| **Statistical analysis plan** | |
|---|---|
| Study code | D419QC00005 (CANTABRICO) |
| Version | 0.2 |
| Date | 10 September 2021 |

# A Phase IIIB Study in Untreated Patients with Extensive-Stage Small Cell Lung Cancer

# A Phase IIIB, Single Arm Study, of Durvalumab in Combination with Platinum-Etoposide for Untreated Patients with Extensive-Stage Small Cell Lung Cancer reflecting Real World Clinical Practice in Spain (CANTABRICO)

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[redacted]

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation or special term | Explanation |
|---|---|
| 12 m OS | Overall survival at 12 months after inclusion |
| 18 m OS | Overall survival at 18 months after inclusion |
| 6 m OS | Overall survival at 6 months after inclusion |
| 12 m PFS | Progression-Free survival at 12 months after inclusion |
| 6 m PFS | Progression-Free survival at 6 months after inclusion |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| CI | Confidence interval |
| CR | Complete response |
| eCRF | Electronic Case report form |
| CTCAE | Common Terminology Criteria for Adverse Event |
| DoR | Duration of Response |
| DoR 12 | Duration of Response at year |
| ES | Extensive-stage |
| ES-SCLC | Extensive-stage- Small Cell Lung Cancer |
| EP | Etoposide and platinum-based chemotherapy |
| HbsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| HPV | Human papilloma virus |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| ICF | Informed consent form |
| imAE | Immune-mediated adverse event |
| IP | Investigational product |
| ITT | Intent to treat |
| IV | Intravenous |
| IWRS | Interactive web response system |
| LSLV | last patient last visit |
| MOA | Mechanism of Action |
| NCI | National Cancer Institute |

| Abbreviation or special term | Explanation |
|---|---|
| NSCLC | Non-small-cell lung cancer |
| NTL | Non-target lesion |
| ORR | Objective response rate |
| OS | Overall survival |
| PD | Progressive disease |
| PFS | Progression-free survival |
| PR | Partial response |
| PRO | Patient-reported outcome |
| PRO-CTCAE | Patient-reported outcomes version of the CTCAE |
| PT | Preferred Term |
| q3w | Every 3 weeks |
| q4w | Every 4 weeks |
| QLQ-C30 v3 | 30-item Core Quality of Life Questionnaire, version 3 |
| QLQ-LC13 | 13-item Lung Cancer Quality of Life Questionnaire |
| QoL | Quality of life |
| QTcF | QT interval corrected for heart rate using Fridericia‘s formula |
| RECIST 1.1 | Response Evaluation Criteria in Solid Tumors, version 1.1 |
| SAE | Serious adverse event |
| SCLC | Small Cell Lung Cancer |
| SD | Stable disease |
| SOC | System Organ Class |
| TL | Target lesion |
| TTD | Time to Treatment Discontinuation |

# AMENDMENT HISTORY

| Date | Brief description of change |
|---|---|
| | Not applicable |

# 1. OBJECTIVES

## 1.1 Primary objective

- To describe safety profile of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC.

## 1.2 Secondary objective

- To describe effectiveness of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC.
- To describe the impact of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC on patients‘ disease-related symptoms and Health Related Quality of Life (HRQoL) and (PROs).
- To describe health care resources use related to management of ES-SCLC patients treated with durvalumab in combination with platinum–etoposide as first-line treatment.

