Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a licence (marketing authorisation) in this indication and is used in combination with standard of care. The information is provided to assist the doctor in prescribing an unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage: https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine.

The prescribing doctor should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document

Information for the healthcare professionals:

1. NAME OF THE MEDICINAL PRODUCT

Atezolizumab 1,200 mg concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL vial of concentrate contains 1,200 mg atezolizumab*.

After dilution (see section 6.6), one mL of solution contains approximately 4.4 mg of atezolizumab.

*Atezolizumab is an Fc-engineered, humanised IgG1 anti-programmed death-ligand 1 (PD-L1) monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to slightly yellowish liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atezolizumab, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC) (see section 5.1).

4.2 Posology and method of administration

Atezolizumab must be initiated and supervised by physicians experienced in the treatment of cancer.

Posology

Please also refer to the full prescribing information for etoposide and carboplatin (see also section 5.1).

During the induction phase, the recommended dose of atezolizumab is 1,200 mg administered by intravenous infusion followed by carboplatin, and then etoposide administered by intravenous infusion on day 1. Etoposide is administered by intravenous infusion on days 2 and 3. This regimen is administered every three weeks for four cycles.

The induction phase is followed by a maintenance phase without chemotherapy in which 1,200 mg atezolizumab is administered by intravenous infusion every three weeks.

Duration of treatment
It is recommended that patients are treated with atezolizumab until loss of clinical benefit (see section 5.1) or unmanageable toxicity.

Delayed or missed doses
If a planned dose of atezolizumab is missed, it should be administered as soon as possible; it is recommended not to wait until the next planned dose. The schedule of administration must be adjusted to maintain a 3-week interval between doses.

Dose modifications during treatment
Dose reductions of atezolizumab are not recommended.

Dose delay or discontinuation (see also sections 4.4 and 4.8)

Table 1: Dose modification advice for atezolizumab

Immune related adverse reaction	Severity	Treatment modification
Pneumonitis	Grade 2	Withhold atezolizumab 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 atezolizumab
Hepatitis	Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] *or* blood bilirubin > 1.5 to 3 x ULN)	Withhold atezolizumab 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 atezolizumab
Colitis	Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) *or* Symptomatic Colitis	Withhold atezolizumab 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 atezolizumab
Hypothyroidism or hyperthyroidism	Symptomatic	Withhold atezolizumab *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 antithyroid medicinal product and thyroid function is improving	
Adrenal insufficiency	Symptomatic	Withhold atezolizumab 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 atezolizumab 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 atezolizumab	
Type 1 diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L)	Withhold atezolizumab 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 atezolizumab	

Rash	Grade 3	Withhold atezolizumab Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day	
	Grade 4	Permanently discontinue atezolizumab	
Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis	All Grades	Permanently discontinue atezolizumab	
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis	Withhold atezolizumab 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 atezolizumab	
Myocarditis	Grade 2	Withhold atezolizumab 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 and 4	Permanently discontinue atezolizumab	
Nephritis	Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN)	Withhold atezolizumab 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 atezolizumab	
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 atezolizumab (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.).

Patients treated with atezolizumab must be given the Patient Alert Card and be informed about the risks of atezolizumab (see also package leaflet).

Special populations

Paediatric population
The safety and efficacy of atezolizumab in children and adolescents aged below 18 years have not been established. No data are available.

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

Renal impairment
Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population.

Hepatic impairment
Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild hepatic impairment. Atezolizumab has not been studied in patients with moderate or severe hepatic impairment (see section 5.2).

Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2
Patients with ECOG performance status ≥ 2 were excluded from the clinical trials in ES-SCLC (see sections 4.4 and 5.1).

Method of administration

Atezolizumab is for intravenous use. The infusions must not be administered as an intravenous push or bolus.

The initial dose of Atezolizumab must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

For instructions on dilution and handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to atezolizumab or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Most immune-related adverse reactions occurring during treatment with atezolizumab were reversible with interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-related adverse reactions affecting more than one body system have been observed. Immune-related adverse reactions with atezolizumab may occur after the last dose of atezolizumab.

