PHARMACOCLINIC PROTOCOL ON THE USE IN THE NATIONAL HEALTH SYSTEM OF ATEZOLIZUMAB (TECENTRIQ®) IN COMBINATION WITH CARBOPLATIN AND ETOPOSIDE, FOR THE FIRST-LINE TREATMENT OF ADULT PATIENTS WITH EXTENSIVE-STAGE SMALL CELL LUNG CANCER

Approved by the Permanent Pharmacy Commission

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The experts who have participated in preparing this protocol (ordered alphabetically by first surname)**:**

Montserrat Gasol Boncompte. Representative for Cataluña.

Lourdes Gil Tornero. Representative for the Directorate General for Common NHS Services Portfolio and Pharmacy.

María Asunción González González. Representative for Castilla y León.

Juan Francisco Marín Pozo. Representative for the Spanish Hospital Pharmacy Society (SEFH).

Concepción Payares Herrera. Representative for the Spanish Clinical Pharmacology Society (SEFC).

Álvaro Rodríguez Lescure. Representative for the Spanish Medical Oncology Society (SEOM).

Marta Rodríguez Martínez. Representative for Castilla-La Mancha.

Coordinated by Mª Dolores Fraga Fuentes. Subdirectorate General of Pharmacy. Directorate General for Common NHS Services Portfolio and Pharmacy.

Participant in designing the protocol for its implementation in VALTERMED: Juan Luis Moreno González. Subdirectorate General of Pharmacy. Directorate General for Common NHS Services Portfolio and Pharmacy.

All the experts have made a conflict of interest declaration

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1. INTRODUCTION

Lung cancer (LC) is the leading cause of death[1] by cancer globally, accounting for 18% of total cancer deaths in 2020[2]. The mean age at diagnosis with LC ranges from 55 to 75 years. Smoking remains the leading cause of LC in most patients (71%)[3].

In Europe, the age-adjusted incidence rate is 53.5 per 100,000 inhabitants/year[3].

In Spain, LC is the fourth most common type of cancer, behind colorectal, prostate and breast cancer[4]. In 2021, it is estimated there will be 29,549 new cases of LC in Spain (21,578 in men and 7,971 in women)[5].

In 2020, 22,930 deaths due to LC were recorded in our country, most of them in men[5].

Lung tumours are classified into two main groups, non-small cell lung carcinomas (NSCLC), which account for 80-90% of LCs, and small cell lung carcinomas (SCLC), the incidence of which has been decreasing over the last two decades[3], with a prevalence in Europe of 1-5 per 10,000[6].

Histological characterisation of the tumour is an essential element due to the implications for the prognosis and treatment of the disease[3]. More than two thirds of patients are diagnosed at an advanced or metastatic stage of the disease (stage IIIB and stage IV), with no potentially curative treatment options, so their prognosis is very poor, especially in metastatic disease, where 5-year survival rates are around 5%[7].

In Spain[8], a multicentre observational cohort study involving patients with lung cancer or other types of thoracic tumours was conducted between August 2016 and January 2020. Presented at the European Society for Medical Oncology (ESMO) Virtual Congress 2020, this study was conducted to assess the clinical reality regarding SCLC in Spain and it has shown that this disease represents around 13% of all lung cancer cases, similar to the data described. Most of these patients are diagnosed in an extensive stage (> 50%) and are symptomatic at the time of diagnosis. The study also showed that SCLC is closely related to smoking. There were 12,897 cases on the Thoracic Tumours Registry TTR. A total of 1,658 patients diagnosed with SCLC were recruited in 67 Spanish hospitals. Of these, 956 were in an extensive stage.

Of the 956 patients, 826 (86.4%) had some comorbidity, the most frequent being arterial hypertension, dyslipidemia, chronic obstructive pulmonary disease (COPD) and diabetes mellitus. The majority of patients had symptoms at diagnosis (92.3%, 882/956). The main symptoms were cough (39.4%), pain (36.7%) and dyspnea (35.6%), followed by weight loss (28.6%). At diagnosis, 189 patients (19.8%) had brain metastases. Other sites of metastasis were liver (44.1%) and bone (34.8%). The study also showed that SCLC is closely related to smoking.

