[h]		X	X	X	X	X	X	X	X
Hepatitis B and C; HIV	X										

Anti PNS antibody testing	X										
Thyroid function test (TSH and fT3 and fT4)	X			X	X	X	X	X	X	X	X
Urinalysis[j]	X			X	X	X	X	X	X	X	X
Pregnancy test[k]	X		Only when clinically indicated								
Durvalumab administration			X		X		X		X	X	
Tremelimumab administration			X		X		X		X		
Tumor assessments (CT/MRI)[l]	X		CT/MRI of chest/abdomen/pelvis and other areas of known disease at screening plus any areas of newly suspected disease should be performed every 8 weeks for the first 48 weeks and then every 12 weeks until confirmed PD.								
Octreoscan / PET/CT[m]	X										
Survival[n]					X		X		X	X	X
Biomarkers[o]		X			X						
Archival tumor block or slides[p]		X									
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs[q]	X	X	X	X	X	X	X	X	X	X	X

AEs = adverse events, BP = blood pressure, CT = computerized tomography, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, HR = heart rate, MRI = magnetic resonance imaging, PET = positron-emission tomography, RECIST = Response Evaluation Criteria In Solid Tumors, RR = respiratory rate, SAEs = serious adverse events, surg = surgical, 99m-Tc MDP = 99m-technetium-methylene diphosphonate, w/in = within.

a) 72 hours before Cycle 1 Day 1 (C1D1). The baseline assessment can be performed on C1D1, prior to treatment. Informed consent may be taken up to 4 weeks prior to C1D1.

b) Efforts should be made to conduct study visits on the day scheduled (± 1 day). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit.

c) ECOG will be performed at the Screening and Baseline Visits and at every subsequent treatment visit thereafter. For ECOG see Appendix II of the protocol.

d) Assessments will include vital signs (supine BP, HR, RR, and body temperature), weight, and height. Height will be measured at the Screening Visit only. Elevated BP (≥140/90 mmHg) should be confirmed by 3 measurements (at least 5 minutes apart). If systolic BP is ≥160 mmHg or diastolic BP ≥100 mmHg, BP should be confirmed by repeat measurements after an hour. Subjects will have their blood pressure and pulse measured before, during, and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes).
- At 30 minutes during the infusion (±5 minutes).
- At the end of the infusion (at 60 minutes ±5 minutes).
- In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated.

If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or more frequently if clinically indicated.

e) Required if screening physical examination was performed > 7 days prior C1D1.

f) A comprehensive physical examination (including a neurological examination) will be performed at the Screening or Baseline Visit, on each visit of the Treatment phase, and at the off-treatment assessment. A symptom-directed physical examination will be performed on Cycle 1/Day 1 and at any time during the study, as clinically indicated.

g) Single 12-lead ECG. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

h) Assessments scheduled may be performed within 72 hours prior to the visit. Assessments during follow up are made every 8-12 weeks, according to investigator's criteria.

i) Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system. Assessments during follow up are made every 8-12 weeks, according to investigator's criteria.

j) Assessments during follow up are made every 8-12 weeks, according to investigator's criteria.

k) A serum or urine pregnancy test will be performed at the Screening Visit, at the Baseline Visit (or within 72 hours prior to the first dose of study medication).

l) Screening tumor assessments using CT of the chest/abdomen/pelvis and other areas of known disease or newly suspected disease should be performed within 28 days prior to C1D1. Scans of the abdomen, pelvis and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be done without IV contrast.

m) Somatostatin receptor schintigraphy (octreoscan) or PET-CT should be performed and/or available within the previous 6 months before C1D1.

n) Survival data will be collected every 4 weeks until end of treatment phase is declared. All anticancer therapies will be collected. Survival data and other cancer treatments received will be collected every 6 months until close of the study database. The study sponsor may elect to discontinue survival follow-up.

o) Collection of blood sample to obtain plasma, serum, or other components to be used for biomarker studies. Samples will be obtained at baseline, Cycle 2/Day 1, and at end-of-treatment visit.

p) All subjects will have collection of most recent archived, tumor-biopsy sections for identification of predictive biomarkers.

q) Throughout the study from the signature of Informed Consent. SAE irrespective of relationship to study treatment must be reported as soon as possible but not later than one business day. AEs and concomitant meds collected 28 days from last dose.

3.6 SAMPLE SIZE

Sample size has been calculated using one-sample Superiority test (function OneSampleProportion. (NIS) of the Trial Size package of R software). According to previous knowledge, it is estimated that the reference value for the likelihood to be progression-free at 9 months is 30% and we expect an increase of 20% with a superiority margin of 10%.With a unilateral alpha level of 5% and 80% power, we estimate to include 28 patients per group, with an expected lost to follow-up rate of 10%, a final sample size in each 1, 2 and 3 cohort will include 31 patients.

For cohort 4, and according to previous knowledge, it is estimated that the reference proportion of patients being alive at 9 months is 13% and we expect an increase of 10% with a superiority margin of 5%. With a unilateral alpha level of 5% and 80% power, we estimate to include 30 patients per group, with an expected lost to follow-up rate of 10%, a final sample size will include 33 patients.

Summarizing, total sample size will include 126 patients: 31 patients for cohorts 1 to 3, and 33 for cohort 4.

3.7 DATA ANALYSIS

3.7.1 Analysis Sets

The analysis sets will be defined as follows:

- **Full Analysis Set** will include all allocated subjects. This will be primary analysis set for the efficacy endpoints.
- **Per Protocol Analysis Set** will include those subjects who were allocated and received at least one dose of the assigned study drug and had no major protocol deviations. The subjects will complete both baseline and at least one post-baseline tumor assessments (week 12).
- S**afety Analysis Set** will include all subjects who were allocated and received at least one dose of the study drug and had at least one post-baseline safety evaluation (week 12). This will be the analysis set for all safety evaluations.
- **Pharmacodynamic Analysis Set**: All the subjects who have received at least one dose of study drug and have evaluable pharmacodynamic data.

3.7.2 Planned Analyses

Demographic and other baseline characteristics

Demographic and other baseline characteristics will be summarized and listed. For continuous demographic/baseline variables including age, weight, and vital signs, results will be summarized and presented as n, number of not available data (NA), mean, standard deviation, median, and minimum and maximum values. For categorical variables such as race/ethnicity, the number and percentage of subjects will be used.

Prior and concomitant medications

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class.

Efficacy Analyses

All efficacy analyses will be based primarily on the Full Analysis Set and secondarily on the Per Protocol Analysis Set.

Data cut-off for the primary study analysis will happen following after the last patient included in the study has performed the first tumor evaluation (week 12 after first dose of study drug).The following tumor evaluations will take place every 12 weeks until documentation of disease progression or start of another anticancer therapy.

Analysis of primary efficacy variable

The analysis of clinical benefit rate and overall survival rate will be performed independently for each study cohort when the last patient included in the corresponding cohort of the study will arrived to 9 months after inclusion in the study or have progressed. The primary objective of the study will be based on the investigator assessment.

3.7.3 Planned Method of Analysis

Summary tables (descriptive statistics and frequency tables) will be provided for all baseline variables, efficacy variables, and safety variables, as appropriate. Continuous variables will be summarized with descriptive statistics (mean, standard deviation, range, and median). Ninety-five (95) percent confidence intervals (95% CI) may also be presented, as appropriate. Frequency counts and percentage of subjects within each category will be provided for categorical data.

The primary efficacy analysis will be performed using the binomial test procedure. Missing data will be treated using statistical multiple random imputation.

Concordance between investigator assessment and independent central radiology review will be analyzed using Cohen's Kappa. Although no significant differences are expected, a sensitivity analysis for the primary efficacy analysis will be performed using as response variable independent central radiology assessment.

Secondary endpoints will be summarized with descriptive statistics. Continuous variables will be summarized with n, mean, standard deviation, and range, frequency counts and percentage of subjects within each category will be provided for categorical data. Multivariate regression models will be used to study relations between explanatory variables and primary endpoint. Survival analysis will be performed to analyze PFS, Kaplan-Meier curves will be presented and possible comparisons will be tested using the log-rank test or the Cox proportional hazard model for multivariate analysis, hazard ratios (HR) and their 95% confidence interval (CI95%) will be provided. Patients with lost of follow-up or treatment discontinuation will be included in the final analysis of primary endpoint if they have at least one tumor evaluation and considered as censored data for survival endpoints.

R software version 3.2.1 will be used for all analysis.

Safety Analyses

Safety analyses will be based on the Safety Analysis Set. All safety analyses will be summarized separately by cohort. Adverse events and serious adverse events, laboratory test results, physical examination findings and vital signs, and their changes from baseline will be summarized using descriptive statistics. Abnormal values will be flagged.

3.7.4 Data management and data cleaning

Data was checked for inconsistencies, unexpected values and missing values. If identified, these values were fed back to the data contributor ([redacted]), along with the patient identifier, for possible correction from source documents. Resubmitted, corrected, and/or transformed missing values were used to update the Data Base. If corrections could not be made, the inconsistencies and unexpected results are transformed to missing values.

Missing dates: In those cases that only the day was missing and month and year were known, in order to be able to use those dates for computing in the analysis, the date was rounded to day 15 of the month reported. Similarly, when month was not reported, the date was rounded to the sixth month of the year (June).