For suspected immune-related adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with systemic corticosteroid use, administration of other systemic immunosuppressants may be considered.

Atezolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reactions, except for endocrinopathies that are controlled with replacement hormones (see sections 4.2 and 4.8).

Immune-related pneumonitis

Cases of pneumonitis, including fatal cases, have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis.

Treatment with atezolizumab should be withheld for Grade 2 pneumonitis, and 1 to 2 mg/kg/day prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 pneumonitis.

Immune-related hepatitis

Cases of hepatitis, some leading to fatal outcomes have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of hepatitis.

Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin should be monitored prior to initiation of treatment, periodically during treatment with atezolizumab and as indicated based on clinical evaluation.

Treatment with atezolizumab should be withheld if Grade 2 event (ALT or AST > 3 to 5 x ULN or blood bilirubin > 1.5 to 3 x ULN) persists for more than 5 to 7 days, and 1 to 2 mg/kg/day of prednisone or equivalent should be started. If the event improves to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month.

Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or Grade 4 events (ALT or AST > 5.0 x ULN or blood bilirubin > 3 x ULN).

Immune-related colitis

Cases of diarrhoea or colitis have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of colitis.

Treatment with atezolizumab should be withheld for Grade 2 or 3 diarrhoea (increase of ≥ 4 stools/day over baseline) or colitis (symptomatic). For Grade 2 diarrhoea or colitis, if symptoms persist > 5 days or recur, treatment with 1 to 2 mg/kg/day prednisone or equivalent should be started. For Grade 3 diarrhoea or colitis, treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 4 (life threatening; urgent intervention indicated) diarrhoea or colitis.

Immune-related endocrinopathies

Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis and type 1 diabetes mellitus, including diabetic ketoacidosis have been observed in clinical trials with atezolizumab (see section 4.8).

Patients should be monitored for clinical signs and symptoms of endocrinopathies. Thyroid function should be monitored prior to and periodically during treatment with atezolizumab. Appropriate management of patients with abnormal thyroid function tests at baseline should be considered.

Asymptomatic patients with abnormal thyroid function tests can receive atezolizumab. For symptomatic hypothyroidism, atezolizumab should be withheld and thyroid hormone replacement should be initiated as needed. Isolated hypothyroidism may be managed with replacement therapy and without corticosteroids. For symptomatic hyperthyroidism, atezolizumab should be withheld and an antithyroid medicinal product should be initiated as needed. Treatment with atezolizumab may be resumed when symptoms are controlled and thyroid function is improving.

For symptomatic adrenal insufficiency, atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and the patient is stable on replacement therapy (if required).

For Grade 2 or Grade 3 hypophysitis, atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started, and hormone replacement should be initiated as needed. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and the patient is stable on replacement therapy (if required). Treatment with atezolizumab should be permanently discontinued for Grade 4 hypophysitis.

Treatment with insulin should be initiated for type 1 diabetes mellitus. For ≥ Grade 3 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L), atezolizumab should be withheld. Treatment with atezolizumab may be resumed if metabolic control is achieved on insulin replacement therapy.

Immune-related meningoencephalitis

Meningoencephalitis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of meningitis or encephalitis.

Treatment with atezolizumab must be permanently discontinued for any grade of meningitis or encephalitis. Treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow.

Immune-related neuropathies

Myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome, which may be life threatening, were observed in patients receiving atezolizumab. Patients should be monitored for symptoms of motor and sensory neuropathy.

Treatment with atezolizumab must be permanently discontinued for any grade of myasthenic syndrome / myasthenia gravis or Guillain-Barré syndrome. Initiation of systemic corticosteroids (at a dose of 1 to 2 mg/kg/day of prednisone or equivalent) should be considered.

Immune-related pancreatitis

Pancreatitis, including increases in serum amylase and lipase levels, have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis.

Treatment with atezolizumab should be withheld for ≥ Grade 3 serum amylase or lipase levels increased (> 2 x ULN), or Grade 2 or 3 pancreatitis, and treatment with intravenous corticosteroids
(1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow. Treatment with atezolizumab may be resumed when serum amylase and lipase levels improve to ≤ Grade 1

within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4, or any grade of recurrent pancreatitis.