Of all lung tumors, SCLC has the worst prognosis[9]. Although this tumour has a high initial response rate, practically all patients become refractory to treatment after a short time, so this histological type has a high mortality[9], with a 5-year survival of 10% in stages I-III, and 4.6% at 2 years in stage IV, the survival rate being slightly higher in women than in men (12.25% vs. 7.51% in stages I-III and 5.94% vs. 3.57% in stage IV)[10].

Classically, a distinction has been made between limited disease SCLC (LD-SCLC) and extensive-stage SCLC (ES-SCLC) based on whether the disease is confined to one hemithorax with or without ipsilateral hilar, mediastinal or supraclavicular lymphatic involvement or, conversely, its extent is not amenable to radiotherapy fields, including metastatic disease[11]. ES-SCLC is the most frequent form of presentation (60-75%), with median survival 9-10 months, 40% survival at one year after diagnosis and less than 5% at 5 years and median survival without treatment is only 1.5 months[12]. For LD-SCLC the median survival is 12-20 months with a 5-year survival of less than 20% and with no treatment only 3 months[12].

Treatment of LD-SCLC in selected patients in good general condition is based on concomitant administration of etoposide- and platinum-based chemotherapy with thoracic radiotherapy and subsequent prophylactic holocranial radiotherapy (PCI), due to its high capacity to generate brain metastases. If the patient is not a candidate for concomitant treatment, sequential chemotherapy and radiotherapy or palliative care may be considered. For ES-SCLC, platinum-based chemotherapy with etoposide is the standard first-line treatment[6,13]. The combination of cisplatin or carboplatin with etoposide has shown response rates ranging from 60% to 70% in patients with ES-SCLC[14]. Several studies on cisplatin or carboplatin in combination with etoposide (at different doses) have shown consistent results, suggesting that their efficacy is equivalent in patients with ES-SCLC. In cases where there is a partial or complete response after chemotherapy, PCI has been shown to decrease the risk

of brain progression and increase overall survival (OS), while thoracic consolidation radiotherapy after chemotherapy can increase progression-free time and OS in selected patients.

In the treatment of SCLC, new treatment strategies are being studied based on an understanding of molecular alterations and the use of new biomarkers. Of these, immunotherapy has been most fully developed at the clinical level. Atezolizumab, in combination with carboplatin and etoposide, was the first immunotherapy in combination with chemotherapy licensed for first-line treatment of adult patients with ES-SCLC.

Subsequently, on 27 August 2020, durvalumab (Imfinzi®) received EMA approval for treatment of ES-SCLC in combination with etoposide and either carboplatin or cisplatin[15].

In first-line treatment of SCLC, based on the results of studies and available treatment options, the most appropriate choice for each patient requires taking into account variables such as tumour type, patient type, predictive factors, toxicity and quality of life in a non-curative situation. In addition, as in other cancer patients, psychological interventions are an essential part of the care of these patients[16].

The combination of atezolizumab with platinum-based chemotherapy and etoposide had a median OS (co-primary endpoint) of 12.3 months *vs*. 10.3 months with standard therapy (platinum-based chemotherapy), stratified HR 0.76; CI 95%: 0.60-0.95, p=0.0154[17]. There was also improvement in the co-primary endpoint progression-free survival (PFS), although this was modest (5.2 *vs*. 4.3 months, stratified HR 0.77; CI 95%: 0.62-0.96, p=0.0170)[18]. The objective response rate was lower in the placebo/carboplatin/etoposide (PCE) arm than in the atezolizumab/carboplatin/etoposide (ACE) arm, 64.4% *vs*. 60.2%, respectively, and the duration of the response was similar in both arms (3.9 months PCE arm *vs*. 4.2 months ACE arm). No reduction in efficacy has been observed in the different prognostic subgroups analysed, although the data available for patients with brain metastases are very limited. To date, no predictive biomarkers have been identified that could condition patient selection for the combination of atezolizumab with platinum-etoposide in the first line treatment of ES-SCLC[19].