# 2. STUDY DESIGN AND SAMPLE SIZE

## 2.1 Overall design

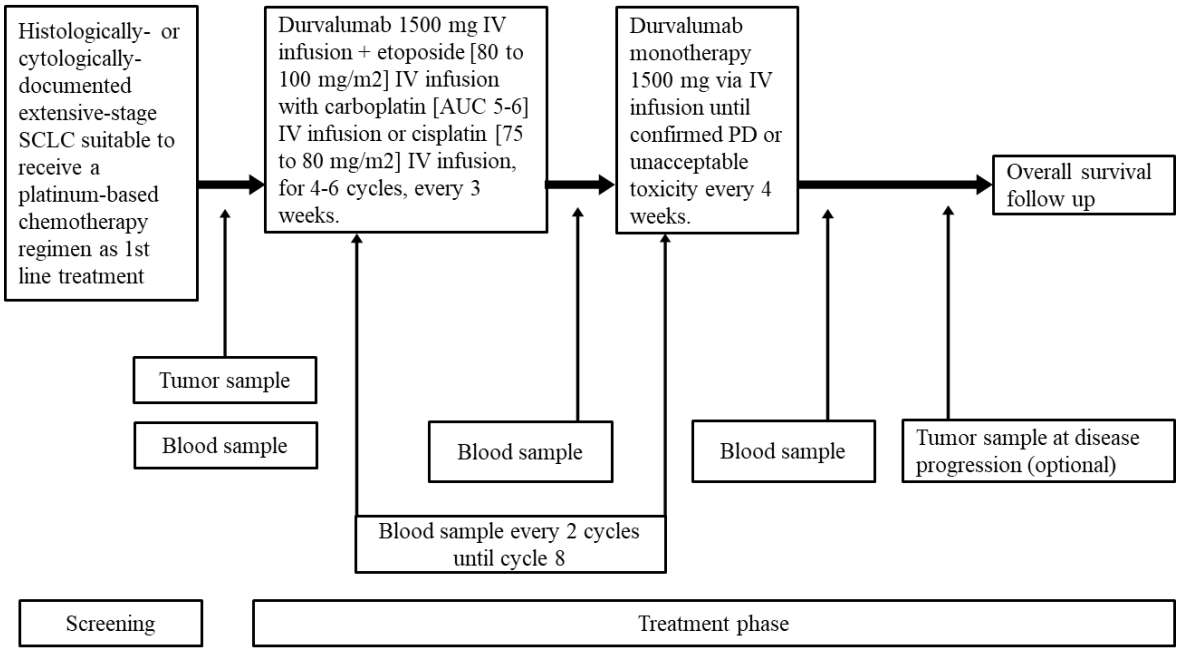
This is a Phase IIIb, interventional, single arm, multicentre study to evaluate safety, effectiveness, use of resources and patient reporting outcomes in patients with ES-SCLC treated with durvalumab in combination with platinum–etoposide as first-line treatment in Spain.

This study will include approximately 85 eligible patients at participating Spanish sites.

Durvalumab will be concurrently administered with first-line chemotherapy (EP) on every 3 week (q3w) schedule for 4 to 6 cycles, and will continue to be administered as monotherapy post-chemotherapy on an every 4 week (q4w) schedule until confirmed progressive disease (PD) or unacceptable toxicity.

Prophylactic cranial irradiation (PCI) is allowed in patients showing complete or partial responses after the durvalumab + EP combination cycles, at the discretion of the investigator according to their local clinical practice.

**Figure 1. General study design**




## 2.2 Sample size

This is a safety study, and given the real-world setting, there is no formal predefined statistical hypothesis, and no formal sample size calculation will be done.

A convenience sample size of approximately 85 patients was estimated based on the expected accrual potential during 6 months in 30 sites, although the recruitment duration may be reduced or extended, until P&R approval of durvalumab in Spain for ES-SCLC based on CASPIAN results, and the number of patients recruited could be higher. A maximum of 30% of recruited patients will have ECOG performance status of 2 at baseline.

# 3. ANALYSIS SETS

## 3.1 Intention to treat (ITT) population

Intention to treat (ITT) population consisted of all enrolled patients who had received at least 1 dose of study drug (chemotherapy or Durvalumab).

## 3.2 Safety analysis set

The safety analysis set will include all included patients that received at least one dose of study treatment. Patients who were enrolled but did not subsequently go on to receive study treatment will not be included in the analysis. Patients who were enrolled but did not subsequently go on to receive study treatment will not be included in the analysis.

## 3.3 Responders analysis set

Responders analysis set will include the subset of patients, within the Safety Analysis Set who are evaluable for response analysis and who achieve an objective response.

# 4. EXPOSURE(S) AND OUTCOMES

## 4.1 Exposures

Exposure of interest: Durvalumab (MEDI4736). It will be administered in combination with first-line chemotherapy (EP), which includes SoC agents' platinum (carboplatin or cisplatin) + Etoposide, and as monotherapy after the chemotherapy phase.

### 4.1.1 Definition of primary drug exposure

The exposure period started when the subject was administered the first cycle of study treatment (Chemotherapy plus Durvalumab).

### 4.1.2 Overall design

Durvalumab will be concurrently administered with first-line chemotherapy (EP) on every 3-week (q3w) schedule for 4 to 6 cycles, and will continue to be administered post-chemotherapy on an every 4 week (q4w) schedule until confirmed progressive disease (PD) or unacceptable toxicity.

Durvalumab + chemotherapy combination:

- Durvalumab 1500 mg via IV infusion q3w concurrently with chemotherapy, starting on Week 0, for 4-6 cycles. If a patient 's weight falls to 30 kg or below (≤30 kg), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab after consultation between the Investigator and Study Physician, until the weight improves to above 30 kg (>30 kg), at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg.

- EP: the dose of etoposide + carboplatin or cisplatin investigated will not exceed the product label dose for the given indication dose (etoposide [80 to 100 mg/m2] via IV infusion with either carboplatin [area under the curve (AUC) 5-6] via IV infusion or cisplatin [75 to 80 mg/m2] via IV infusion), starting on Week 0, for 4-6 cycles.

