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 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 licence 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.

For further updates of the safety information, please refer to the product information of Tecentriq (atezolizumab) on the EMA website": https://www.ema.europa.eu/documents/product-information/tecentriq-epar-product-information_en.pdf

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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 EAMS indication

Atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) with EGFR activating or ALK-positive tumour mutations after failure of appropriate targeted therapies (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

During the induction phase, the recommended dose of atezolizumab is 1,200 mg administered by intravenous infusion, followed by bevacizumab 15 mg/kg, paclitaxel 200 mg/m^2, and then carboplatin (AUC 6) every three weeks for four or six cycles.

The induction phase is followed by a maintenance phase without chemotherapy in which 1,200 mg atezolizumab followed by bevacizumab 15 mg/kg, is administered by intravenous infusion every three weeks. Please refer to Table 6 for information on the IMpower150 treatment regimen.

Duration of treatment
It is recommended that patients are treated with the combination of atezolizumab and bevacizumab until disease progression or unmanageable toxicity. If bevacizumab is permanently discontinued, atezolizumab monotherapy should be continued until loss of clinical benefit or unacceptable toxicity (see section 5.1).

Delayed or missed doses
If a planned dose of atezolizumab is missed, it should be administered as soon as possible. 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 specified adverse drug reactions

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 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 anti-thyroid 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	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 or 4	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 Treatment Protocol for Patients).

Patients should also be informed about the risks of bevacizumab, carboplatin and paclitaxel. Please refer to the Summary of Product Characteristics (SPC) and Patient Information Leaflets (PIL) of these products for detailed information on dose modification, contraindications, precautions and adverse events.

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 (see sections 4.8 and 5.1). Efficacy and safety data are limited in patients over 75 years.

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).

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.

Please refer to the SPCs of bevacizumab, paclitaxel and carboplatin for instructions regarding the method of administration of these medicinal products.

For instructions on dilution and handling of atezolizumab 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 EAMS and batch numbers of the administered products should be clearly recorded 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 section 4.2).

Immune-related pneumonitis

Cases of pneumonitis, including fatal cases, have been observed in clinical trials with atezolizumab. 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 ients 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 a 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. 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.

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 anti-thyroid 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. 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. 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 2 mg/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 tirals with atezolizumab. 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 2 mg/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

Infusion related reactions have been observed in clinical trials with atezolizumab.

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 IMpower150

Patients with Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 and those with the following conditions were excluded from the clinical trial: a history of autoimmune disease, history of pneumonitis, active brain metastasis, HIV, hepatitis B or hepatitis C infection. 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 also excluded.

Patients that had clear tumour infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging, were also excluded after several cases of fatal pulmonary haemorrhage were observed, which is a known risk factor of treatment with bevacizumab.

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

Health care professionals are advised to consult the Summary of Products Characteristics for bevacizumab, carboplatin and paclitaxel for the specific precautions and contraindications of these proudcts.

Patient Alert Card

The prescriber must discuss the risks of atezolizumab therapy with the patients and provide them with the Patient Alert Card.

Each patient must be given a Patient Alert Card before they start treatment with atezolizumab. The patients must keep this alert card with them at all times during the treatment and for at least 5 months after their last treatment dose. The card summarises that they are currently receiving atezolizumab, the important side effects for which patients need to seek assistant should they occur, details of the patient's treating oncologist managing their treatment, out of hours contact details and the company contact details.

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.

In study IMpower150, the recommended regimen induced a higher incidence of Grade 3/4 and serious adverse events compared with chemotherapy combined with either atezolizumab or bevacizumab; one third of the patients discontinued treatment due to adverse events. The safety profile of this regimen combines the immune-related reactions of atezolizumab and the antiangiogenic toxic effects of bevacizumab leading to a significant incidence of fatalities (6%).

The safety of atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab, is based on 793 patients with metastatic non-squamous NSCLC. In patients having received atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, the most common adverse reactions (> 10%) were peripheral neuropathy (43.3%), neutropenia (36.9%), fatigue (31.6%), nausea (38.4%), diarrhoea (30.8%), rash (28.8%), anaemia (28.5%), constipation (28.2%), decreased appetite (28.0%), thrombocytopenia (26.2%), arthralgia (25.2%), asthenia (20.4%), cough (18.1%), pyrexia (18.1%), vomiting (17.6%), dyspnoea (13.7%), hypomagnesaemia (13.0%), hypothyroidism (12.7%), stomatitis (12.7%), back pain (11.5%), pruritus (11.5%), musculoskeletal pain (10.4%) and febrile neutropenia (10.2%).