From a safety point of view, the toxicity of atezolizumab is consistent with that expected for an immunotherapy and is in line with that of other anti-PD-L1 drugs, while immuno-related adverse events (AEs) and treatment withdrawals due to a high rate of AEs should be highlighted. No new safety alerts have been reported. The most common AEs were: anaemia, nausea, fatigue, and neutropenia[1,19].

These results show a modest survival benefit from the combination of atezolizumab with chemotherapy, and it is therefore considered an option for chemotherapy in patients with ES-SCLC in first-line treatment. Treatment with atezolizumab will be maintained until progression is confirmed radiologically or clinically or until unacceptable toxicity is reported. Only very limited data are available for patients with brain metastases. To date, no biomarkers have been identified to select the group of patients who may benefit most from treatment[1].

Given the uncertainties regarding the efficacy of atezolizumab and its transferability to clinical practice, it was considered necessary for the NHS to support the inclusion of this indication in the pharmaceutical provision in order to give a chance to those patients considered long-term survivors of SCLC who are able to achieve an OS of at least 18 months.

2. TREATMENT OBJECTIVE

The goal of treatment with atezolizumab in combination with carboplatin and etoposide in the first-line treatment of adult patients with ES-SCLC is to extend survival to a larger number of long responders based on the results of the clinical trial. To do this, OS results will be recorded in patients with ES-SCLC treated with first-line ACE in order to confirm expectations in these patients.

Monitoring of the OS results has been established, determined on the basis of the following tranches considered in the financing of this indication:

- OS: **≤10 months**
- OS**: 11-13 months**
- OS: **14 months and 17 months**
- OS: **18 months and up**

3. PATIENT SELECTION CRITERIA

Patients who meet all the following inclusion criteria are considered candidates for treatment with atezolizumab:

1. Histologically or cytologically confirmed ES-SCLC (based on the Veterans Affair Lung Study Group (VALG) staging system) and with measurable disease based on RECIST version 1.1 criteria.
2. No previous treatment for ES-SCLC
3. Eastern Cooperative Oncology Group (ECOG) Functional status 0 or 1,
4. Adequate haematological and organic function[a].

Note: Patients who have received prior chemoradiation therapy for LD-SCLC must have been treated with curative intent and with a treatment-free interval of at least 6 months since the last course of chemotherapy, radiation therapy, or chemoradiation therapy since diagnosis with ED-SCLC. Patients with a history of previously treated and asymptomatic brain metastases must meet the following criteria: supratentorial and cerebellar metastases (i.e. no metastases in the midbrain, pons, medulla or spinal cord), no corticosteroid requirements and no evidence of progression between completion of CNS-directed therapy and initiation of atezolizumab treatment.

Criteria for **exclusion from treatment**:

1. Patients with a history of autoimmune disease, history of pneumonitis, idiopathic pulmonary fibrosis, bronchiolitis obliterans, uncontrolled pleural effusion, pericardial effusion or ascites and with uncontrolled or symptomatic hypercalcaemia.
2. Patients with active or cortico-dependent brain metastases.
3. Patients with leptomeningeal disease, with spinal cord compression, HIV+, with active hepatitis B or hepatitis C infection, active tuberculosis or severe infections and with baseline ECOG ≥ 2 performance status.

[a] ANC ≥ 1500 cells /µL; lymphocyte count ≥ 500 /µL; platelet count ≥ 100,000 /µL; haemoglobin ≥ 9.0 g/dL; AST, ALT and alkaline phosphatase ≤ 2.5 × ULN, with the following exceptions: Patients with documented liver metastases: AST and/or ALT ≤ 5 × ULN Patients with documented liver or bone metastases: alkaline phosphatase ≤ 5 × ULN; serum bilirubin ≤ 1.25 × ULN; serum creatinine ≤ 1.5 × ULN

