PHARMACOCLINICAL PROTOCOL FOR THE USE OF ATEZOLIZUMAB (TECENTRIQ®) IN COMBINATION WITH NAB-PACLITAXEL IN THE TREATMENT OF UNRESECTABLE LOCALLY ADVANCED OR METASTATIC TRIPLE-NEGATIVE BREAST CANCER IN THE NATIONAL HEALTH SYSTEM

Approved by the Permanent Pharmacy Commission

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All the experts have made a conflict of interest declaration.

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1. INTRODUCTION

Breast cancer ranks third among the most frequently diagnosed cancers in Spain in 2021, with 33,375 new cases[1].

Triple-negative breast cancer (TNBC) is considered responsible for 15% to 20% of all breast carcinomas. This tumour subtype is characterised by the absence of oestrogen and progesterone receptors and the overexpression and/or amplification of the human epidermal growth factor receptor 2 (HER2) gene. It is the most aggressive subtype of breast cancer and is characterised by a very high risk of early disease recurrence and mortality[2]. Compared to other breast cancers, patients with TNBC have a higher risk of early recurrence or distant metastasis, the onset is usually more rapid, the percentage of visceral spread is higher and it is a fast-growing tumour[3,4]. These factors result in a worse prognosis that is associated with worse survival rates compared to hormone receptor (HR)-positive breast cancer[5]. Overall survival (OS) in the metastatic stage is less than 12 months while in the general breast cancer population it is more than 36 months[6]. Estimated 5-year survival rate is 12.2%[7]. In terms of age of onset, it is associated with young patients and is most commonly diagnosed in patients under 40 years of age.

In the early stages of the disease, recommendations for chemotherapy, surgery or radiotherapy are similar to those adopted for the other histological subtypes. Specifically, and in relation to chemotherapy, schemes based on anthracyclines, alkylating agents, platinum based compounds and taxanes, continue to be the current reference treatments[8].

In patients with metastatic TNBC, the purpose of treatment is to prolong survival and maintain or increase the quality of life of the patients by alleviating their symptoms. In these patients, hormonal treatments and HER2-targeted therapies are ineffective, as there are no receptors for these drugs, and chemotherapy is the mainstay of treatment. According to the ESMO guidelines[9] , combination chemotherapy regimens are reserved for patients with rapid clinical progression, or when rapid disease control is needed. For the remaining patients, sequential monotherapy treatments are prioritised, where no single agent has demonstrated superiority over the others. In patients who have not received prior treatment, the use of anthracyclines and/or taxanes is recommended, preferably both in sequential

treatment, although they can also be given concomitantly if deemed necessary for a more rapid response. Patients may receive anthracyclines and/or taxanes again, even if they have previously received them in a (neo)adjuvant setting, if they remained progression-free for more than one year after finishing that treatment. To be candidates for anthracyclines, they must also not exceed the maximum cumulative dose and have no risk factors that would make their use inadvisable due to cardiotoxicity. In these patients, therapeutic options will therefore depend on whether or not anthracycline and taxane treatment has been exhausted and on other factors, such as the presence of BRCA1/BRCA2 mutations, where platinum combinations are an additional option[9]. PARP inhibitors have recently been approved for the treatment of advanced TNBC with BRCA1/2 germline mutations in patients who have been previously treated with an anthracycline and/or a taxane.

Recent research has established the influence of the immune system on disease progression in TNBC patients. These studies have shown that the mutational burden of this histological subtype is high. These mutations can act as antigens and trigger an anti-tumour immune response[10]. Based on this evidence, studies have been undertaken with immunotherapeutic drugs in breast cancer patients, such as anti-PD-L1 monoclonal antibodies[11].

The drug atezolizumab has been approved in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer with PD-L1 tumour expression ≥1% and who have not received prior chemotherapy for metastasis, based on results from the IMpassion 130[12] study, which shows that adding atezolizumab to nab-paclitaxel increases progression-free survival (PFS) by 2.5 months (HR 0.62; 95% CI 0.49 - 0.78; p<0.0001) versus nab-paclitaxel. In addition, the increase in median overall survival (OS) is 7 months (HR 0.71; 95% CI 0.54-0.94; p=0,0133). However, the benefit obtained in OS in the subgroup of patients with PD-L1 tumour expression ≥1%, which could be considered clinically relevant, lacks statistical validity because it is based on a non-statistically significant result in the intention-to-treat analysis[13].

There are doubts about the efficacy of the combination of atezolizumab with nab-paclitaxel in the subgroup of patients with PD-L1-positive tumour expression, previously treated with anthracyclines[14].