Durvalumab monotherapy:

- Durvalumab 1500 mg via IV infusion q4w, starting 3 weeks after the last infusion of the combination, until confirmed progressive disease (PD) or unacceptable toxicity. If a patient 's weight falls to 30 kg or below (≤30 kg), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab q4w after consultation between Investigator and Study Physician, until the weight improves to above 30 kg (>30 kg), at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q4w.

Unless specific treatment discontinuation criteria are met, patients will continue therapy until clinical progression or confirmed radiological progression.

### 4.1.3 Definition of comparison drug exposure

Not applicable.

## 4.2 Outcomes

### 4.2.1 Primary outcome

**Primary objective:** To describe safety profile of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC.

**Endpoints analyzed:**

- Incidence of grade ≥ 3 AEs
- Incidence of imAE.

This analysis will be performed for Safety analysis set. For all summaries of AEs, only treatment-emergent AEs will be included. Treatment-emergent AEs are defined as events present at baseline that worsen in intensity after administration of IP or events absent at baseline that emerge after administration of IP, for the period extending to 90 days after the last dose of IP.

The analysis will be performed with the information completed into the adverse event eCRF section.

Total SAEs, AESIs, AEs leading to death, and AEs leading to study drug interruption or discontinuation will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and Preferred Term (PT), causality, and maximum NCI CTCAE Grade. Deaths from all causes will be also summarized.

### 4.2.2 Secondary outcome(s)

#### 4.2.2.1 Secondary outcome 1

To describe effectiveness of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC:

**Endpoints analyzed:**

- Progression-free survival (PFS): This analysis will be performed for the Intention-to-Treat population (ITT). PFS is defined as the time from the first date of treatment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from IP or receives another anticancer therapy prior to progression.

  **PFS (days)** = Date of event or Censor date – treatment start date +1

  Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable assessment prior to the 2 missed visits. If the patient has no evaluable visits or does not have baseline data, he/she will be censored at Day 1 unless he/she dies within 2 visits of baseline, in which case the date of death is the event date.

The PFS analysis will be based on the programmatically derived RECIST 1.1 using the Investigator tumor assessments. It will be analysed PFS, PFS at 6 months (6mPFS) and PFS at 12 months (12mPFS).

- Objective response rate (ORR): This outcome will be analysed for the responder's analysis set. The ORR will be based on the programmatically derived RECIST 1.1 using the investigator tumor data.

- Duration of response (DoR): This outcome will be analysed for the responder's analysis set. DoR is defined as the time from the date of first documented response per RECIST1.1 until the first date of documented progression per RECIST1.1 or death in the absence of disease progression.

  DoR (days) = Date of PFS event or censoring – Date of first response +1

  The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a patient does not progress following a response, then the patients' DoR will be censored at the PFS censoring time. DoR will not be defined for those patients who do not have a documented response. It will be analysed DoR and DoR at 1 year (DoR12)

- Overall survival (OS): This analysis will be performed for the Intention-to-Treat population (ITT). OS is defined as the time from the first date of treatment until death due to any cause.

  OS (days) = Death date or Censor date - treatment start date +1

  Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive. It will be analysed OS, OS at 6 months (6mOS) and OS at 12 months (12mOS) and OS at 18 months (18mOS).

- Time to Treatment Discontinuation (TTD): This analysis will be performed for the Intention-to-Treat population (ITT). TTD is defined as the time from the first date of treatment until date of discontinuation of treatment. Date of discontinuation will be the date reported in end of study form. It will be performed just on the patients that report treatment discontinuation, determined if any of the following occurs:
  - Withdrawal of consent from further treatment with IP.
  - An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing.
  - Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines or as defined in the local prescribing information for the EP treatment.
  - Pregnancy or intent to become pregnant.
  - Non-compliance with the study protocol.
  - Initiation of alternative anticancer therapy including another investigational agent.
  - Clinical progression or confirmed radiological progression and Investigator determination that the patient is no longer benefiting from treatment with IP.

#### 4.2.2.2 Secondary outcome 2

To describe the impact of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC on patients'disease-related symptoms and Health Related Quality of Life (HRQoL) and (PROs).

**Endpoints analyzed:**

- Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30):

This analysis will be performed for the Intention-to-Treat population (ITT). For the following endpoints, change from baseline is defined as the post-treatment value minus the value at baseline. The % change from baseline will be calculated as:

(Postbaseline value - baseline value) / baseline value x 100.