4. Patients with significant cardiovascular disease, New York Heart Association class III or higher heart disease, myocardial infarction or stroke within the previous 3 months, significant arrhythmias or unstable angina, and patients with malignant neoplasms within 5 years prior to initiation of treatment, with the exception of those at very low risk of metastasis or death.
5. Patients with prior allogeneic bone marrow transplantation or solid organ transplantation.
6. Patients who have received a live attenuated virus vaccine within 4 weeks prior to the start of treatment.
7. Administration of systemic immunosuppressive medicinal products within 14 days prior to initiation of treatment.
8. Major surgical intervention in the 28 days prior to the start of treatment.
9. Prior treatment with CD137 agonists or immune checkpoint blockade, anti-PD-1 and anti-PD-L1 therapies.
10. Known contraindication or hypersensitivity to the treatment.

Criteria for **discontinuation of treatment**:

1. The presence of adverse effects related to the infusion of the medicinal product that prevent the continued safe infusion of the medicinal product or the occurrence of unmanageable toxicity.

2. If measurable disease progression is observed, by radiographic assessment based on the RECIST v1.1 criteria or clinical progression. Rule out pseudoprogression.

4. GENERAL CONSIDERATIONS FOR TREATMENT WITH ATEZOLIZUMAB[20]

In the induction phase, the recommended dose of atezolizumab is 1,200 mg given by intravenous infusion followed by carboplatin and etoposide on day 1 of each three-week cycle. Etoposide is also given on days 2 and 3 of each three-week cycle. This regimen is given every three weeks for four cycles. The induction phase is followed by a chemotherapy-free maintenance phase in which 1,200 mg atezolizumab is administered every three weeks.

Scaling up or decreasing the atezolizumab dose is not recommended, but administration may be delayed or discontinued depending on individual safety and tolerability. Atezolizumab may

be administered until loss of clinical benefit or occurrence of unmanageable toxicity.

Treatment regimen	**Induction phase (4 cycles of 21 days)**	**Maintenance (21-day cycles)**
	atezolizumab (1,200 mg)¥ + carboplatin (AUC 4.5-5)b + etoposide (75-100 mg / m2)Ω,µ	atezolizumab (1,200 mg) ¥

¥Atezolizumab is administered on day 1 of each 21-day cycle, until unacceptable toxicity or loss of clinical benefit.

Ω Carboplatin is given on day 1 of each 21-day cycle, until the end of all 4 cycles, disease progression or unacceptable toxicity, whichever occurs first.

µ Etoposide is given on days 1, 2 and 3 of each 21-day cycle, until the end of all 4 cycles, disease progression or unacceptable toxicity, whichever occurs first.

Duration of treatment: Until loss of clinical benefit or unmanageable toxicity

Dose modification during treatment: Dose reductions of Tecentriq are not recommended

Dose modification advice for atezolizumab[20]

Immune related adverse reaction	Severity	Treatment modification
Pneumonitis	Grade 2	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4	Permanently discontinue Tecentriq
Hepatitis in patients without HCC	Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] *or* blood bilirubin > 1.5 to 3 x ULN)	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4: (ALT or AST > 5 x ULN *or* blood bilirubin > 3 x ULN)	Permanently discontinue Tecentriq
Hepatitis in patients with HCC	If AST/ALT is within normal limits at baseline and increases to > 3x to ≤ 10x ULN *or* If AST/ALT is > 1 to ≤ 3x ULN at baseline and increases to > 5x to ≤ 10x ULN *or* If AST/ALT is > 3x to ≤ 5x ULN at baseline and increases to >8x to ≤ 10x ULN	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	If AST/ALT increases to > 10x ULN or total bilirubin increases to > 3x ULN	Permanently discontinue Tecentriq
Colitis	Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) *or* Symptomatic Colitis	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	Permanently discontinue Tecentriq