Tabulated list of adverse reactions

The Adverse Drug Reactions (ADRs) are listed by MedDRA system organ class (SOC) and categories of frequency. The following categories of frequency have been used: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2 summarises the additional ADRs associated with the use of atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab.

Table 2: Summary of adverse reactions occurring in patients treated with atezolizumab in combination therapy in study IMpower150

	Atezolizumab + Bevacizumab + Paclitaxel + Carboplatin (n=393)		**Atezolizumab + Paclitaxel + Carboplatin (n=400)**
Blood and lymphatic system disorders			
Very Common	anaemia, febrile neutropenia[+], neutropenia[a, +], thrombocytopenia[‡, b]	Very common	anaemia, neutropenia[a,+], thrombocytopenia[‡, b]
-	-	Common	febrile neutropenia[+]
Endocrine disorders			
Very common	hypothyroidism[‡, c]	Very common	-
Common	hyperthyroidism[‡]	Common	hypothyroidism[‡, c], hyperthyroidism[‡]
Uncommon	hypophysitis[‡]	Uncommon	-
Metabolism and nutrition disorders			
Very common	hypomagnesaemia	Very common	-
Common	-	Common	hypomagnesaemia
Nervous system disorders			
Very common	peripheral neuropathy[d]	Very common	peripheral neuropathy[d]
Uncommon	noninfective encephalitis[‡, e]	Uncommon	-
Gastrointestinal disorders			
Very common	constipation, stomatitis	Very common	constipation
Common	-	Common	stomatitis
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[‡]	Very common	-
Common	-	Common	musculoskeletal pain[‡]

[+] Fatal cases of febrile neutropenia have been observed when atezolizumab is given in combination with bevacizumab, paclitaxel and carboplatin.

[‡] Observed rate in the combination represents a clinically relevant difference in comparison to atezolizumab monotherapy.

[a] Includes reports of neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis.

[b] Includes reports of thrombocytopenia and platelet count decreased.

[c] Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, blood thyroid stimulating hormone decreased, autoimmune thyroiditis, goitre, thyroiditis, thyroxine free decreased, tri−iodothyronine free decreased.

[d] Includes reports of neuropathy peripheral, peripheral sensory neuropathy, polyneuropathy, herpes zoster, peripheral motor neuropathy, neuralgic amyotrophy, peripheral sensorimotor neuropathy, toxic neuropathy.

[e] Includes reports of encephalitis.

Description of selected adverse reactions

For information on significant adverse reactions of atezolizumab as monotherapy, please refer to the SPC of Tecentriq. The management guidelines for these adverse reactions are described in sections 4.2 and 4.4.

Immunogenicity

In study IMpower150, 36.4% of patients treated with atezolizumab, bevacizumab, paclitaxel and carboplatin tested positive for treatment-emergent anti-atezolizumab antibodies (ADAs) at one or more time points, and 38.5% of patients treated with atezolizumab, paclitaxel and carboplatin tested positive for treatment-emergent ADAs. Overall, while exposure to atezolizumab was decreased, ADA positivity measured 4 weeks after the first administration appeared to have no clinically relevant impact on efficacy or safety.

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

Elderly patients
No overall differences in safety were observed between patients ≥ 65 years of age and younger patients receiving Tecentriq monotherapy. In study IMpower150, age ≥ 65 was associated with an increased risk of developing adverse events in patients receiving atezolizumab in combination with bevacizumab, carboplatin and paclitaxel. Data for patients ≥ 75 years of age are too limited to draw conclusions from this population (see section 5.1).

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

Duration of treatment

Treatment with atezolizumab was permitted until loss of clinical benefit 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

IMpower150 (GO29436): Randomised phase III trial in chemotherapy-naïve patients with metastatic non-squamous NSCLC, in combination with paclitaxel and carboplatin with or without bevacizumab

A phase III, open-label, multicentre, international, randomised study, IMpower150, was conducted to evaluate the efficacy and safety of atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab, in chemotherapy-naïve patients with metastatic non-squamous NSCLC.

Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumour specimens were evaluated for PD-L1 expression on tumour cells (TC) and tumour-infiltrating immune cells (IC) and the results were used to define the PD-L1 expression subgroups for the analyses described below. The co-primary endpoints of the study were progression free survival (PFS) and overall survival (OS) in the ITT-WT population, WT representing patients without activating intra-tumoural mutations or rearrangements of ALK or EGFR.

A total of 1202 patients with metastatic or locally advanced non-squamous NSCLC were randomised in the study. There were 157 patients with endothelial growth factor receptor (EGFR) mutant and anaplastic lymphoma kinase (ALK) mutation positive disease included in the study with the inclusion criteria of having progressed on or been intolerant to previous TKI therapy.