3.7.5 Missing Data

Assuming that the pattern of missingness in the primary endpoint variable (clinical benefit rate at 9 months) are missing at random (1), missing data will be treated using statistical multiple random imputation (2,3,4). Once date are collected, according to the missing data pattern observed, it should be considered if pre-specified methods are appropriate. A full reporting of all reasons for patient discontinuation should be given where possible, in order to identify the most important reasons that caused it. As suggested by the EMA (2), the seed of the pseudorandom number generator that will be used to randomly generate imputations for the missing values is pre-specified ("55881234") to avoid bias being introduced by *post hoc* selection of the seed and therefore the random numbers to be imputed.

3.7.6 Interim Analyses

Not applicable

3.7.7 Data Monitoring

The sponsor's or representative (e.g., CRO's CRA) will maintain contact with the investigator and designated staff by telephone, and/or letter, and/or email between study visits. Monitoring visits to each investigational site will be conducted by the assigned CRA as described in the monitoring plan. The investigator (if regionally required, the heads of the medical institutions) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with Good Clinical Practices and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to the study protocol and data accuracy in accordance with federal regulations. All records at the investigational site, including source documents, are subject to inspection by the regulatory authorities and to review by the Ethical Committee.

3.7.8 SUMMARY OF STUDY DATA

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. Frequency counts and percentage of subjects within each category will be provided for categorical data. Ninety-five (95) percent confidence intervals (95% CI) may also be presented, as appropriate. In general, all data will be listed, sorted by site, treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each cohort in the order (cohort 1, 2, 3 and 4) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

3.8 GENERAL CONSIDERATIONS

3.8.1 Timing of Analyses

- Recruitment period will be: 24 months

- Research Agreement executed: July 2016
- Projected IRB/IEC approval: Nov 2016
- First Subject In: Dec 2016
- 50% Enrollment: Dec2017
- Last Subject In (100% enrollment): Dec 2018
- Last Subject Last Visit: Dec 2019
- Clinical Study Report April 2020

End of study is defined as Last Subject Last Visit.

1 TABLES, LISTING FIGURES

1.1 STUDY POPULATION

1.1.1 Recruited patients (sites/investigators)

In this section, the number of recruited patients overall and by sites is listed.

Table 2 Recruited patients by Hospital

Hospital	n (%)
Hospital 1:	
Hospital 2:	
Hospital 3:	
Hospital 4:	
Hospital 5:	
Hospital 6:	
Hospital 7:	
Hospital 8:	
Hospital 9:	
Hospital 10:	
Hospital 11:	
Hospital 12:	
Hospital 13:	
Hospital 14:	
Hospital 15:	
Hospital 16:	
Hospital 17:	
Hospital 18:	
Hospital 19:	
Hospital 20:	
Total	

1.1.2 Analyzed patients

If any patient is excluded from the study, it is listed in the table below, along with the reason for exclusion.

Table 3 Recruied patients and Analysis sets

	n	%[1]

Recruited patients		100,0
Reason for exclusion		
- Reason1		
- Reason 2		
...		
Analysis Sets		
Full Analysis Set: *All allocated patients. Patients that fulfil every inclusion criteria and none of the exclusion criteria, without any other reason for their exclusion*	**Yes**	
	No	
Per Protocol Analysis Set: *Patients who were allocated and received at least one dose of the assigned study drug and had no major protocol deviations. The subjects will complete both baseline and at least one post-baseline tumor assessments (week 12).*	**Yes**	
	No	
Safety Analysis Set*: Patients who were allocated and received at least one dose of the study drug and had at least one post-baseline safety evaluation (week 12). This will be the analysis set for all safety evaluations.*	**Yes**	
	No	
Pharmacodynamic Analysis Set*: Patients who have received at least one dose of study drug and have evaluable pharmacodynamic dats.*	**Yes**	
	No	

In the following table, those patints excluded from any of the analysis sets will be listed along with the reasons for exclusion.

Table 4 List of patients excluded from any of the analysis set

Number of patient	Cohort	Hospital	Analysis set	Reason for exclusion

The number of patients included and excluded from each hospital will be reported.

Table 5 Included/Excluded patients by Hospital

	Included	Excluded	Total
Hospital	**n (%)**	**n (%)**	**n (%)**

Hospital 1	
Hospital 2	
Hospital 3	
Hospital 4	
Hospital 5	
Hospital 6	
Hospital 7	
Hospital 8	
Hospital 9	
Hospital 10	
Hospital 11	
Hospital 12	
Hospital 13	
Hospital 14	
Hospital 15	
Hospital 16	
Hospital 17	
Hospital 18	
Hospital 19	
Hospital 20	
Total	n (100.0)

In the following table, the number of allocated patients in each one of the 4 cohorts by hospital will be shown.

Table 6 Patients allocated in each cohort by hospital

	Cohort 1	**Cohort 2**	**Cohort 3**	**Cohort 4**	**Total**
Hospital	**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%)
Hospital 7					n (100%)
Hospital 8					n (100%)
Hospital 9					n (100%)

Hospital 10	n (100%)
Hospital 11	n (100%)
Hospital 12	n (100%)
Hospital 13	n (100%)
Hospital 14	n (100%)
Hospital 15	n (100%)
Hospital 16	n (100%)
Hospital 17	n (100%)
Hospital 18	n (100%)
Hospital 19	n (100%)
Hospital 20	n (100%)
Total	n (100%)

1.2 DEMOGRAPHIC AND CLINICAL BASELINE CHARACTERISTICS

For the descriptive analysis of the patients, the full analysis set is used (see section29).

Table 7 Sociodemographic characteristics in overall

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Age (years)					
	n		**%[1]**	**95% CI of the proportion**	
Gender					
Male					
Female					
UNK					
Race/ethnicity					
Caucasic					
Afro-american					
Others					
UNK					

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

Table 8 Vital signs in overall

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Weight (kg)					
Height (cm)					

BMI	
Temperature	
Respiratory rate	
Systolic blood pressure	
Diastolic blood pressure	

Table 9 ECOG in overall

	n	%[1]	95% CI of the proportion
ECOG			
0			
1			
2			
3			
4			
UNK			

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

Table 10 Tumor characteristics overall

	n	%[1]	95% CI of the proportion
Histological type			
Well differentiated			
Moderately differentiated			
Poorly differentiated			
Ki-67 Index			
≤2			
3-20			
>20			
Mitotic Index 10 CGA			
GEP-NETs			
<2			
2-20			
>20			
Lung/thymus			
<2			
2-10			

>10	
Octreoscan/PET	
Positive	
Negative	
Number or extranodal locations	
0	
1	
2	
3 or more	
UNK	

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

Table 11 Time since radiological progression to inclusion

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Time since radiological PE to inclusion					

Table 12 Previous antineoplasic therapy

Name	n	%[1]	95% CI of the proportion
Therapy 1			
Therapy 2			
Therapy 3			
Therapy 4			
Therapy 5			
Therapy 6			

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

Table 13 Best response to previous antineoplasic therapy

	n	%[1]	95% CI of the proportion
Complete response			
Partial response			
Stable Disease			
Progression			
UNK			
Total			

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

Table 14 Baseline hematology laboratory test in overall

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Basophils					
Eosinphils					
Hematocrit					
Hemoglobin					
Lymphocytes					
Mean corpuscular hemoglobin					
Mean corpuscular hemoglobin concentration					
Mean corpuscular volume					
Monocytes					
Neutrophils					
Platelet count					
Red blood cell count					
Total white cell count					

Table 15 Baseline clinical chemistry (serum or plasma) laboratory test in overall

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Albumin					
Alkaline phosphatase					
Alanine aminotransferase					
Amylase					
Aspartate aminotransferase					
Bicarbonate					
Calcium					
Chloride					
Creatinine					
Clearance creatinine					
Gamma glutamyltransferase					

Glucose					
Lactate dehydrogenase					
Lipase					
Magnesium					
Potassium					
Sodium					
Total bilirubin					
Total protein					
Urea or blood urea nitrogen, depending on local practice					
Uric acid					

Table 16 Baseline urinalysis test in overall

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Bilirubin					
Blood					
Glucose					
Ketones					
pH					
Protein					
Specific gravity					
Colour and appearance					

Table 17 Baseline TSH, fT3 and fT4 in overall

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
TSH					
fT3					
fT4					

Table 18 Baseline coagulation in overall

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean

Partial thromboplastin Time (PTT)			
Prothrombin Time (PT)			
International Normalized Ratio (INR)			

	n	%1	95% CI of the proportion
Anti PNS			
Positive			
Negative			
UNK			

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

Table 19 Hepatitis and HIV serologies in overall

	n	%[1]	95% CI of the proportion
Hepatitis HCV			
Positive			
Negative			
HBsAg			
Positive			
Negative			
HBcAg			
Positive			
Negative			
HIV			
Positive			
Negative			

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

Table 20 Disease-specific tumor markers and Anti PNS

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cg A					
Neuron specific enolase					

Concomitant medications will be coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class.