Immune-related myocarditis

Myocarditis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of myocarditis.

Treatment with atezolizumab should be withheld for Grade 2 myocarditis, and treatment with systemic corticosteroids at a dose of 1 to 2mg/kg/day of prednisone or equivalent should be started. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 myocarditis.

Immune-related nephritis

Nephritis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for changes in renal function.

Treatment with atezolizumab should be withheld for Grade 2 nephritis, and treatment with systemic corticosteroids at a dose of 1 to 2mg/kg/day of prednisone or equivalent should be started. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 nephritis.

Infusion-related reactions

Severe infusion related reactions, including hypersensitivity and anaphylaxis, have been observed in clinical trials with atezolizumab (see section 4.8).
The rate of infusion should be reduced or treatment should be interrupted in patients with Grade 1 or 2 infusion related reactions. Atezolizumab should be permanently discontinued in patients with Grade 3 or 4 infusion related reactions. Patients with Grade 1 or 2 infusion-related reactions may continue to receive atezolizumab with close monitoring; premedication with antipyretic and antihistamines may be considered.

Patients excluded from clinical trial IMpower133

Patients with the following conditions were excluded from IMpower133: active or untreated CNS metastases, uncontrolled pleural effusion, a history of autoimmune disease, history of or active pneumonitis, HIV, hepatitis B or hepatitis C infection, active tuberculosis, significant cardiovascular disease, allogenic bone marrow transplantation or solid organ transplant, prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti−PD-1, and anti−PD-L1 therapeutic antibodies. Patients who were administered a live, attenuated vaccine within 28 days prior to enrolment; systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to study entry were excluded from clinical trials.

Patients with a baseline performance status ≥ 2 were excluded (see section 5.1).

In the absence of data, atezolizumab should be used with caution in these populations after careful evaluation of the balance of benefits and risks for the patient.

Healthcare professionals are advised to consult the SPCs of carboplatin and etoposide for the specific precautions and contraindications of these medicines.

Patient Alert Card

All prescribers of atezolizumab must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of atezolizumab therapy with the patient. The patient will be provided with the Patient Alert Card and instructed to carry the card at all times.

4.5 Interaction with other medicinal products and other forms of interaction

No formal pharmacokinetic drug interaction studies have been conducted with atezolizumab. Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting atezolizumab (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during and for 5 months after treatment with atezolizumab.

Pregnancy

There are no data from the use of atezolizumab in pregnant women. No developmental and reproductive studies were conducted with atezolizumab. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway in murine pregnancy models can lead to immune-related rejection of the developing foetus resulting in foetal death (see section 5.3). These results indicate a potential risk, based on its mechanism of action, that administration of atezolizumab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth.

Human immunoglobulins G1 (IgG1) are known to cross the placental barrier and atezolizumab is an IgG1; therefore, atezolizumab has the potential to be transmitted from the mother to the developing foetus.

Atezolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with atezolizumab.

Breast-feeding

It is unknown whether atezolizumab is excreted in human milk. Atezolizumab is a monoclonal antibody and is expected to be present in the first milk and at low levels afterwards. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue atezolizumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No clinical data are available on the possible effects of atezolizumab on fertility. No reproductive and development toxicity studies have been conducted with atezolizumab; however, based on the 26-week repeat dose toxicity study, atezolizumab had an effect on menstrual cycles at an

estimated AUC approximately 6 times the AUC in patients receiving the recommended dose and was reversible (see section 5.3). There were no effects on the male reproductive organs.

4.7 Effects on ability to drive and use machines

atezolizumab has minor influence on the ability to drive and use machines. Patients experiencing fatigue should be advised not to drive and use machines until symptoms abate (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

For the safety of atezolizumab as monotherapy, please refer to the SPC of Tecentriq® (atezolizumab)

For the safety of carboplatin as monotherapy, please refer to the SPC of the carboplatin containing medicine that is used for treatment

For the safety of etoposide as monotherapy, please refer to the SPC of the etoposide containing medicine that is used for treatment

The safety of atezolizumab given in combination with carboplatin and etoposide has been evaluated in 198 patients with first-line ES-SCLC. The most common adverse reactions (⩾ 20%) were anaemia (43.4%), nausea (37.9%), fatigue (27.3%), and decreased appetite (27.3%).