Table 3: Intravenous treatment regimens (IMpower150)

Treatment regimen	Induction (Four or Six 21-day cycles)	Maintenance (21-day cycles)
A	Atezolizumab[a] (1,200 mg) + paclitaxel (200 mg/m^2)[b,c] + carboplatin[c] (AUC 6)	Atezolizumab[a] (1,200 mg)
B	Atezolizumab[a] (1,200 mg) + bevacizumab[d] (15 mg/kg) + paclitaxel (200 mg/m^2)[b,c] + carboplatin[c] (AUC 6)	Atezolizumab[a] (1,200 mg) + bevacizumab[d] (15 mg/kg)
C	Bevacizumab[d] (15 mg/kg) + paclitaxel (200 mg/m^2)[b,c] + carboplatin[c] (AUC 6)	Bevacizumab[d] (15 mg/kg)

[a] Atezolizumab is administered until loss of clinical benefit as assessed by the investigator
[b] The paclitaxel starting dose for patients of Asian race/ethnicity was 175 mg/m^2 due to higher overall level of haematologic toxicities in patients from Asian countries compared with those from non-Asian countries
[c] Paclitaxel and carboplatin are administered until completion of 4 or 6 cycles, or progressive disease, unacceptable toxicity or death, whichever occurs first
[d.] Bevacizumab is administered until progressive disease or unacceptable toxicity

In the EGFR/ALK + patient subgroup, 78% harboured an EGFR mutation and 22% and ALK rearrangement. More than half of these tumours had TC0 and IC0 (= PD-L1 negative) status by IHC. The distribution across the treatment arms was as follows: 53 patients in A, 41 patients in B and 63 patients in C.

PFS was prolonged in Arm B compared with Arm C: median of 10.0 months (95% CI 7.9, 15.2) and 6.1 months (95% CI 5.6, 8.4), respectively (HR 0.55 (0.34, 0.90); p = 0.017 (see Figure 1). The estimated 1-year PFS rate was 42.5% in Arm B vs 20.6% in Arm C.

Treatment with atezolizumab, bevacizumab and CP also resulted in improvement in overall survival compared to bevacizumab and CP (see Figure 2). Median OS in Arm B was not reached (95% CI 17.0, NE), compared to 17.5 months in Arm C (95% CI 10.4, NE), HR 0.57 (0.29, 1.11), p= 0.093. The estimated 1-year OS rate was 77.7% in Arm B vs 60.1% in Arm C.

Figure 1: Kaplan-Meier Plot for Progression Free Survival in the EGFR/ALK+ Patients (IMpower150)