Immune related adverse reaction	Severity	Treatment modification
Hypothyroidism or hyperthyroidism	Symptomatic	Withhold Tecentriq *Hypothyroidism:* Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing *Hyperthyroidism:* Treatment may be resumed when symptoms are controlled by anti-thyroid medicinal product and thyroid function is improving
Adrenal insufficiency	Symptomatic	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy
Hypophysitis	Grade 2 or 3	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy
	Grade 4	Permanently discontinue Tecentriq
Type 1 diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L)	Withhold Tecentriq Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Infusion-related reactions	Grade 1 or 2	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved
	Grade 3 or 4	Permanently discontinue Tecentriq
Rash/Severe cutaneous adverse reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	Permanently discontinue Tecentriq
Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis	All Grades	Permanently discontinue Tecentriq

Immune related adverse reaction	Severity	Treatment modification
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis	Withhold Tecentriq Treatment may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue Tecentriq
Myocarditis	Grade 2	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4	Permanently discontinue Tecentriq
Nephritis	Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN)	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4: (creatinine level > 3.0 x baseline or > 3.0 x ULN)	Permanently discontinue Tecentriq
Myositis	Grade 2 or 3	Withhold Tecentriq
	Grade 4 or Grade 3 recurrent myositis	Permanently discontinue Tecentriq
Other immune-related adverse reactions	Grade 2 or Grade 3	Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day.
	Grade 4 or recurrent Grade 3	Permanently discontinue Tecentriq (except endocrinopathies controlled with replacement hormones)

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.0 (NCI-CTCAE v.4.).

[1] Regardless of severity

Special populations

Paediatric population: The safety and efficacy of atezolizumab in children and adolescents below 18 years of age have not yet been established.

Elderly patients. Based on population pharmacokinetic analysis, no dose adjustment of atezolizumab is necessary in patients ≥ 65 years of age.

Renal impairment. Based on population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions in this population.

Hepatic impairment: Based on population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild or moderate renal impairment. Atezolizumab has not been studied in patients with severe hepatic impairment.

Administration method. Atezolizumab is administered intravenously. Infusions should not be given as a rapid infusion or intravenous bolus. The initial dose of atezolizumab should be administered over 60 minutes. If the first infusion is well tolerated, subsequent infusions may be given over 30 minutes.

5. EVALUATION AND MONITORING

The doctor responsible for the patient in each of the stages of the process must register the following information in VALTERMED.

General patient details (to be collected in VALTERMED before starting treatment to carry out the evaluation):

- NHS Code[b]
- CIP/CITE Code[b]
- NIF/NIE[b]
- Health Card No.[b]
- Medical Record No.:
- Sex[c]:
- Date of birth[c]:
- Anthropometric data prior to therapy. Weight (Kg): height (cm):

Disease characterisation at the beginning of treatment

Date of diagnosis:

- Histologically or cytologically confirmed ED-SCLC (based on the Veterans Affair Lung Study Group (VALG) staging system) and with measurable disease based on RECIST version 1.1 criteria.

Prior to atezolizumab administration:

- No previous treatment for ED-SCLC
- ECOG: 0 ☐ 1 ☐
- No presence of active or cortico-dependent brain metastases
- Adequate haematological and organic function.

Comorbidities (optional):

Administration of ATEZOLIZUMAB (1200 mg)

Start date of treatment:

[b] It is mandatory to fill in at least one of these fields.
[c] Required fields.

- If administration was not performed, specify the reason: (optional)
- Premature discontinuation of treatment (Complete treatment without premature discontinuation

  / premature discontinuation due to serious side effects* / intolerance / liver disorders / worsening / death/ supply shortage):

  * in case of adverse effects, complete description in the safety section End date of treatment:
- Number of atezolizumab 1200 mg vials administered: _____

Concomitant treatments received (optional)

Record of the patient's overall survival (18 MONTHS after commencing treatment):

- OS **≤10 months:** YES/NO
- OS **11-13 months:** YES/NO
- OS **14 months and 17 months:** YES/NO
- OS **18 months and up:** YES/NO

Safety (optional)

- Infusion-associated and hypersensitivity reactions: YES/NO
- Other adverse effects.

Under no circumstances should any data collection compete with the legal obligations under which all suspected adverse reactions will be reported through your pharmacovigilance centre (www.notificaram.es).

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