Tabulated list of adverse reactions

Table 2 summarises the additional ADRs associated with the use of atezolizumab in combination with carboplatin and etoposide. ADRs with a clinically relevant difference when compared to monotherapy are also presented.

Table 2: Summary of adverse reactions occurring in patients treated with atezolizumab in combination with carboplatin and etoposide in a clinical trial

Blood and Lymphatic System Disorders	
Very common	anaemia[*], thrombocytopenia[‡, a]
Endocrine Disorders	
Very common	hypothyroidism[*, ‡, b]
Uncommon	hypophysitis[‡, c]

* ADR occurring at a frequency ≥ 5% (All grades) or ≥ 2% (Grades 3-4) compared to the control arm.
‡ Observed rate in the combination represents a clinically relevant difference in comparison to atezolizumab monotherapy.
[a] Includes reports of thrombocytopenia and platelet count decreased.
[b] Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, blood thyroid stimulating, hormone decreased, autoimmune thyroiditis, thyroiditis, thyroxine free increased, tri−iodothyronine free increased.
[c] Includes reports of hypophysitis, temperature regulation disorder.

Description of selected adverse reactions

The data below reflect exposure to atezolizumab for clinically significant adverse reactions in clinical study IMpower133 (see section 5.1). For information on significant adverse reactions of atezolizumab as monotherapy, please refer to the SPC of Tecentriq ® (atezolizumab).
The management guidelines for these adverse reactions are described in sections 4.2 and 4.4.

Immune-related endocrinopathies
Hypothyroidism occurred in 12.6% (25/198) of patients who received atezolizumab in clinical study IMpower133. The median time to onset was 4.2 months (range: 1.7 to 11.3 months).

Hypophysitis occurred in 0.5% (1/198) of patients who received atezolizumab. The time to onset for this patient was 13.7 months.

Immunogenicity
In clinical study IMpower133, 18.6 % of patients developed treatment-emergent anti-drug antibodies (ADAs). Overall, ADA positivity appeared to have no clinically relevant impact on safety.

No data are available to allow conclusions to be drawn on possible effects of neutralising antibodies.

4.9 Overdose

There is no information on overdose with atezolizumab.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01XC

Mechanism of action

Programmed death-ligand 1 (PD-L1) may be expressed on tumour cells and/or tumour-infiltrating immune cells, and can contribute to the inhibition of the antitumour immune response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

Atezolizumab is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist.

Clinical efficacy and safety

IMpower133 (GO30081): Randomised phase I/III trial in patients with chemotherapy-naïve extensive-stage SCLC, in combination with carboplatin and etoposide

A Phase I/III, randomised, multicentre, double-blind, placebo controlled study, IMpower133, was conducted to evaluate the efficacy and safety of atezolizumab in combination with carboplatin and etoposide in patients with chemotherapy-naïve extensive-stage small cell lung cancer (ES-SCLC).

Patients were excluded if they had active or untreated CNS metastases; history of autoimmune disease; administration of live, attenuated vaccine within 4 weeks prior to randomisation; administration of systemic immunosuppressive medications within 1 week prior to randomisation. Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Patients treated beyond disease progression had tumour assessment conducted every 6 weeks until treatment discontinuation.

A total of 403 patients were enrolled and randomised (1:1) to receive one of the treatment regimens described in Table 3. Randomisation was stratified by sex, ECOG performance status, and presence of brain metastases.