Table 21 Concomitant medication

Concomitant medication Drug	n	%[1]
Drug class 1		
Drug 1.1		
Drug 1.2		
Drug 1….		
Drug class 2		
Drug 2.1		
Drug 2.2		
Drug 2….		
Drug class 3		
Drug 3.1		
Drug 3.2		
Drug 3….		

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

1.2.1 Demographic and other baseline characteristics in cohort 1

For the descriptive analysis of the patients, the full analysis set is used (see section 29).

Table 22 Sociodemographic characteristics in overall in cohort 1

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Age (years)					

	n	%[1]	95% CI of the proportion
Gender			
Male			
Female			
UNK			
Race/ethnicity			
Caucasic			
Afro-american			
Others			
UNK			

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

Table 23 Vital signs in overall in cohort 1

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Weight (kg)					

Height (cm)	
BMI	
Temperature	
Respiratory rate	
Systolic blood pressure	
Diastolic blood pressure	

Table 24 ECOG in overall in cohort 1

	n	%[1]	95% CI of the proportion
ECOG			
0			
1			
2			
3			
4			
UNK			

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

Table 25 Tumor characteristics overall in cohort 1

	n	%[1]	95% CI of the proportion
Histological type			
Well differentiated			
Moderately differentiated			
Poorly differentiated			
Ki-67 Index			
≤2			
3-20			
>20			
Mitotic Index 10 CGA			
GEP-NETs			
<2			
2-20			
>20			
Lung/thymus			
<2			

2-10	
>10	
Octreoscan/PET	
Positive	
Negative	
Number or extranodal locations	
0	
1	
2	
3 or more	
UNK	

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

Table 26 Time since radiological progression to inclusion in cohort 1

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Time since radiological PE to inclusion					

Table 27 Previous antineoplastic therapy in cohort 1

Name	n	%[1]	95% CI of the proportion
Therapy 1			
Therapy 2			
Therapy 3			
Therapy 4			
Therapy 5			
Therapy 6			

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

Table 28 Best response to previous antineoplastic therapy in cohort 1

	n	%[1]	95% CI of the proportion
Complete response			
Partial response			
Stable Disease			
Progression			
UNK			

Total					

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

Table 29 Baseline hematology laboratory test in overall in cohort 1

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Basophils					
Eosinphils					
Hematocrit					
Hemoglobin					
Lymphocytes					
Mean corpuscular hemoglobin					
Mean corpuscular hemoglobin concentration					
Mean corpuscular volume					
Monocytes					
Neutrophils					
Platelet count					
Red blood cell count					
Total white cell count					

Table 30 Baseline clinical chemistry (serum or plasma) laboratory test in overall in cohort 1

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Albumin					
Alkaline phosphatase					
Alanine aminotransferase					
Amylase					
Aspartate aminotransferase					
Bicarbonate					
Calcium					
Chloride					
Creatinine					
Clearance creatinine					

Gamma glutamyltransferase					
Glucose					
Lactate dehydrogenase					
Lipase					
Magnesium					
Potassium					
Sodium					
Total bilirubin					
Total protein					
Urea or blood urea nitrogen, depending on local practice					
Uric acid					

Table 31 Baseline urinalysis test in overall in cohort 1

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Bilirubin					
Blood					
Glucose					
Ketones					
pH					
Protein					
Specific gravity					
Colour and appearance					

Table 32 Baseline TSH, fT3 and fT4 in overall in cohort 1

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
TSH					
fT3					
fT4					

Table 33 Baseline coagulation in overall in cohort 1

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean

Partial thromboplastin Time (PTT)			
Prothrombin Time (PT)			
International Normalized Ratio (INR)			

	n	%1	95% CI of the proportion
Anti PNS			
Positive			
Negative			
UNK			

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

Table 34 Hepatitis and HIV serologies in overall in cohort 1

	n	%[1]	95% CI of the proportion
Hepatitis HCV			
Positive			
Negative			
HBsAg			
Positive			
Negative			
HBcAg			
Positive			
Negative			
HIV			
Positive			
Negative			

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

Table 35 Disease-specific tumor markers and Anti PNS in cohort 1

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cg A					
Neuron specific enolase					

Concomitant medications will be coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class.

Table 36 Concomitant medication in cohort 1

Concomitant medication Drug	n	%[1]
Drug class 1		
Drug 1.1		
Drug 1.2		
Drug 1….		
Drug class 2		
Drug 2.1		
Drug 2.2		
Drug 2….		
Drug class 3		
Drug 3.1		
Drug 3.2		
Drug 3….		

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

1.2.2 Demographic and other baseline characteristics in cohort 2

For the descriptive analysis of the patients, the full analysis set is used (see section 29).

Table 37 Sociodemographic characteristics in overall in cohort 2

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Age (years)					
	n		**%[1]**	**95% CI of the proportion**	
Gender					
Male					
Female					
UNK					
Race/ethnicity					
Caucasic					
Afro-american					
Others					
UNK					

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

Table 38 Vital signs in overall in cohort 2

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Weight (kg)					

Height (cm)	
BMI	
Temperature	
Respiratory rate	
Systolic blood pressure	
Diastolic blood pressure	

Table 39 ECOG in overall in cohort 2

	n	%[1]	95% CI of the proportion
ECOG			
0			
1			
2			
3			
4			
UNK			

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

Table 40 Tumor characteristics overall in cohort 2

	n	%[1]	95% CI of the proportion
Histological type			
Well differentiated			
Moderately differentiated			
Poorly differentiated			
Ki-67 Index			
≤2			
3-20			
>20			
Mitotic Index 10 CGA			
GEP-NETs			
<2			
2-20			
>20			
Lung/thymus			
<2			

2-10	
>10	
Octreoscan/PET	
Positive	
Negative	
Number or extranodal locations	
0	
1	
2	
3 or more	
UNK	

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

Table 41 Time since radiological progression to inclusion in cohort 2

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Time since radiological PE to inclusion					

Table 42 Previous antineoplastic therapy in cohort 2

Name	n	%[1]	95% CI of the proportion
Therapy 1			
Therapy 2			
Therapy 3			
Therapy 4			
Therapy 5			
Therapy 6			

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

Table 43 Best response to previous antineoplastic therapy in cohort 2

	n	%[1]	95% CI of the proportion
Complete response			
Partial response			
Stable Disease			
Progression			
UNK			
Total			

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

Table 44 Baseline hematology laboratory test in overall in cohort 2

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Basophils					
Eosinphils					
Hematocrit					
Hemoglobin					
Lymphocytes					
Mean corpuscular hemoglobin					
Mean corpuscular hemoglobin concentration					
Mean corpuscular volume					
Monocytes					
Neutrophils					
Platelet count					
Red blood cell count					
Total white cell count					

Table 45 Baseline clinical chemistry (serum or plasma) laboratory test in overall in cohort 2

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Albumin					
Alkaline phosphatase					
Alanine aminotransferase					
Amylase					
Aspartate aminotransferase					
Bicarbonate					
Calcium					
Chloride					
Creatinine					
Clearance creatinine					
Gamma					

glutamyltransferase					
Glucose					
Lactate dehydrogenase					
Lipase					
Magnesium					
Potassium					
Sodium					
Total bilirubin					
Total protein					
Urea or blood urea nitrogen, depending on local practice					
Uric acid					

Table 46 Baseline urinalysis test in overall in cohort 2

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Bilirubin					
Blood					
Glucose					
Ketones					
pH					
Protein					
Specific gravity					
Colour and appearance					

Table 47 Baseline TSH, fT3 and fT4 in overall in cohort 2

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
TSH					
fT3					
fT4					

Table 48 Baseline coagulation in overall in cohort 2

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean

Partial thromboplastin Time (PTT)			
Prothrombin Time (PT)			
International Normalized Ratio (INR)			

	n	%1	95% CI of the proportion
Anti PNS			
Positive			
Negative			
UNK			

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

Table 49 Hepatitis and HIV serologies in overall in cohort 2

	n	%[1]	95% CI of the proportion
Hepatitis HCV			
Positive			
Negative			
HBsAg			
Positive			
Negative			
HBcAg			
Positive			
Negative			
HIV			
Positive			
Negative			

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

Table 50 Disease-specific tumor markers and Anti PNS in cohort 2

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cg A					
Neuron specific enolase					

Concomitant medications will be coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class.

Table 51 Concomitant medication in cohort 2

Concomitant medication Drug	n	%[1]
Drug class 1		
Drug 1.1		
Drug 1.2		
Drug 1….		
Drug class 2		
Drug 2.1		
Drug 2.2		
Drug 2….		
Drug class 3		
Drug 3.1		
Drug 3.2		
Drug 3….		

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

1.2.3 Demographic and other baseline characteristics in cohort 3

For the descriptive analysis of the patients, the full analysis set is used (see section 29).