The **EORTC QLQ-C30 v3 questionnaire** is included for the purpose of assessing HRQoL and is a well-established measure of HRQoL/health status. It assesses HRQoL/health status through 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life (QoL) scale. Six single-item symptom measures are also included dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. For each of the 15 domains, final scores are transformed such that they range from 0 to 100, where higher scores indicate greater functioning, greater HRQoL, or greater level of symptoms [(1)].

The principle for scoring these scales is the same in all cases:

- Estimate the average of the items that contribute to the scale; this is the raw score.
- Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + \ldots + I_n)/n$$

Then for **Functional scales**:

$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} x\ 100$$

For **Symptom scales/ items** and **Global health status/ QoL**:

$$Score = \left\{\frac{(RS - 1)}{range}\right\} x\ 100$$

The following outcomes will be analysed for this endpoint:

- Time to symptom deterioration: defined as the time from start of study drug until the date of the first clinically meaningful symptom deterioration (a decrease in the score from baseline of ≥ 10 points) that is confirmed at the subsequent assessment (at least 14 days apart) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from study drug or receives another anticancer therapy prior to symptom deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the symptom change could be evaluated.
  Patients whose QoL (as measured by EORTC QLQ-C30) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the QoL/function could be evaluated. Also, if QoL deteriorates after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where QoL/function could be evaluated. If a patient has no evaluable visits or does not have baseline data, he/she will be censored at Day 1.

- Time to quality of life/ function deterioration: defined as the time from start of study drug until the date of the first clinically meaningful deterioration (a decrease in the function scales or the global health status/QoL from baseline of ≥ 10 points) that is confirmed at the subsequent assessment (at least 14 days apart) or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the patient withdraws from study drug or receives another anticancer therapy prior to QoL/function deterioration. Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the QoL/function change could be evaluated.

- Symptom improvement rate: defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (an increase from baseline score ≥ 10 points for EORTC QLQ-C30 symptom scales/items) in that symptom from baseline.

- Quality of life/function improvement rate: defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement (an increase from baseline score ≥ 10 points for EORTC QLQ-C30 functional scales and global health status/QoL) in that scale from baseline.

- Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life. Questionnaire-Lung Cancer 13 (EORTC QLQLC13):

  This analysis will be performed for the Intention-to-Treat population (ITT). For patients with SCLC, a disease-specific 13-item self-administered questionnaire for lung cancer was developed to be used in conjunction with the EORTC QLQ-C30. It comprises both multi-item and single-item measures of lung cancer-associated symptoms (i.e., coughing, haemoptysis, dyspnoea, and pain) and side effects from conventional

chemotherapy and radiotherapy (i.e., hair loss, neuropathy, sore mouth, and dysphagia). Similar to the EORTC QLQ-C30, all questions except one have a 4-point scale: (not at all, a little, quite a bit and very much). One question (no. 43, ―Did you take any medicine for pain?) has a response option (Yes; No). The scoring approach for the EORTC QLQ-LC13 is similar to the EORTC QLQ-C30.
The following outcomes will be analysed for this endpoint:

- Time to symptom deterioration
- Symptom improvement rate

- Changes from baseline in PRO-CTCAE:

The **PRO-CTCAE** is included to address tolerability from the patients‘ perspective. It was developed in recognition that collecting symptom data directly from patients using PRO tools can improve the accuracy and efficiency of symptomatic AE data collection.
In this study, only items that are considered relevant for the study, site of cancer, and cancer treatment are selected.

#### 4.2.2.3 Secondary outcome 3

To describe health care resources use related to management of ES-SCLC patients treated with durvalumab in combination with platinum– etoposide as first-line treatment.

This analysis will be performed for the Intention-to-Treat population (ITT). To investigate the impact of treatment and disease on health care resource use, the following variables will be captured:

- Number of hospitalizations (Categorical and continous)
- Length of hospitalizations: time from date of admission to discharge date (Continuous)
- Number of visits to oncology service (Categorical and continous)
- Number of emergency visits (Categorical and continous)
- Number of outpatients visits (Categorical and continous)
- Number of imaging tests (Categorical and continous)
- Number of biopsy-related procedures (Categorical and continous)
- Listing of treatments administered, including: Treatment name, dose, duration and number of cycles (Categorical)
- Assessment of health economic resource: Costs associated with HCRU use will be quantified by multiplying the natural units of use of each resource by the cost of each resource retrieved from Spanish databases.It will be described the overall costs and health care resources use as well as costs and health care resources use adjusted by time in years.

## 4.3 Other variables and covariates

### 4.3.1 Screening failure

A detailed listing of screening failure patients will be provided, containing the following information:

- Site
- Patient ID

- Screening failure reason: If not compliance with any inclusion/exclusion criteria, criteria will be provided. If other reason, specific reason will be provided.
- Re-screening (Yes; No). If affirmative:
  - Date of re-screening.