Table 3: Intravenous Treatment Regimen (IMpower133)

Treatment regimen	Induction (Four 21-Day Cycles)	Maintenance (21-Day Cycles)
A	atezolizumab (1,200 mg)[a] + carboplatin (AUC 5)[b] + etoposide (100 mg/m^2)[b,c]	atezolizumab (1,200 mg) [a]
B	placebo + carboplatin (AUC 5)[b] + etoposide (100 mg/m^2)[b,c]	placebo

[a]Atezolizumab was administered until loss of clinical benefit as assessed by investigator
[b]Carboplatin and etoposide were administered until completion of 4 cycles, or progressive disease or unacceptable toxicity, whichever occurs first
[c]Etoposide was administered on day 1, 2 and 3 of each cycle

Duration of treatment

Treatment with atezolizumab until loss of clinical benefit was permitted as defined by the following criteria:

- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcaemia]) indicating unequivocal progression of disease
- No decline in ECOG performance status
- Absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilised by protocol-allowed medical interventions prior to repeat dosing
- Evidence of clinical benefit as assessed by the investigator

The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. The median age was 64 years (range: 26 to 90 years). The majority of patients were male (65%), white (80%), and 9% had brain metastases and most patients were current or previous smokers (97%). Baseline ECOG performance status was 0 (35%) or 1 (65%).

At the time of the primary analysis, patients had a median survival follow up time of 13.9 months. The key results are summarised in Table 4. Kaplan-Meier curves for OS and PFS are presented in Figure 1 and 2.

Table 4: Summary of efficacy (IMpower133)

Key efficacy endpoints	Arm A (Atezolizumab + carboplatin + etoposide)	Arm B (Placebo + carboplatin + etoposide)	
Co-primary endpoints			
OS analysis	n=201	n=202	
No. of deaths (%)	104 (51.7%)	134 (66.3%)	
Median time to events (months)	12.3	10.3	
95% CI	(10.8, 15.9)	(9.3, 11.3)	
Stratified hazard ratio‡ (95% CI)	0.70 (0.54, 0.91)		
p-value	0.0069		
12-month OS (%)	51.7	38.2	
Investigator-assessed PFS (RECIST v1.1)	n=201	n=202	
No. of events (%)	171 (85.1%)	189 (93.6%)	
Median duration of PFS (months)	5.2	4.3	
95% CI	(4.4, 5.6)	(4.2, 4.5)	
Stratified hazard ratio‡ (95% CI)	0.77 (0.62, 0.96)		
p-value	0.0170		
6-month PFS (%)	30.9	22.4	
12-month PFS (%)	12.6	5.4	
Secondary endpoints			
Investigator-assessed ORR (RECIST 1.1)	n=201	n=202	
No. of responders (%)	121 (60.2%)	130 (64.4%)	
95% CI	(53.1, 67.0)	(57.3, 71.0.)	
No. of complete response (%)	5 (2.5%)	2 (1.0%)	
No. of partial response (%)	116 (57.7%)	128 (63.4%)	
Investigator-assessed DOR (RECIST 1.1)	n =121	n = 130	
Median in months	4.2	3.9	
95% CI	(4.1, 4.5)	(3.1, 4.2)	

PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1.; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival
‡ Stratified by sex and ECOG performance status

The treatment effect on OS and PFS was broadly consistent across clinical subgroups with the following exceptions 1) A numerically lower OS benefit in younger subjects <65 years (n=217) compared to that of the older age group of ≥65 years (n=186) was seen with an OS HR of 0.92; 95% CI 0.64, 1.32 and HR 0.53, 95% CI 0.36, 0.77 respectively. Hazard ratios for PFS were the same for both age groups (HR 0.76; 95% CI 0.57, 1.01 and 95% CI 0.56, 1.03 respectively). 2) In patients with brain metastases, there is limited evidence of efficacy although the number of patients treated was small: the OS HR was 1.07; 95% CI 0.47 – 2.43 in the atezolizumab + CE arm (n=35) with PFS HR 0.98; 95% CI 0.49 – 2.00. However, the IMpower 133 trial was not designed to statistically test clinical benefit in subgroups of patients; therefore, this data should be interpreted with caution.