Table 52 Sociodemographic characteristics in overall in cohort 3

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Age (years)					
	n		**%[1]**	**95% CI of the proportion**	
Gender					
Male					
Female					
UNK					
Race/ethnicity					
Caucasic					
Afro-american					
Others					
UNK					

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

Table 53 Vital signs in overall in cohort 3

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Weight (kg)					

Height (cm)	
BMI	
Temperature	
Respiratory rate	
Systolic blood pressure	
Diastolic blood pressure	

Table 54 ECOG in overall in cohort 3

	n	%[1]	95% CI of the proportion
ECOG			
0			
1			
2			
3			
4			
UNK			

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

Table 55 Tumor characteristics overall in cohort 3

	n	%[1]	95% CI of the proportion
Histological type			
Well differentiated			
Moderately differentiated			
Poorly differentiated			
Ki-67 Index			
≤2			
3-20			
>20			
Mitotic Index 10 CGA			
GEP-NETs			
<2			
2-20			
>20			
Lung/thymus			
<2			

2-10	
>10	
Octreoscan/PET	
Positive	
Negative	
Number or extranodal locations	
0	
1	
2	
3 or more	
UNK	

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

Table 56 Time since radiological progression to inclusion in cohort 3

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Time since radiological PE to inclusion					

Table 57 Previous antineoplastic therapy in cohort 3

Name	n	%[1]	95% CI of the proportion
Therapy 1			
Therapy 2			
Therapy 3			
Therapy 4			
Therapy 5			
Therapy 6			

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

Table 58 Best response to previous antineoplastic therapy in cohort 3

	n	%1	95% CI of the proportion
Complete response			
Partial response			
Stable Disease			
Progression			
UNK			
Total			

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

Table 59 Baseline hematology laboratory test in overall in cohort 3

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Basophils					
Eosinphils					
Hematocrit					
Hemoglobin					
Lymphocytes					
Mean corpuscular hemoglobin					
Mean corpuscular hemoglobin concentration					
Mean corpuscular volume					
Monocytes					
Neutrophils					
Platelet count					
Red blood cell count					
Total white cell count					

Table 60 Baseline clinical chemistry (serum or plasma) laboratory test in overall in cohort 3

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Albumin					
Alkaline phosphatase					
Alanine aminotransferase					
Amylase					
Aspartate aminotransferase					
Bicarbonate					
Calcium					
Chloride					
Creatinine					
Clearance creatinine					
Gamma glutamyltransferase					
Glucose					

Lactate dehydrogenase					
Lipase					
Magnesium					
Potassium					
Sodium					
Total bilirubin					
Total protein					
Urea or blood urea nitrogen, depending on local practice					
Uric acid					

Table 61 Baseline urinalysis test in overall in cohort 3

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Bilirubin					
Blood					
Glucose					
Ketones					
pH					
Protein					
Specific gravity					
Colour and appearance					

Table 62 Baseline TSH, fT3 and fT4 in overall in cohort 3

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
TSH					
fT3					
fT4					

Table 63 Baseline coagulation in overall in cohort 3

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Partial thromboplastin Time (PTT)					
Prothrombin Time (PT)					

International Normalized Ratio (INR)			
	n	%1	95% CI of the proportion
Anti PNS			
Positive			
Negative			
UNK			

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

Table 64 Hepatitis and HIV serologies in overall in cohort 3

	n	%[1]	95% CI of the proportion
Hepatitis HCV			
Positive			
Negative			
HBsAg			
Positive			
Negative			
HBcAg			
Positive			
Negative			
HIV			
Positive			
Negative			

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

Table 65 Disease-specific tumor markers and Anti PNS in cohort 3

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cg A					
Neuron specific enolase					

Concomitant medications will be coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class.

Table 66 Concomitant medication in cohort 3

Concomitant medication Drug	n	%[1]

Drug class 1	
Drug 1.1	
Drug 1.2	
Drug 1….	
Drug class 2	
Drug 2.1	
Drug 2.2	
Drug 2….	
Drug class 3	
Drug 3.1	
Drug 3.2	
Drug 3….	

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

1.2.4 Demographic and other baseline characteristics in cohort 4

For the descriptive analysis of the patients, the full analysis set is used (see section 29).

Table 67 Sociodemographic characteristics in overall in cohort 4

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Age (years)					
	n		**%[1]**	**95% CI of the proportion**	
Gender					
Male					
Female					
UNK					
Race/ethnicity					
Caucasic					
Afro-american					
Others					
UNK					

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

Table 68 Vital signs in overall in cohort 4

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Weight (kg)					
Height (cm)					

BMI	
Temperature	
Respiratory rate	
Systolic blood pressure	
Diastolic blood pressure	

Table 69 ECOG in overall in cohort 4

	n	%[1]	95% CI of the proportion
ECOG			
0			
1			
2			
3			
4			
UNK			

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

Table 70 Tumor characteristics overall in cohort 4

	n	%[1]	95% CI of the proportion
Histological type			
Well differentiated			
Moderately differentiated			
Poorly differentiated			
Ki-67 Index			
≤2			
3-20			
>20			
Mitotic Index 10 CGA			
GEP-NETs			
<2			
2-20			
>20			
Lung/thymus			
<2			
2-10			

>10	
Octreoscan/PET	
Positive	
Negative	
Number or extranodal locations	
0	
1	
2	
3 or more	
UNK	

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

Table 71 Time since radiological progression to inclusion in cohort 4

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Time since radiological PE to inclusion					

Table 72 Previous antineoplastic therapy in cohort 4

Name	n	%[1]	95% CI of the proportion
Therapy 1			
Therapy 2			
Therapy 3			
Therapy 4			
Therapy 5			
Therapy 6			

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

Table 73 Best response to previous antineoplastic therapy in cohort 4

	n	%[1]	95% CI of the proportion
Complete response			
Partial response			
Stable Disease			
Progression			
UNK			

Total					

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

Table 74 Baseline hematology laboratory test in overall in cohort 4

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Basophils					
Eosinphils					
Hematocrit					
Hemoglobin					
Lymphocytes					
Mean corpuscular hemoglobin					
Mean corpuscular hemoglobin concentration					
Mean corpuscular volume					
Monocytes					
Neutrophils					
Platelet count					
Red blood cell count					
Total white cell count					

Table 75 Baseline clinical chemistry (serum or plasma) laboratory test in overall in cohort 4

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Albumin					
Alkaline phosphatase					
Alanine aminotransferase					
Amylase					
Aspartate aminotransferase					
Bicarbonate					
Calcium					
Chloride					
Creatinine					

Clearance creatinine
Gamma glutamyltransferase
Glucose
Lactate dehydrogenase
Lipase
Magnesium
Potassium
Sodium
Total bilirubin
Total protein
Urea or blood urea nitrogen, depending on local practice
Uric acid

Table 76 Baseline urinalysis test in overall in cohort 4

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Bilirubin					
Blood					
Glucose					
Ketones					
pH					
Protein					
Specific gravity					
Colour and appearance					

Table 77 Baseline TSH, fT3 and fT4 in overall in cohort 4

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
TSH					
fT3					
fT4					

Table 78 Baseline coagulation in overall in cohort 4

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Partial thromboplastin Time (PTT)					
Prothrombin Time (PT)					
International Normalized Ratio (INR)					

	n	%1	95% CI of the proportion
Anti PNS			
Positive			
Negative			
UNK			

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

Table 79 Hepatitis and HIV serologies in overall in cohort 4

	n	%[1]	95% CI of the proportion
Hepatitis HCV			
Positive			
Negative			
HBsAg			
Positive			
Negative			
HBcAg			
Positive			
Negative			
HIV			
Positive			
Negative			

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

Table 80 Disease-specific tumor markers and Anti PNS in cohort 4

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cg A					
Neuron specific enolase					

Concomitant medications will be coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized

and listed by drug and drug class.

Table 81 Concomitant medication in cohort 4

Concomitant medication Drug	**n**	**%[1]**
Drug class 1		
Drug 1.1		
Drug 1.2		
Drug 1….		
Drug class 2		
Drug 2.1		
Drug 2.2		
Drug 2….		
Drug class 3		
Drug 3.1		
Drug 3.2		
Drug 3….		

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

1.3 STUDY MEDICATION

For the descriptive analysis of the patients, the full analysis set is used (see section 29).

Table 82 Adherence to Durvalumab

	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles received					
12 Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
0					
1					
2					
3					
4					
5					
6					
7					
8					

9					
10					
11					
12					
Cycles delayed		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles delayed					
Cycles omitted		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles omitted					

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

Table 83 Adherence to Tremelimumab

	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles received					
4 Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
0					
1					
2					
3					
4					
Cycles delayed		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles delayed					
Cycles omitted		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cycles omitted					

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

1.3.1 Study medication in cohort 1

For the descriptive analysis of the patients, the full analysis set is used (see section 29).

Table 84 Adherence to Durvalumab in cohort 1

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cycles received					
12 Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
0					
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Cycles delayed		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles delayed					
Cycles omitted		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cycles omitted					

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

Table 85 Adherence to Tremelimumab in cohort 1

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cycles received					
4 Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
0					
1					
2					
3					
4					
Cycles delayed		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles delayed					
Cycles omitted		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles omitted					

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

1.3.2 Study medication in cohort 2

For the descriptive analysis of the patients, the full analysis set is used (see section 29).