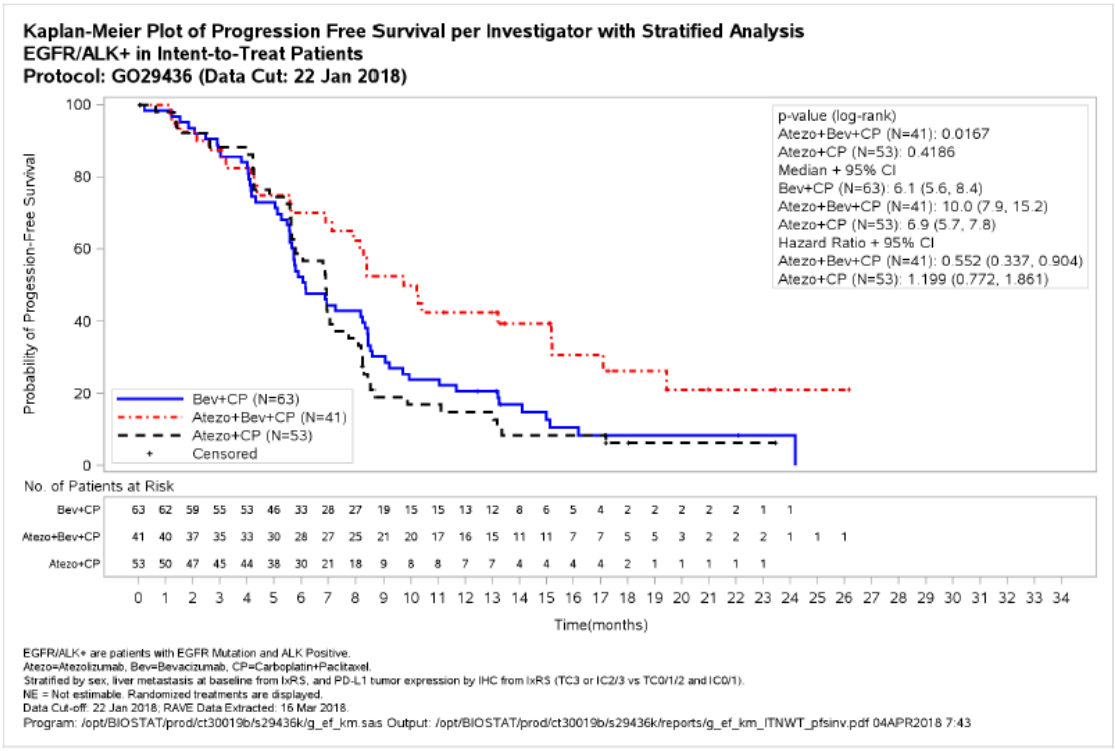
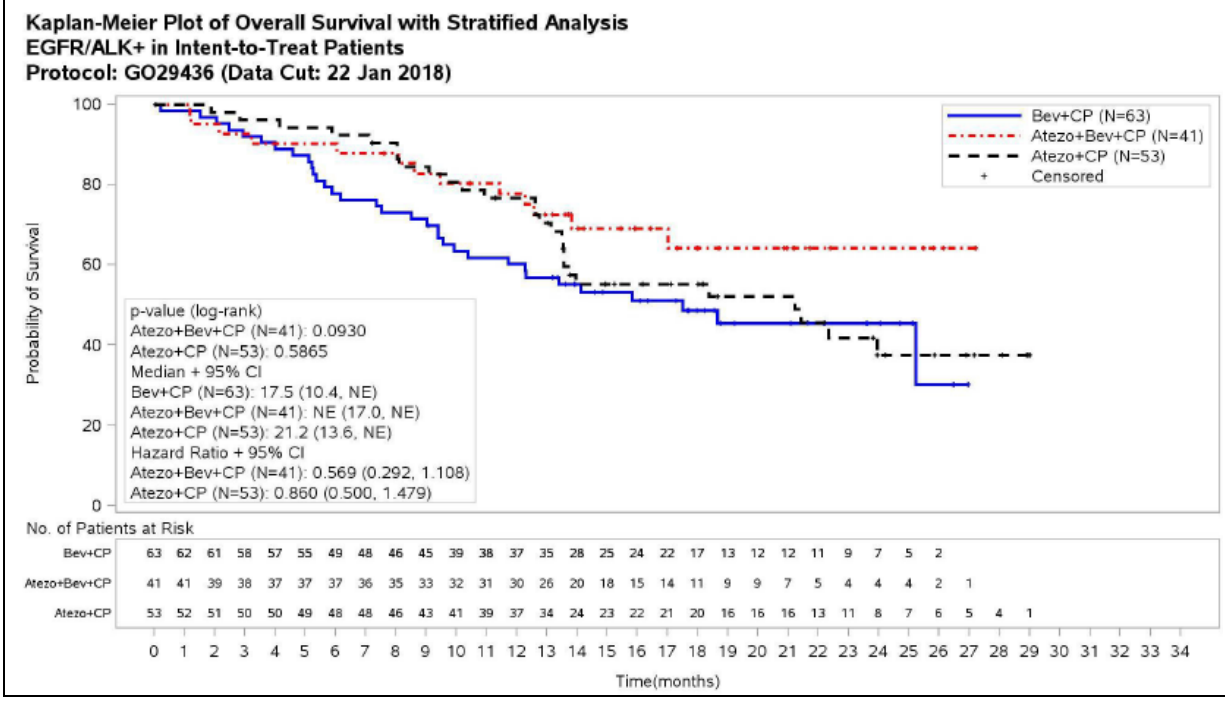


Figure 2: Kaplan-Meier Plot for Overall Survival in the EGFR/ALK+ Patients (IMpower150)



The safety profile of atezolizumab, bevacizumab and chemotherapy in the EGFR mutant and ALK mutation positive patients was in line with the overall safety profile observed in Arm B of IMpower150.

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 ≤ ULN and AST > ULN or bilirubin > 1.0 × to 1.5 × ULN and any AST, n= 71) and normal hepatic function (bilirubin and AST ≤ 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 fetal harm, including embryo-fetal lethality.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

In the absence of compatibility studies, 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.

No other medicinal products should be administered through the same infusion line.

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

00031/0005

9. DATE OF SCIENTIFIC OPINION

21 December 2018

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, 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):

Medicines & Healthcare products Regulatory Agency

MHRA

welwyn.atezolizumabeams@roche.com

Contact Details for Medical Information

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