Figure 1: Kaplan-Meier curve for overall survival (IMpower133)

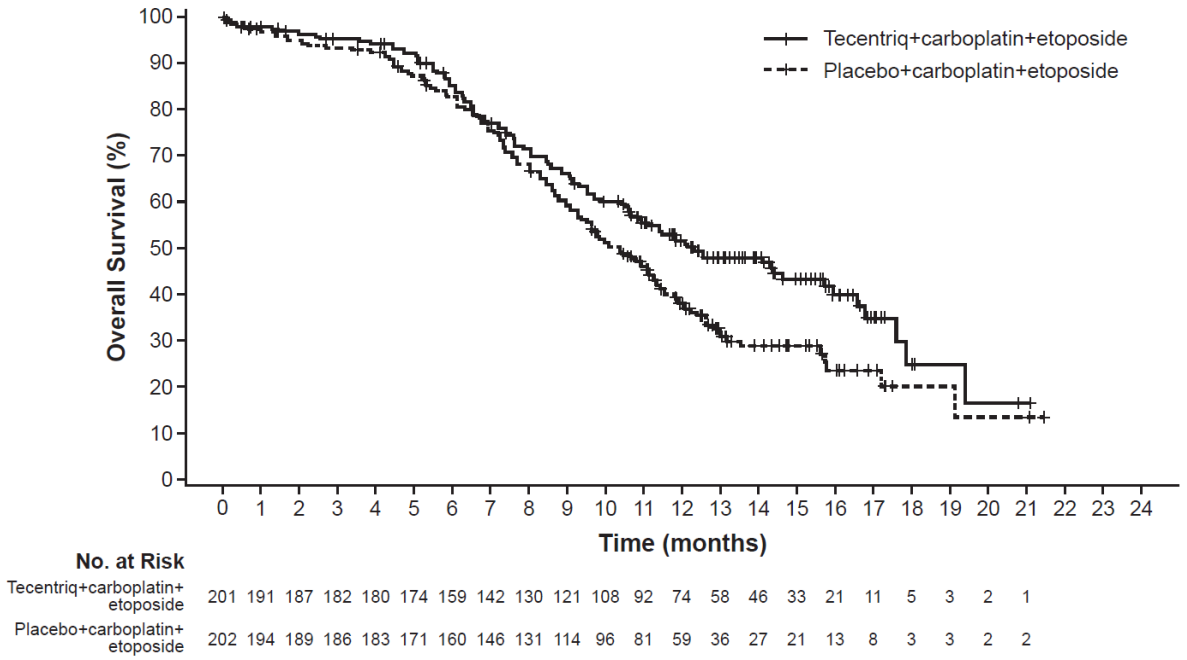
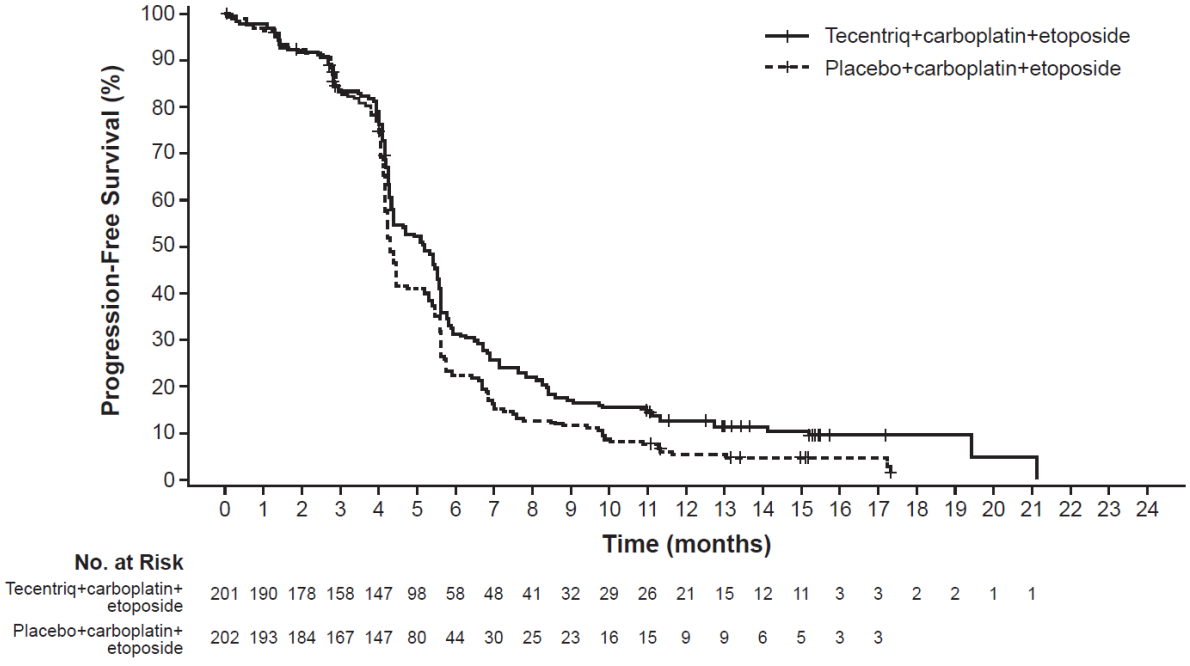