Table 86 Adherence to Durvalumab in cohort 2

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cycles received					
12 Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					

Cycles received	n	%[1]	95% CI of the proportion
0			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			

Cycles delayed	n	%[1]	95% CI of the proportion
Yes			
No			

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cycles delayed					

Cycles omitted	n	%[1]	95% CI of the proportion
Yes			
No			

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cycles omitted					

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

Table 87 Adherence to Tremelimumab in cohort 2

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cycles received					

4 Cycles received	n	%[1]	95% CI of the proportion
Yes			
No			

Cycles received	n	%[1]	95% CI of the proportion
0			
1			
2			

3					
4					
Cycles delayed		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles delayed					
Cycles omitted		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles omitted					

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

1.3.3 Study medication in cohort 3

For the descriptive analysis of the patients, the full analysis set is used (see section 29).

Table 88 Adherence to Durvalumab in cohort 3

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cycles received					
12 Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
0					
1					
2					
3					
4					
5					
6					
7					
8					
9					

10					
11					
12					
Cycles delayed		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles delayed					
Cycles omitted		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles omitted					

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

Table 89 Adherence to Tremelimumab in cohort 3

	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles received					
4 Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
0					
1					
2					
3					
4					
Cycles delayed		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles delayed					
Cycles omitted		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**

Cycles omitted					

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

1.3.4 Study medication in cohort 4

For the descriptive analysis of the patients, the full analysis set is used (see section 29).

Table 90 Adherence to Durvalumab in cohort 4

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cycles received					
12 Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
0					
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Cycles delayed		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles delayed					
Cycles omitted		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**

Cycles omitted					

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

Table 91 Adherence to Tremelimumab in cohort 4

	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cycles received					
4 Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
Cycles received		**n**	**%[1]**	**95% CI of the proportion**	
0					
1					
2					
3					
4					
Cycles delayed		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles delayed					
Cycles omitted		**n**	**%[1]**	**95% CI of the proportion**	
Yes					
No					
	n	**Mean (SD)**	**Median (IQR)**	**Min-Max**	**95% CI of the mean**
Cycles omitted					

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

2 EFFICACY ANALYSES

All efficacy analyses will be based primarily on the Full Analysis Set and secondarily on the Per Protocol Analysis Set.

2.1 PRIMARY EFFICACY ANALYSES

The analysis of clinical benefit rate and overall survival rate will be performed independently for each study cohort when the last patient included in the corresponding cohort of the study will arrived to 9 months after inclusion in the study or have progressed. According to the protocol, the primary objective of the study will be based on the investigator assessment. 9-months clinical benefit rate (CBR) by Response Evaluation Criteria In Solid Tumors (RECIST version 1.1), which is defined as the percentage of patients achieving complete response (CR), partial response (PR), or stable disease (SD) at month 9 after durvalumab plus tremelimumab was started.

2.1.1 Primary efficacy analyses in the Full Analysis Set

The primary endpoint for cohort 1, 2 and 3 is the CBR, nevertheless the result for all the cohorts will be shown below:

Table 92 Clinical benefit rate (investigator assessment) at 9 months in the Full Analysis Set

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
CBR at 9 months	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
Yes (CR, PR, SD)					
No (PD)					
Total	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)

The primary endpoint for cohort 4 is 9-months overall survival rate, which is defined as the percentage of patients alive at 9 months after durvalumab plus tremelimumab was started, nevertheless the result for all the cohorts will be shown in the following table.

Table 93 Overall survival rate at 9 months in the Full Analysis Set

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
Overall survival rate at 9 months	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
Alive					
Death					
Total	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)

Concordance between investigator assessment and independent central radiology review will be analyzed using Cohen's Kappa. Although no significant differences are expected, a sensitivity analysis for the primary efficacy analysis will be performed using as response variable independent central radiology assessment.

Table 94 Agreement in CBR by Cohen's kappa coefficient in the Full Analysis Set

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
CBR at 9 months	**Kappa *k***	**Kappa *k***	**Kappa *k***	**Kappa *k***	**Kappa *k***
Investigator assessment vs. Independent review					

9-months clinical benefit rate (CBR) by Response Evaluation Criteria In Solid Tumors (RECIST version 1.1), according to independent central radiology.

Table 95 Clinical benefit rate (independent central radiology) at 9 months in the Full Analysis Set

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
CBR at 9 months	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
Yes (CR, PR, SD)					
No (PD)					
Total	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)

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2.1.2 Primary efficacy analyses in the Per Protocol Analysis Set

The primary endpoint for cohort 1, 2 and 3 is the CBR, nevertheless the result for all the cohorts will be shown below:

Table 96 Clinical benefit rate (investigator assessment) at 9 months in the Per Protocol Analysis Set

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
CBR at 9 months	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
Yes (CR, PR, SD)					
No (PD)					
Total	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)

The primary endpoint for cohort 4 is 9-months overall survival rate, which is defined as the percentage of patients alive at 9 months after durvalumab plus tremelimumab was started, nevertheless the result for all the cohorts will be shown in the following table.

Table 97 Overall survival rate at 9 months in the Per Protocol Analysis Set

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
Overall survival rate at 9 months	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
Alive					
Death					
Total	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)

Concordance between investigator assessment and independent central radiology review will be analyzed using Cohen's Kappa. Although no significant differences are expected, a sensitivity analysis for the primary efficacy analysis will be performed using as response variable independent

central radiology assessment.

Table 98 Agreement in CBR by Cohen's kappa coefficient in the Per Protocol Analysis Set

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
CBR at 9 months	**Kappa *k***	**Kappa *k***	**Kappa *k***	**Kappa *k***	**Kappa *k***
Investigator assessment vs. Independent review					

9-months clinical benefit rate (CBR) by Response Evaluation Criteria In Solid Tumors (RECIST version 1.1), according to independent central radiology.

Table 99 Clinical benefit rate (independent central radiology) at 9 months in the Per Protocol Analysis Set

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
CBR at 9 months	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
Yes (CR, PR, SD)					
No (PD)					
Total	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)

2.2 SECONDARY EFFICACY ANALYSES

The analysis of clinical benefit rate and overall survival rate will be performed independently for each study cohort when the last patient included in the corresponding cohort of the study will arrived to 9 months after inclusion in the study or have progressed. According to the protocol, the secondary objectives of the study will be based on the investigator assessment. 9-months clinical benefit rate (CBR) by Immune-related Response Evaluation Criteria In Solid Tumors (irRECIST), is defined as the percentage of patients achieving complete response (CR), partial response (PR), or stable disease (SD) at month 9 after durvalumab plus tremelimumab was started.

2.2.1 Overall response rate (ORR)

The Overall response rate (ORR) by irRECIST and the duration of the response is shown in the following tables for the Full Analysis Set:

Table 100 ORR in the Full Analysis Set

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
ORR	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
CR					
PR					
SD					
PD					
Total	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%)

Table 101 Duration of the response in the Full Analysis Set

Duration of the response (months)	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cohort 1					
Cohort 2					
Cohort 3					
Cohort 4					
Total					

The Overall response rate (ORR) by irRECIST and the duration of the response is shown in the following table for the Per Protocol Analysis Set:

Table 102 ORR in the Per Protocol Analysis Set

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
ORR	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
CR					
PR					
SD					
PD					
Total	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%)

Table 103 Duration of the response in the Per Protocol Analysis Set

Duration of the response (months)	n	Mean (SD)	Median (IQR)	Min-Max	95% CI of the mean
Cohort 1					
Cohort 2					
Cohort 3					
Cohort 4					
Total					

2.2.2 Response status at 6 and 12 months

The response status according to irRECIST at 6 and 12 months after start of study treatment is shown in the following tables for the Full Analysis Set:

Table 104 Response status at 6 months in the Full Analysis Set

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
Response at 6 months	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
CR					
PR					
SD					
PD					
Total	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%)

Table 105 Response status at 12 months in the Full Analysis Set

	Cohort 1	**Cohort 2**	**Cohort 3**	**Cohort 4**	**Total**
Response at 12 months	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
CR					
PR					
SD					
PD					
Total	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%)

The response status according to irRECIST at 6 and 12 months after start of study treatment is shown in the following tables in the Per Protocol Analysis Set:

Table 106 Response status at 6 months in the Per Protocol Analysis Set

	Cohort 1	**Cohort 2**	**Cohort 3**	**Cohort 4**	**Total**
Response at 6 months	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
CR					
PR					

SD					
PD					
Total	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%)

Table 107 Response status at 12 months in the Per Protocol Analysis Set

	Cohort 1	**Cohort 2**	**Cohort 3**	**Cohort 4**	**Total**
Response at 12 months	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
CR					
PR					
SD					
PD					
Total	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%)

2.2.3 Progression Free Survival (PFS)

The median progression-free survival time (PFS) according to irRECIST, along with PFS at 6 and 12 months is shown in the following tables for the Full Analysis Set:

Table 108 Progression Free Survival in the Full Analysis Set

		Number of PD	N of patients at risk	% of cumulative progression free survival		95% CI of PFS
At 6 months	**Cohort 1**					
	Cohort 2					
	Cohort 3					
	Cohort 4					
	Total					
At 12 months	**Cohort 1**					
	Cohort 2					
	Cohort 3					
	Cohort 4					
	Total					
		N (%) of PD	**Median (months)**	**Min-Max**	**Standard error**	**95% CI of the median**
Progression Free Survival	**Cohort 1**					
	Cohort 2					
	Cohort 3					
	Cohort 4					
	Total					

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Figure 1. Progression Free Survival (Full Analysis Set)