In terms of safety, the most frequent AEs detected were alopecia, nausea, diarrhoea, anaemia and constipation, largely due to the taxane. However, the combination with atezolizumab added adverse reactions to the taxane chemotherapy: more nausea occurred (45% *vs.* 37%), cough (25% *vs.* 20%), neutropenia (13% *vs.* 7%),
pyrexia (19% *vs.* 11%) and hypothyroidism (14% *vs.* 4%). Clinically relevant grade 3-4 adverse effects were 49% with atezolizumab vs. 43% in the control[13].

Given the uncertainties about the efficacy of atezolizumab and its transferability to clinical practice, it was deemed necessary to limit its use to patients with locally advanced or metastatic TNBC with PD-L1 expression ≥ 1% without prior anthracycline treatment, after an individualised assessment of the potential benefits and risks compared to commonly used alternative options.

2. TREATMENT OBJECTIVE

The goal of treatment with atezolizumab in combination with nab-paclitaxel for the treatment of adult patients with unresectable locally advanced or metastatic TNBC with PD-L1 tumour expression ≥1%, previously untreated with chemotherapy in metastatic disease, is to extend survival to a larger number of long responders based on the results of the clinical trial. To this end, overall survival outcomes will be recorded in adult patients with unresectable locally advanced or metastatic triple-negative breast cancer treated with atezolizumab in combination with nab-paclitaxel, with ECOG 0-1 whose tumours have PD-L1 expression ≥ 1%, who have not received prior chemotherapy for metastasis and without prior anthracycline treatment.

Monitoring of the OS results has been established, determined on the basis of the following tranches:

- OS less than or equal to 22 months
- OS equal to 23-24 months
- OS equal to or greater than 25 months

3. PATIENT SELECTION CRITERIA

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

1. Adult patients diagnosed with unresectable locally advanced or metastatic triple-negative breast cancer and who have not received prior chemotherapy for metastasis
2. Patients whose tumours have PD-L1 expression ≥ 1%
3. No prior treatment with anthracyclines
4. ECOG 0-1
5. Adequate haematological and organic function[a]

Criteria for **exclusion from treatment**:

1. Confirmed symptomatic disease at the central nervous system (CNS) level or with leptomeningeal involvement.
2. 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.
3. 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.
4. Patients with prior allogeneic stem cell or solid organ transplantation.
5. Patients with HIV, active hepatitis B or hepatitis C infection, active tuberculosis or severe infections and with baseline ECOG ≥ 2.
6. Adjuvant or neo-adjuvant chemotherapy in the past 12 months.
7. Patients who have received a live attenuated virus vaccine within the

[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 hepatic or bone metastases: alkaline phosphatase ≤ 5 × ULN; serum bilirubin ≤ 1.25 × ULN; CLcr≥30 ml/min.

4 weeks before the start of treatment.

8. Administration of systemic immunosuppressive medicinal products within 14 days prior to initiation of treatment.
9. Major surgical intervention in the 28 days prior to the start of treatment.
10. Prior treatment with CD137 agonists or immune checkpoint blockade, anti-PD-1 and anti-PD-L1 therapies.
11. Known contraindication or hypersensitivity to atezolizumab or nab-paclitaxel.

Criteria for **discontinuation of treatment:**

1. The presence of adverse effects related to the infusion of the medicinal product that prevents 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.

4. GENERAL CONSIDERATIONS FOR TREATMENT WITH ATEZOLIZUMAB[15]

Atezolizumab in combination with nab-paclitaxel in first-line unresectable locally advanced or metastatic TNBC: the recommended dose of atezolizumab is 840 mg administered by intravenous infusion, followed by 100 mg/m2 nab-paclitaxel. For each 28-day cycle, atezolizumab is given on days 1 and 15 and nab-paclitaxel is given on days 1, 8 and 15.

Treatment duration: it is recommended that patients be treated with atezolizumab until disease progression or onset of unmanageable toxicity

Dose modification during treatment: reductions in the atezolizumab dose are not recommended.

Dose modification advice for atezolizumab[15].

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: 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 hepatic 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 of unresectable locally advanced or metastatic disease:

- Confirmed diagnosis of PD-L1 expression (Positive: ≥1%), as determined by immunohistochemical assays. Date: PD-L1 positivity (%):

Prior to atezolizumab administration:

- Metastatic disease previously untreated with chemotherapy
- Previous treatment with anthracyclines YES/NO
- ECOG: 0 ☐ 1 ☐
- Presence of CNS metastasis or leptomeningeal involvement YES/NO
- Administration of taxanes in adjuvant or neoadjuvant: YES/NO
- Adequate haematological and organic function: YES/NO

Comorbidities (optional):

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

Administration of ATEZOLIZUMAB (840 mg presentation based on the indicated dosage)

Start date of treatment:

- 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 vials administered of atezolizumab 840 mg: _____

Concomitant treatments received (optional)

Record of the patient's overall survival (25 MONTHS after the start of the treatment):

OS ≤ 22 months YES/NO

OS equal to 23-24 months

YES/NO OS ≥ 25 months:

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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