Figure 2: Kaplan-Meier curve for progression-free survival (IMpower133)



Patient reported endpoints indicted that overall, patients treated with atezolizumab in combination with carboplatin and etoposide achieved more pronounced and enduring improvements in health-related quality of life (≥10-point score increases at most visits through Week 48) compared to patients treated with placebo, carboplatin and etoposide, who reported nominal improvements (<10-point score increases) at most study treatment visits.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with atezolizumab in all subsets of the paediatric population in the treatment of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Exposure to atezolizumab increased dose proportionally over the dose range 1 mg/kg to 20 mg/kg including the fixed dose 1,200 mg administered every 3 weeks. A population analysis that included 472 patients described atezolizumab pharmacokinetics for the dose range: 1 to 20 mg/kg with a linear two-compartment disposition model with first-order elimination. A population pharmacokinetic analysis suggests that steady-state is obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in area under the curve, maximum concentration and trough concentration was 1.91, 1.46 and 2.75-fold, respectively.

Absorption

Atezolizumab is administered as an intravenous infusion. There have been no studies performed with other routes of administration.

Distribution

A population pharmacokinetic analysis indicates that central compartment volume of distribution is 3.28 L and volume at steady-state is 6.91 L in the typical patient.

Biotransformation

The metabolism of atezolizumab has not been directly studied. Antibodies are cleared principally by catabolism.

Elimination

A population pharmacokinetic analysis indicates that the clearance of atezolizumab is 0.200 L/day and the typical terminal elimination half-life is 27 days.

Special populations

Based on population PK and exposure-response analyses age (21-89 years), region, ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG performance status have no effect on atezolizumab pharmacokinetics. Body weight, gender, positive ADA status, albumin levels and tumour burden have a statistically significant, but not clinically relevant effect on atezolizumab pharmacokinetics. No dose adjustments are recommended.

Elderly

No dedicated studies of atezolizumab have been conducted in elderly patients. The effect of age on the pharmacokinetics of atezolizumab was assessed in a population pharmacokinetic analysis. Age was not identified as a significant covariate influencing atezolizumab pharmacokinetics based on patients of age range of 21-89 years (n=472), and median of 62 years of age. No clinically important difference was observed in the pharmacokinetics of atezolizumab among patients < 65 years (n=274), patients between 65–75 years (n=152) and patients > 75 years (n=46) (see section 4.2).

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of atezolizumab in children or adolescents.

Renal impairment

No dedicated studies of atezolizumab have been conducted in patients with renal impairment. In the population pharmacokinetic analysis, no clinically important differences in the clearance of atezolizumab were found in patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2; n=208) or, moderate (eGFR 30 to 59 mL/min/1.73 m^2; n=116) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m^2; n=140) renal function. Only a few patients had severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2; n=8) (see section 4.2). The effect of severe renal impairment on the pharmacokinetics of atezolizumab is unknown.