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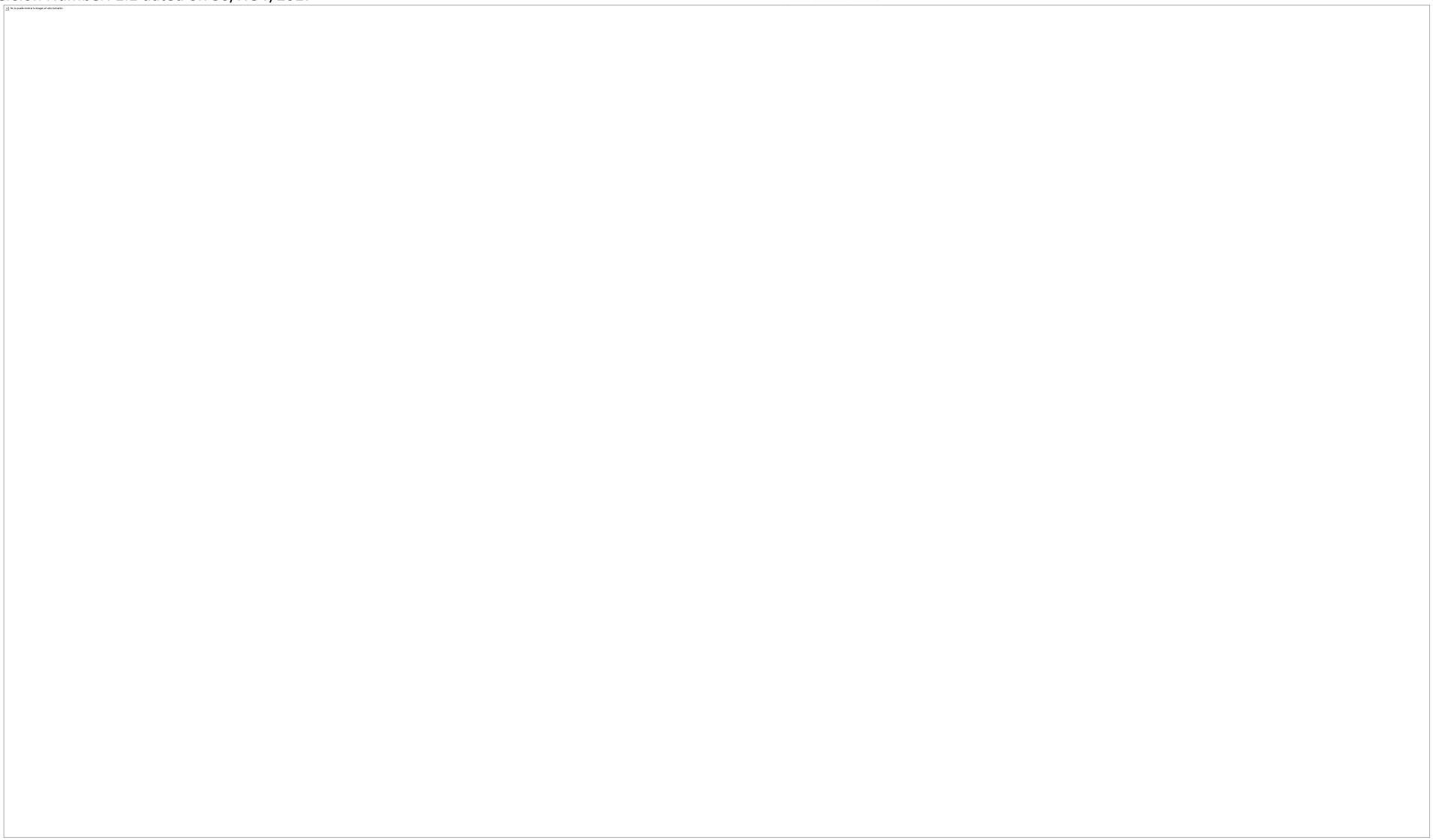

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The median progression-free survival time (PFS) according to irRECIST, along with PFS at 6 and 12 months is shown in the following tables for the Per-Protocol Analysis Set:

Table 109 Progression Free Survival in the Per-Protocol Analysis Set

		Number of PD	N of patients at risk	% of cumulative progression free survival		95% CI of PFS
At 6 months	**Cohort 1**					
	Cohort 2					
	Cohort 3					
	Cohort 4					
	Total					
At 12 months	**Cohort 1**					
	Cohort 2					
	Cohort 3					
	Cohort 4					
	Total					
		N (%) of PD	**Median (months)**	**Min-Max**	**Standard error**	**95% CI of the median**
Progression Free Survival	**Cohort 1**					
	Cohort 2					
	Cohort 3					
	Cohort 4					
	Total					

Figure 2. Progression Free Survival (Per-Protocol Analysis Set)

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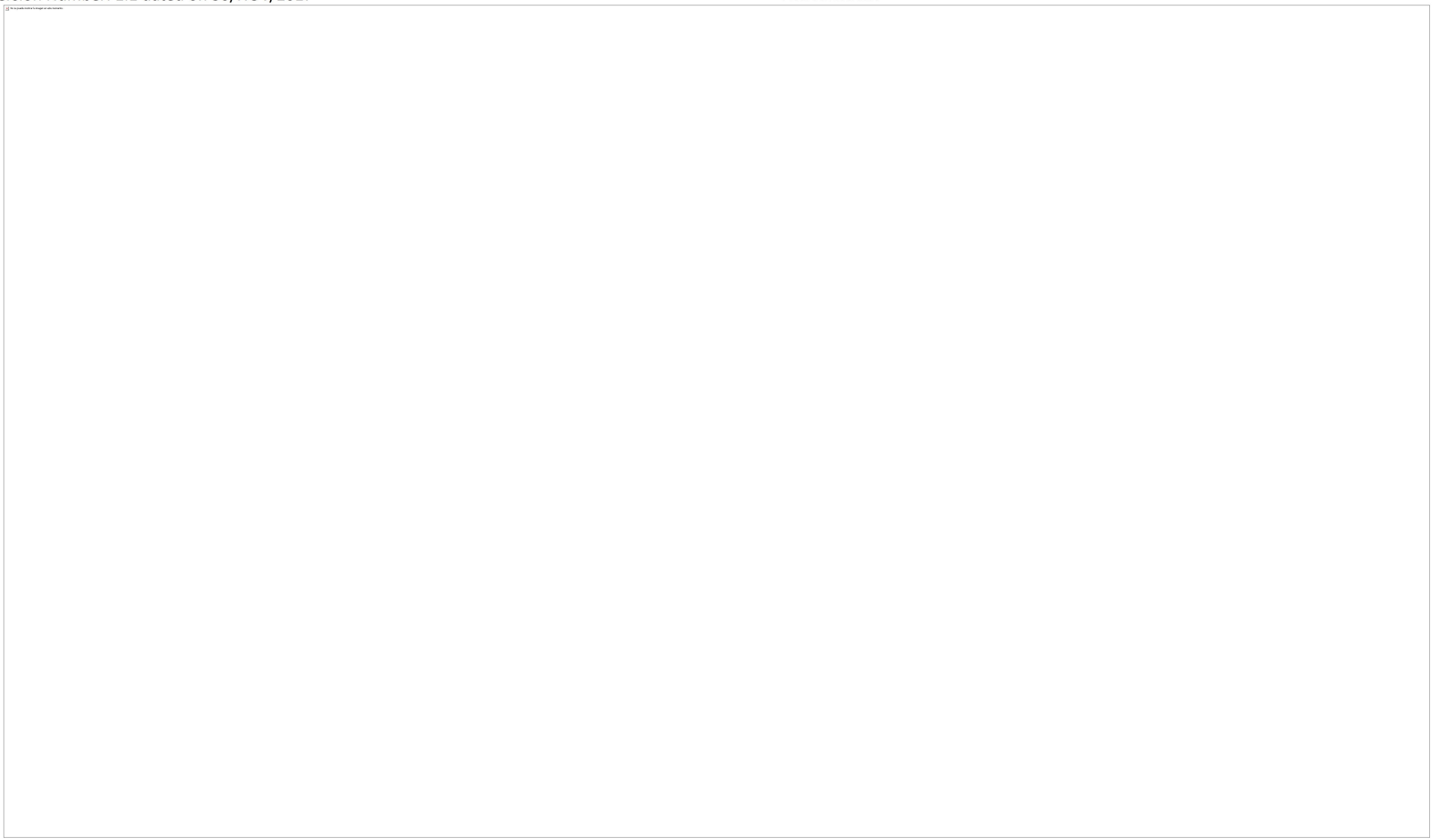

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2.2.4 Overall Survival (OS)

The median overall survival time (OS), along with OS at 6 and 12 months is shown in the following tables for the Full Analysis Set:

Table 110 Overall Survival in the Full Analysis Set

		Number of exitus	N of patients at risk	% of cumulative overall survival	95% CI of OS
At 6 months	**Cohort 1**				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Total				
At 12 months	**Cohort 1**				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Total				

		N (%) of exitus	Median (months)	Min-Max	Standard error	95% CI of the median
Overall Survival	**Cohort 1**					
	Cohort 2					
	Cohort 3					
	Cohort 4					
	Total					

Figure 3. Overall Survival (Full Analysis Set)