### 4.3.2 Demographic data and clinical characteristic

The demographic, baseline description and clinical characteristics will be performed for the Intent-to-treat (ITT) population. The following variables will be described:

- Age (Categorical and continuous): Categorical data will be provided by defining two categories: <65 years and >65 years
- Gender (Categorical)
- Race (Categorical)
- Ethnicity (Categorical)
- Status of cigarette smoking (Categorical). If former or current smoker:
  - Number pack/year (Continuous)
- Vital signs at baseline:
  - Height (Continuous)
  - Weight (Continuous)
  - SBP (Continuous)
  - DBP (Continuous)
  - Pulse (Continuous)
  - Respiratory rate (Continuous)
  - Temperature (Continuous)
- Physical exam at baseline:
  - System (Categorical)
  - Finding (Categorical)
- Medical history (Yes; No): If affirmative:
  - Illness/Surgery/Intercurrent illness (Categorical)
- Serology:
  - Tuberculosis (Categorical)
  - HBsAg (Categorical)
  - HCV ab (Categorical): If positive:
    - HCV-RNA (Categorical)
  - VIH
- ECG (Done; Not done): If done:
  - Overall evaluation (Categorical): If abnormal:
    - Listing of the abnormalities detected, including if clinically significant.
- Charlson comorbidity index available (Yes; No): If affirmative:
  - Myocardial infarction (Yes; No) (Categorical)
  - Congestive heart failure (Yes; No) (Categorical)
  - Peripheral vascular disease (Yes; No) (Categorical)
  - Cerebrovascular disease (Yes; No) (Categorical)

- Dementia (Yes; No) (Categorical)
- Chronic obstructive pulmonary disease (Yes; No) (Categorical)
- Connective tissue disease (Yes; No) (Categorical)
- Peptic ulcer disease (Yes; No) (Categorical)
- Chronic liver disease mild (Yes; No) (Categorical)
- Diabetes mellitus (mild) (Yes; No) (Categorical)
- Hemiplegic (Yes; No) (Categorical)
- Chronic Kidney disease moderate-severe (Yes; No) (Categorical)
- Diabetes mellitus with lesion in target organ (moderate-severe) (Yes; No) (Categorical)
- Tumor or solid neoplasia (Yes; No) (Categorical)
- Leukemia (Yes; No) (Categorical)
- Lymphoma (Yes; No) (Categorical)
- Chronic liver disease moderate-severe (Yes; No) (Categorical)
- Tumor or solid neoplasia with metastasis (Yes; No) (Categorical)
- Acquired immunodeficiency syndrome (AISD) (Yes; No) (Categorical)
- Total score (Continuous)
- Presence of other comorbidities (Yes; No): If affirmative:
  - Other comorbidities (Categorical)

### 4.3.3 Cancer history & Performance status

The following cancer history data will be described for the for the Intent-to-treat (ITT) population.

- WHO/ECOG-PS (Categorical): It will be described at baseline, start of chemotherapy phase, start of post-chemotherapy phase and end of study.
- Subject autonomy (Categorical): It will be described at baseline, start of chemotherapy phase, start of post-chemotherapy phase and end of study.
- Time from initial diagnosis (Continuous): Defined as time, in months, from initial diagnosis date to informed consent date (enrolment in the study).
- Histology (Categorical)
- Initial stage (Categorical):
- Initial TNM stage (Categorical)
- Actual stage (Categorical)
- Actual TNM stage (Categorical)
- Primary tumor location (Categorical)
- Metastatic location (Yes; No) (Categorical). If affirmative:
  - Number of metastatic locations (Continuous)
  - Metastatic location (Categorical):
    - It will be provided the frequency of brain or CNS metastases (Categorical)
    - It will be provided the frequency of liver metastases (Categorical)
- Family history of cancer (Yes, No): If affirmative:

- Cancer type (Categorical)
- Relative degree per cancer type (Categorical)

### 4.3.4 Treatment description

#### 4.3.4.1 Chemotherapy phase (Cycle 1 to 4-6)

This analysis will be performed for the Intention-to-Treat population (ITT). Treatment duration will be defined as time elapsed between treatment end date and treatment start date in chemotherapy phase. It will be described as continuous data for durvalumab, etoposide and platinum.

It will be described the number of cycles administered as continuous data. It will be considered as cycle administered when the patient receives a complete pattern of durvalumab + EP.