Hepatic impairment

No dedicated studies of atezolizumab have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of atezolizumab between patients with mild hepatic impairment (bilirubin $\leq$ ULN and AST $>$ ULN or bilirubin $> 1.0 \times$ to $1.5 \times$ ULN and any AST, n= 71) and normal hepatic function (bilirubin and AST $\leq$ ULN, n= 401). No data are available in patients with either moderate or severe hepatic impairment. Hepatic impairment was defined by the National Cancer Institute (NCI) criteria of hepatic dysfunction (see section 4.2). The effect of moderate or severe hepatic impairment (bilirubin > 1.5 × to 3 × ULN and any AST or bilirubin > 3 × ULN and any AST) on the pharmacokinetics of atezolizumab is unknown.

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been performed to establish the carcinogenic potential of atezolizumab.

Mutagenicity

Mutagenicity studies have not been performed to establish the mutagenic potential of atezolizumab. However, monoclonal antibodies are not expected to alter DNA or chromosomes.

Fertility

No fertility studies have been conducted with atezolizumab; however assessment of the cynomolgus monkey male and female reproductive organs was included in the chronic toxicity study. Weekly administration of atezolizumab to female monkeys at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose caused an irregular menstrual cycle pattern and a lack of newly formed corpora lutea in the ovaries which were reversible. There was no effect on the male reproductive organs.

Teratogenicity

No reproductive or teratogenicity studies in animals have been conducted with atezolizumab. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to immune-related rejection of the developing foetus resulting in foetal death. Administration of atezolizumab could cause foetal harm, including embryo-foetal lethality.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
Glacial acetic acid
Sucrose
Polysorbate 20
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years.

Diluted solution

Chemical and physical in-use stability has been demonstrated for no more than 24 hours at 2 °C to 8 °C or 24 hours at ≤ 30 °C from the time of preparation.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C or 8 hours at ambient temperature (≤ 25 °C).

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial with a butyl rubber stopper containing 20 mL of solution.

Pack of one vial.

6.6 Special precautions for disposal and other handling

Atezolizumab does not contain any antimicrobial preservative and should be prepared by a healthcare professional using aseptic technique.

Do not shake.

Instructions for dilution

Twenty mL of atezolizumab concentrate should be withdrawn from the vial and diluted into a 250 mL PVC, polyethylene (PE) or polyolefin infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection. After dilution, one mL of solution should contain approximately 4.4 mg of atezolizumab (1,200 mg/270 mL). The bag should be gently inverted to mix the solution in order to avoid foaming. Once the infusion is prepared it should be administered immediately (see section 6.3).

Parenteral medicinal products should be inspected visually for particulates and discolouration prior to administration. If particulates or discoloration are observed, the solution should not be used.

No incompatibilities have been observed between atezolizumab and intravenous bags with product-contacting surfaces of polyvinyl chloride (PVC), polyethylene (PE) or polyolefin (PO). In addition, no incompatibilities have been observed with in-line filter membranes composed of polyethersulfone or polysulfone, and infusion sets and other infusion aids composed of PVC, PE, polybutadiene, or polyetherurethane. The use of in-line filter membranes is optional.

Disposal

The release of atezolizumab in the environment should be minimised. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SCIENTIFIC OPINION HOLDER

Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. EAMS NUMBER

00031/0007

9. DATE OF SCIENTIFIC OPINION

07/06/2019

Additional information:

Each prescribing physician will be required to complete the initial application and drug supply request form to confirm eligibility within the scheme, once the patient has signed the informed consent form. These forms can be requested by sending an email to welwyn.atezolizumabeams@roche.com

A Physician Agreement and Safety Data Exchange agreement will be signed by the prescribing physician. Once the signed documents are returned, Roche will arrange safety training and each prescribing oncologist will also be provided with a physician pack containing all the relevant

documents needed including adverse events reporting form, needed to manage patients receiving atezolizumab under EAMS.

Contact information:

Contact details for reporting Adverse Events /Pregnancies:

SAE Email Address: welwyn.uk_dsc@roche.com

SAE Facsimile Transmission: +44 1707 367582

SAE TELEPHONE CONTACT: +44 1707 367554

Name: UK Drug Safety Centre

Contact email for the EAMS programme (excluding AE reporting):

welwyn.atezolizumabeams@roche.com

Contact Details for Medical Information

Roche Medical Information on 0800 328 1629 or email medinfo.uk@roche.com