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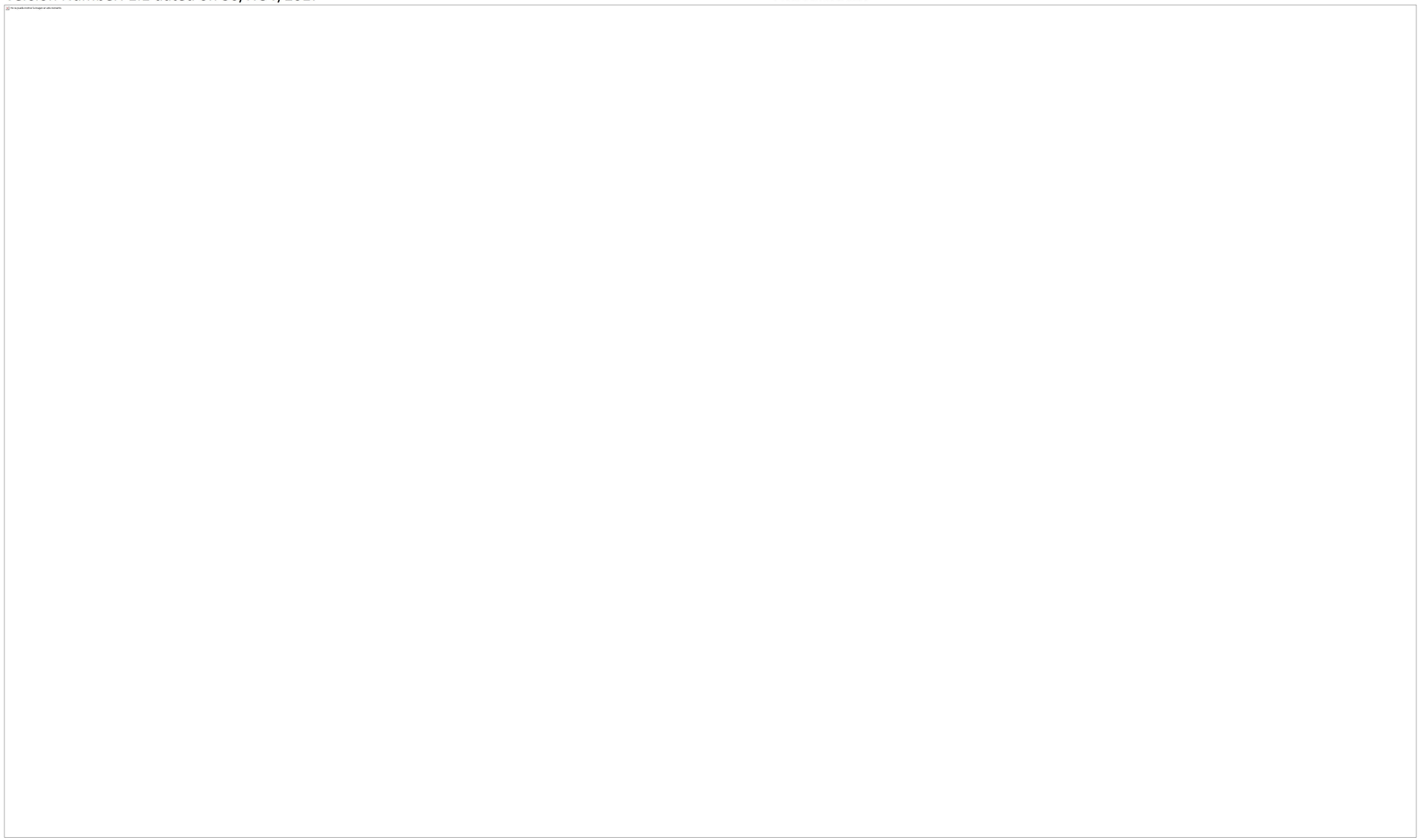

The median overall survival time (OS), along with OS at 6 and 12 months is shown in the following tables for the Per-Protocol Analysis Set:

Table 111 Overall Survival in the Per-Protocol Analysis Set

		Number of exitus	N of patients at risk	% of cumulative overall survival	95% CI of OS
At 6 months	**Cohort 1**				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Total				
At 12 months	**Cohort 1**				
	Cohort 2				
	Cohort 3				
	Cohort 4				
	Total				

		N (%) of exitus	Median (months)	Min-Max	Standard error	95% CI of the median
Overall Survival	**Cohort 1**					
	Cohort 2					
	Cohort 3					
	Cohort 4					
	Total					

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Figure 4. Progression Free Survival (Per-Protocol Analysis Set)

3 SAFETY ANALYSES

The aim of this section is to assess the safety profile of durvalumab and tremelimumab in subjects with advanced neuroendocrine neoplasms.

3.1 MOST FREQUENT TOXICITIES

In the following tables, the most frequent toxicities, those which presented a frequency>10% will be anlayzed in overall and by cohort.

Table 112 Most frequent toxicities in overall

		Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
		n (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)	n (%, 95% CI)
Toxicity 1	Yes					
	No					
	Total					
Grade toxicity 1	Grade 1					
	Grade 2					
	Grade 3					
	Grade 4					
	Total					
Toxicity 2	Yes					
	No					
	Total					
Grade toxicity 2	Grade 1					
	Grade 2					
	Grade 3					
	Grade 4					

	Total
...	**Yes**
	No
	Total
...	**Grade 1**
	Grade 2
	Grade 3
	Grade 4
	Total

3.2 TOXICITIES GRADE≥3

In the following table, the number and relative frequencies of patients with at least one grade ≥3 toxicity are summarised:

Table 113 Toxicities grade ≥3 during follow-up

	Cohort 1	**Cohort 2**	**Cohort 3**	**Cohort 4**	**Total**
Toxicities grade 3	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
Yes					
No					
Total	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)

In the following table, every toxicity grade ≥3 will be summarised, separately in each one of the 4 cohorts and in overall.

Table 114 Every toxicity grade ≥3 in overall and by cohort

	Cohort 1	**Cohort 2**	**Cohort 3**	**Cohort 4**	**Total**

Toxicities	n (%, CI 95%)	n (%, CI 95%)	n (%, CI 95%)	n (%, CI 95%)	n (%, CI 95%)
Toxicity 1 G≥*3*					
Toxicity 2 G≥*3*					
Toxicity 3 G≥*3*					
Toxicity 4 G≥*3*					
Toxicity 5 G≥*3*					
Toxicity 6 G≥*3*					
Toxicity 7 G≥*3*					
...					

In the following table, details of every toxicity grade ≥3 will be summarised:

Table 115 Details of every toxicity grade ≥3 by patient

Patient number	Hospital	Cohort	Toxicity	Grade

3.3 EVERY TOXICITY

In the following table, the number and relative frequencies of patients with at least one toxicity are summarised:

Table 116 Patients with at least one toxicity during follow-up

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
At least one toxicity	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
Yes					
No					
Total	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)

In the following table, every toxicity grade ≥3 will be summarised, separately in each one of the 4 cohorts and in overall.

Table 117 Every toxicity grade ≥3 in overall and by cohort

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Total
Toxicities	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**	**n (%, CI 95%)**
Toxicity 1 G*1*					
Toxicity 1 G*2*					
Toxicity 1 G*3*					
Toxicity 1 G*4*					
Toxicity 2 G*1*					
Toxicity 2 G*2*					
Toxicity 2 G*3*					
Toxicity 2 G*4*					
Toxicity 3 G*1*					

Toxicity 3 G*2*	
Toxicity 3 G*3*	
Toxicity 3 G*4*	
…	

4 EXPLORATORY ANALYSES

The aims of this section are:

- To evaluate biochemical response (changes in CgA and NSE levels) and its association with response rate and progression-free survival.
- To assess whether baseline tumor and blood biomarkers may be predictive of response to durvalumab and tremelimumab therapy.
- To explore additional hypotheses related to biomarkers and relationship to durvalumab and tremelimumab efficacy and/or toxicity and neuroendocrine tumors evolution that may arise from internal or external research activities.

4.1 LOGISTIC REGRESSION: PREDICTOR FACTORS OF RESPONSE (CBR AT 9 MONTHS) IN EACH COHORT

A multivariate analysis will be carried out using the Logistic Regression model in order to determine predictor factors for response (CBR at 9 months) ***in each cohort***. Firstly univariate analysis are carried out separately for each one of the possible predictor factors to decide which variables are entered in the multivariate models; only those with a statistical association with the dependent variable would be selected. Backward elimination stepwise process would be used to select the model. In the first step all possible predictors are entered in the model and in each step, the variable that is least significant (that is, the one with the largest P value) is removed and the model is refitted. Each subsequent step removed the least significant variable in the model until all remaining variables have individual P values smaller than 0.05.