Additionally, the following data will be described:

**Durvalumab**

- Durvalumab total dose administered (mg) (Continuous)
- Number of durvalumab doses (Categorical and continuous):
  - It will be provided the number and percentage of patients receiving 12 or more durvalumab doses (Categorical)
- Duration of treatment with durvalumab in weeks (Continuous)
- Treatment interruption (Yes, No): If affirmative:
  - Number and percentage of patients with at least one treatment interruption
  - Reason for interruption (Categorical)
  - Total number of cycles interrupted and percentage regarding total cycles

**EP**

- Platinum administered (Cisplatin; Carboplatin): The following data will be described for each category.
- Total dose administered (mg) (Continuous)
- Total dose programmed ($mg/m^2$ for Cisplatin / AUC for Carboplatin) (Continuous)
- Number and percentage of patients receiving 4 or more cycles of EP (Categorical)
- Number and percentage of patients receiving 5 or more cycles of EP (Categorical)
- Number and percentage of patients receiving 6 or more cycles of EP (Categorical)
- Duration of EP treatment in weeks (Continuous)
- Treatment interruption (Yes, No): If affirmative:
  - Number and percentage of patients with at least one treatment interruption
  - Reason for interruption (Categorical)
  - Total number of cycles interrupted and percentage regarding total cycles
- Dose delay (Yes, No): If affirmative:
  - Number and percentage of patients with at least one dose delay
  - Reason for delay (Categorical)
- Dose reduction (Yes, No): If affirmative:

- Number and percentage of patients with at least one dose reduction
- Reason for reduction (Categorical)

- Number and percentage of patients who received prophylactic cranial irradiation (PCI) in patients showing complete or partial responses after the durvalumab + EP combination cycles will be described. To calculate the number of patients receiving PCI, the information collected on concomitant study medication will be considered.

#### 4.3.4.2 Post-Chemotherapy phase (Cycle 5-7 to X): Durvalumab monotherapy

This analysis will be performed for the Intention-to-Treat population (ITT). Treatment duration will be defined as time elapsed between treatment end date and treatment start date in post-chemotherapy phase. It will be described as continuous data.

In will be considered as cycle administered when the patient receives at least one dose of durvalumab in post-chemotherapy phase. It will be described the number of cycles administered as continuous data. It will be described the number and percentage of patients with 12 cycles or more (Categorical).

Additionally, the following data will be described:

- Durvalumab total dose administered (mg) (Continuous)
- Duration of post-chemotherapy treatment with durvalumab in weeks (Continuous)
- Treatment interruption (Yes, No): If affirmative:
  - Number and percentage of patients with at least one treatment interruption
  - Reason for interruption (Categorical)
  - Total number of cycles interrupted and percentage regarding total cycles
- Dose delay (Yes, No): If affirmative:
  - Number and percentage of patients with at least one dose delay
  - Reason for delay (Categorical)

# 5. ANALYSIS METHODS

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, quartiles (Q1 and Q3), minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. The number of missing data will be provided for every analysed variable.

Missing values will not be considered for calculating percentages or any other descriptive, meaning that only valid values will be presented. No use of any method for the handling of missing data is foreseen.

For patients excluded from the statistical analyses, descriptive of the reasons for non-evaluability will be provided.

The software package SAS version 9.4 will be used for data analysis.

## 5.1 Primary outcome

**Primary objective:** To describe safety profile of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC.

**Endpoints analyzed:**

- Incidence of grade ≥ 3 AEs
- Incidence of imAE.

Safety data will be summarized descriptively overall, by seriousness, by causality, and by maximum NCI CTCAE Grade. The exact 95% CIs around the incidence of Grade 3 and Grade 4 AEs will be reported. All outputs will be summarized for the Safety analysis set.

A subgroup analysis may be conducted in the following subgroups, assuming sufficient sample size per subgroup: platinum therapy receiving (carboplatin or cisplatin), age, gender, performance status, smoking status and CNS metastasis at baseline (Yes/No).

For this aims, the following summaries of AEs will be provided:

- Number and percentage of patients with AEs in total and by causality and severity
- Number and proportion of patients with Grade 3 and Grade 4 AEs in total and by casualty
- Number and proportion of patients with SAEs in total and by causality
- Number and proportion of patients with AEs leading to death
- Number and proportion of patients with AEs leading to treatment interruption and/or discontinuation
- Number and proportion of patients with AESI, by predefined type (or newly defined by this study) in total and by seriousness, severity and causality, including immune relatedness
- Number and proportion of patients who received steroids, immunosuppressants, and/or hormone replacement therapy to manage AESIs
- Time from start of durvalumab to the onset of an AESI predefined type, all interventions of AESIs by type of intervention (including intervention with steroids, immunosuppressants, and/or hormone replacement therapy), and time from onset of an AESI type to resolution.
- Duration of the intervention with steroids, immunosuppressants, and/or hormone replacement therapy until the resolution of AESI.
- Number and proportion of patients with imAEs. The imAEs will be assessed as a subset of AESIs. An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated MOA and where there is no clear alternate etiology.
- Listing of SAEs per patient, including the following variables:
    - Patient ID
    - AE number
    - AE description
    - PT Term
    - Grade NCI-CTACAE v5.0 (1-5)
    - Onset date (DD-MMM-YYYY)