Table 118 Univariate Logistic Regression for Response (CBR at 9 months) in cohort 1 (Full Analysis Set)

p-value (variable)		OR	CI 95% of OR	N	p-value (categories)
Factor 1	**Category 1**				
	Category 2				

Factor 2	**Category 1**					
	Category 2					
Factor 3	**Category 1**					
	Category 2					
Factor 4	**Category 1**					
	Category 2					
…	**Category 1**					
	Category 2					

Table 119 Final multivariate Logistic Regression for Response (CBR at 9 months) in cohort 1 (Full Analysis Set)

	p-value (variable)		**OR**	**CI 95% of OR**	**N**	**p-value (categories)**
Factor 1		**Category 1**				
		Category 2				
Factor 2		**Category 1**				
		Category 2				
…		**Category 1**				
		Category 2				

Table 120 Univariate Logistic Regression for Response (CBR at 9 months) in cohort 2 (Full Analysis Set)

	p-value (variable)		**OR**	**CI 95% of OR**	**N**	**p-value (categories)**
Factor 1		**Category 1**				
		Category 2				

Factor 2	**Category 1**				
	Category 2				
Factor 3	**Category 1**				
	Category 2				
Factor 4	**Category 1**				
	Category 2				
…	**Category 1**				
	Category 2				

Table 121 Final multivariate Logistic Regression for Response (CBR at 9 months) in cohort 2 (Full Analysis Set)

p-value (variable)		**OR**	**CI 95% of OR**	**N**	**p-value (categories)**
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
…	**Category 1**				
	Category 2				

Table 122 Univariate Logistic Regression for Response (CBR at 9 months) in cohort 3 (Full Analysis Set)

p-value (variable)		**OR**	**CI 95% of OR**	**N**	**p-value (categories)**
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				

	Category 2					
Factor 3	**Category 1**					
	Category 2					
Factor 4	**Category 1**					
	Category 2					
…	**Category 1**					
	Category 2					

Table 123 Final multivariate Logistic Regression for Response (CBR at 9 months) in cohort 3 (Full Analysis Set)

	p-value (variable)		**OR**	**CI 95% of OR**	**N**	**p-value (categories)**
Factor 1		**Category 1**				
		Category 2				
Factor 2		**Category 1**				
		Category 2				
…		**Category 1**				
		Category 2				

Table 124 Univariate Logistic Regression for Response (CBR at 9 months) in cohort 4 (Full Analysis Set)

	p-value (variable)		**OR**	**CI 95% of OR**	**N**	**p-value (categories)**
Factor 1		**Category 1**				
		Category 2				
Factor 2		**Category 1**				
		Category 2				

Factor 3	**Category 1**					
	Category 2					
Factor 4	**Category 1**					
	Category 2					
…	**Category 1**					
	Category 2					

Table 125 Final multivariate Logistic Regression for Response (CBR at 9 months) in cohort 4 (Full Analysis Set)

p-value (variable)		**OR**	**CI 95% of OR**	**N**	**p-value (categories)**
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
…	**Category 1**				
	Category 2				

4.2 COX REGRESSION: PREDICTOR FACTORS OF SURVIVAL IN EACH COHORT

4.2.1 Cox Regression: predictor factors of PFS in each cohort

A multivariate analysis will be carried out using the Cox Regression model in order to determine predictor fators for PFS ***in each cohort***. Firstly univariate analysis are carried out separately for each one of the possible predictor factors to decide which variables are entered in the multivariate models; only those with a statistical association with the dependent variable would be selected. Backward elimination stepwise process would be used to select the model. In the first step all possible predictors are entered in the model and in each step, the variable that is least significant (that is, the one with the largest P value) is removed and the model is refitted. Each subsequent step removed the least significant variable in the model until

all remaining variables have individual P values smaller than 0.05.

Table 126 Univariate Cox Regression for PFS in cohort 1 (Full Analysis Set)

		HR	CI 95% of HR	p-value	n
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
Factor 3	**Category 1**				
	Category 2				
Factor 4	**Category 1**				
	Category 2				
...	**Category 1**				
	Category 2				

Table 127 Final multivariate Cox Regression for PFS in cohort 1 (Full Analysis Set)

		HR	CI 95% of HR	p-value	n
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
...	**Category 1**				
	Category 2				

Table 128 Univariate Cox Regression for PFS in cohort 2 (Full Analysis Set)

		HR	CI 95% of HR	p-value	n
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
Factor 3	**Category 1**				
	Category 2				
Factor 4	**Category 1**				
	Category 2				
...	**Category 1**				
	Category 2				

Table 129 Final multivariate Cox Regression for PFS in cohort 2 (Full Analysis Set)

		HR	CI 95% of HR	p-value	n
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
...	**Category 1**				
	Category 2				

Table 130 Univariate Cox Regression for PFS in cohort 3 (Full Analysis Set)

	HR	CI 95% of HR	p-value	n

Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
Factor 3	**Category 1**				
	Category 2				
Factor 4	**Category 1**				
	Category 2				
…	**Category 1**				
	Category 2				

Table 131 Final multivariate Cox Regression for PFS in cohort 3 (Full Analysis Set)

		HR	**CI 95% of HR**	**p-value**	**n**
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
…	**Category 1**				
	Category 2				

Table 132 Univariate Cox Regression for PFS in cohort 4 (Full Analysis Set)

		HR	**CI 95% of HR**	**p-value**	**n**
Factor 1	**Category 1**				
	Category 2				

Factor 2	**Category 1**				
	Category 2				
Factor 3	**Category 1**				
	Category 2				
Factor 4	**Category 1**				
	Category 2				
...	**Category 1**				
	Category 2				

Table 133 Final multivariate Cox Regression for PFS in cohort 4 (Full Analysis Set)

		HR	**CI 95% of HR**	**p-value**	**n**
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
...	**Category 1**				
	Category 2				

4.2.2 Cox Regression: predictor factors of OS in each cohort

A multivariate analysis will be carried out using the Cox Regression model in order to determine predictor fators for OS ***in each cohort***. Firstly univariate analysis are carried out separately for each one of the possible predictor factors to decide which variables are entered in the multivariate models; only those with a statistical association with the dependent variable would be selected. Backward elimination stepwise process would be used to select the model. In the first step all possible predictors are entered in the model and in each step, the variable that is least significant (that is, the one with the largest P value) is removed and the model is refitted. Each subsequent step removed the least significant variable in the model until all remaining variables have individual P values smaller than 0.05.

Table 134 Univariate Cox Regression for OS in cohort 1 (Full Analysis Set)

		HR	CI 95% of HR	p-value	n
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
Factor 3	**Category 1**				
	Category 2				
Factor 4	**Category 1**				
	Category 2				
…	**Category 1**				
	Category 2				

Table 135 Final multivariate Cox Regression for OS in cohort 1 (Full Analysis Set)

		HR	CI 95% of HR	p-value	n
Factor 1	**Category 1**				
	Category 2				

Factor 2	**Category 1**				
	Category 2				
...	**Category 1**				
	Category 2				

Table 136 Univariate Cox Regression for OS in cohort 2 (Full Analysis Set)

		HR	**CI 95% of HR**	**p-value**	**n**
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
Factor 3	**Category 1**				
	Category 2				
Factor 4	**Category 1**				
	Category 2				
...	**Category 1**				
	Category 2				

Table 137 Final multivariate Cox Regression for OS in cohort 2 (Full Analysis Set)

		HR	**CI 95% of HR**	**p-value**	**n**
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				

	Category 2				
...	**Category 1**				
	Category 2				

Table 138 Univariate Cox Regression for OS in cohort 3 (Full Analysis Set)

		HR	**CI 95% of HR**	**p-value**	**n**
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
Factor 3	**Category 1**				
	Category 2				
Factor 4	**Category 1**				
	Category 2				
...	**Category 1**				
	Category 2				

Table 139 Final multivariate Cox Regression for OS in cohort 3 (Full Analysis Set)

		HR	**CI 95% of HR**	**p-value**	**n**
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
...	**Category 1**				

	Category 2				

Table 140 Univariate Cox Regression for OS in cohort 4 (Full Analysis Set)

		HR	**CI 95% of HR**	**p-value**	**n**
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
Factor 3	**Category 1**				
	Category 2				
Factor 4	**Category 1**				
	Category 2				
…	**Category 1**				
	Category 2				

Table 141 Final multivariate Cox Regression for OS in cohort 4 (Full Analysis Set)

		HR	**CI 95% of HR**	**p-value**	**n**
Factor 1	**Category 1**				
	Category 2				
Factor 2	**Category 1**				
	Category 2				
…	**Category 1**				
	Category 2				

5 GENERAL CONSIDERATIONS

5.1 TIMING OF ANALYSES

- Recruitment period will be: 24 months
- Research Agreement executed: July 2016
- Projected IRB/IEC approval: Nov 2016
- First Subject In: Dec 2016
- 50% Enrollment: Dec2017
- Last Subject In (100% enrollment): Dec 2018
- Last Subject Last Visit: Dec 2019
- Clinical Study Report April 2020

End of study is defined as Last Subject Last Visit.

5.2 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. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

5.3 TECHNICAL DETAILS

This SAP has been based on the PROTOCOL version 3.1 dated on 30/NOV/2017. R software version 3.2.1 will be used for all analysis (or the last version available at the time of the analysis).
Databases, syntax code and any other files used for the analysis will be electronically stored by [redacted] Following standard operating practices (SOPs), working practice documents, and applicable regulations and guidelines.

6 REFERENCES

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(4) Little, R. J., y D. Rubin (2002), Statistical analysis with missing data (Sec. Ed.), New York, Wiley.