- End date (DD-MMM-YYYY)
- Ongoing (Yes; No)
- Outcome
- Seriousness criteria
- AESI (Yes; No)
- Relationship
- Action taken

## 5.2 Secondary outcome(s)

### 5.2.1 Secondary outcome 1

To describe effectiveness of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC:

**Endpoints analyzed:**

- Progression-free survival (PFS): The PFS analysis will be based on the programmatically derived RECIST 1.1 using the Investigator tumor assessments. The analysis will be performed using Kaplan Meier plots. Summaries of the number and percentage of patients experiencing a PFS event will be provided along with median PFS and its 95% confidence interval. In addition, the proportion of patients who are progression-free at 6 (PFS 6) and 12 (PFS 12) months will be presented.

  A subgroup analysis may be conducted comparing PFS in the following subgroups, assuming sufficient sample size per subgroup: platinum therapy receiving (carboplatin or cisplatin), age (≥65, <65), gender, performance status, smoking status, CNS metastasis at baseline (Yes/No) and number of chemotherapy cycles (5 or 6 cycles vs 4 or less cycles)

  For each subgroup, the HR and 95% CI will be calculated by Cox regression and a log-rank test will be provided.

- Objective response rate (ORR): The ORR will be based on the programmatically derived RECIST 1.1 using the investigator tumor data. Summaries will be produced that present the number and percentage of patients with a tumor response (CR/PR). 95% CI will also be presented.

  A subgroup analysis may be conducted comparing ORR in the following subgroups, assuming sufficient sample size per subgroup: platinum therapy receiving (carboplatin or cisplatin), age (≥65, <65), gender, performance status, smoking status, CNS metastasis at baseline (Yes/No) and number of chemotherapy cycles (5 or 6 cycles vs 4 or less cycles). Results will be compared using Chi-Squared test.

- Duration of response (DoR): DoR will be analyzed using the investigator tumor data in responding patients. Descriptive data will be provided for the DoR in responding patients (continuous data), including the associated Kaplan-Meier curves. In addition, the DoR at 1 year (DoR 12) will be analyzed.
  A subgroup analysis may be conducted comparing DoR in the following subgroups, assuming sufficient sample size per subgroup: platinum therapy receiving (carboplatin

or cisplatin), age (≥65, <65), gender, performance status, smoking status, CNS metastasis at baseline (Yes/No) and number of chemotherapy cycles (5 or 6 cycles vs 4 or less cycles)

For each subgroup, the HR and 95% CI will be calculated by Cox regression and a log-rank test will be provided.

- Overall survival (OS): OS will be analyzed using a Kaplan-Meier plots. Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up, and those who have withdrawn consent will be provided along with the median OS and corresponding 95% CI. In addition, the survival rate at 6 (OS 6), 12 (OS 12), and 18 (OS 18) months will be presented.

  A subgroup analysis may be conducted comparing OS in the following subgroups, assuming sufficient sample size per subgroup: platinum therapy receiving (carboplatin or cisplatin), age (≥65, <65), gender, performance status, smoking status, CNS metastasis at baseline (Yes/No) and number of chemotherapy cycles (5 or 6 cycles vs 4 or less cycles)

  For each subgroup, the HR and 95% CI will be calculated by Cox regression and a log-rank test will be provided.

- Time to Treatment Discontinuation (TTD): Summaries for the TTD will be provided (continuous data).

### 5.2.2 Secondary outcome 2

To describe the impact of durvalumab in combination with platinum–etoposide as first-line treatment for patients with ES-SCLC on patients'disease-related symptoms and Health Related Quality of Life (HRQoL) and (PROs).

**Endpoints analyzed:**

- Change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30) and Questionnaire-Lung Cancer 13 (EORTC QLQLC13):

Scores for the QLQ-C30 and QLQ-LC13 questionnaires will be calculated according to published scoring manuals or the developer's guidelines. Raw scores from scales in both questionnaires will be standardized by linear transformation so that they range from 0 to 100. Higher scores for symptom items indicate greater symptom severity, while higher scores for function and global health status/QoL items indicate better function and health status/QoL. For both questionnaires, a clinically meaningful change will be prespecified as an absolute change in score from baseline of ≥10 points (either deterioration or improvement). For the five key disease-related symptoms (cough, dyspnea, and chest pain [QLQ-LC13], and fatigue and appetite loss [QLQ-C30]), changes at each visit from baseline to disease progression or end of follow-up (whichever came first) will be analyzed using a mixed model for repeated measures (MMRM) to derive an overall adjusted mean change from baseline, reflecting the average treatment effect over visits. The model assumes PROs will be collected at multiple visits per

patient. Visits with >75% missing data will be excluded from the analysis. The MMRM included treatment, age at baseline (<65 vs ≥65 years), sex, smoking history (smoker vs non-smoker) and visit interaction as fixed factors, and baseline score as a covariate; the model further adjusted for baseline score-by-visit interaction.

Summaries of original and change from baseline values of each symptom scale/item, the global HRQoL score, and each functional domain will be reported by visit.

Time to symptom deterioration and time to quality of life / function deterioration (defined in 4.2.2) will be analyzed by product limit methods to provide summaries of the number and percentage of patients experiencing a clinically meaningful deterioration or death, the median time to deterioration together with the corresponding 95% CIs, as well as the Kaplan-Meier plot. An stratified log-rank test adjusted for therapy will be used with HR s and 95% CIs calculated using a stratified Cox proportional hazards model.

Symptom improvement rate and Quality of life / function improvement (defined in 4.2.2) will be summarized.

- Changes from baseline in PRO-CTCAE:

PRO-CTCAE data will be presented using summaries and descriptive statistics for categorical data for each question of the questionnaire.

### 5.2.3 Secondary outcome 3

- To describe health care resources use related to management of ES-SCLC patients treated with durvalumab in combination with platinum– etoposide as first-line treatment. It will be described the overall costs and health care resources use as well as costs and health care resources use adjusted by time in years.

The following data will be described as appropriate:

- Number of hospitalizations (Categorical and continuous)
- Length of hospitalizations: time from date of admission to discharge date (Continuous).
- Number of visits to oncology service (Categorical and continuous)
- Number of emergency visits (Categorical and continuous)
- Number of outpatients visits (Categorical and continuous)
- Number of imaging tests (Categorical and continuous)
- Number of biopsy-related procedures (Categorical and continuous)
- Listing of treatments administered, including: Treatment name, dose, duration and number of cycles
- Assessment of health economic resource: Costs associated with HCRU use will be quantified by multiplying the natural units of use of each resource by the cost of each resource retrieved from Spanish databases

# 6. BIAS

## 6.1 Methods to minimize bias

### 6.1.1 Patient enrolment

This is a single arm, open label study; no randomization or blinding will be performed.

Investigators should keep a record (ie, the patient screening log) of patients who entered screening.

At screening/baseline (Days -28 to -1), the Investigators or suitably trained delegate will:

- Obtain signed informed consent before any study specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of inclusion.

- Obtain a unique enrolment number (E-code), through the Interactive Web Response System (IWRS). This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).

- Determine patient eligibility based on inclusion/exclusion criteria. If the patient is ineligible and not included, the IWRS should be contacted to terminate the patient in the system.

Patients will start treatment on Day 1. Treatment should start no more than 3 working days after being included. Patients must not be included and treated unless all eligibility criteria have been met.

If a patient withdraws from participation in the study, then his or her enrolment code cannot be reused.

### 6.1.2 Procedures for handling incorrectly enrolled patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is included in error, or incorrectly started on treatment, the Investigator should inform the Study Medical Monitor immediately, and a discussion should occur between the Study Medical Monitor and the Investigator regarding whether to continue or discontinue the patient from treatment. The Study Medical Monitor must ensure all decisions are appropriately documented and that the potential benefit: risk profile remains positive for the patient.

## 6.2 Handling of missing data

Missing values will not be considered for calculating percentages or any other descriptives, meaning that only valid values will be presented. The number of missing data will be provided for every analysed variable. No use of any method or imputation of data for the handling of missing data is foreseen.

For the questionnaires EORTC QLQ-C30, EORTC QLQ-LC13 and PRO-CTCAE, for each subscale, if < 50% of the subscale items are missing, then the subscale score will be divided by the number of non missing items and multiplied by the total number of items on the subscales. If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized.

## 6.3 Adjustment for multiple comparisons

Not applicable.

# 7. INTERIM ANALYSES

Not applicable by study protocol.

Following interim analysis will be performed:

- Sept 2021: Demographic data & Cancer history: sections 4.3.2 and 4.3.3.
- Oct 2021: Treatment administration: Section 4.3.4. and 5.1. (subgroup analysis will not be included).
- Feb 2022: Progression free survival and QoL: Section 5.2.1 Progression free survival and 5.2.2.

# 8. REFERENCES

(1) Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.