ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tecentriq 1 200 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tecentriq 1 200 mg concentrate for solution for infusion

One 20 mL vial of concentrate contains 1 200 mg atezolizumab*

After dilution (see section 6.6), the final concentration of the diluted solution should be between 3.2 and 16.8 mg/mL.

*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

Urothelial carcinoma (UC)

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic UC:
- after prior platinum-containing chemotherapy, or
- who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5% (see section 5.1).

Early-stage non-small cell lung cancer (NSCLC)

Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1 for selection criteria).

Metastatic NSCLC

Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies (see section 5.1).

Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1).

Tecentriq as monotherapy is indicated for the first-line treatment of adult patients with metastatic NSCLC whose tumours have a PD-L1 expression ≥ 50% TC or ≥ 10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC (see section 5.1).

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving Tecentriq (see section 5.1).

Small cell lung cancer (SCLC)

Tecentriq, 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).

Hepatocellular carcinoma (HCC)

Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy (see section 5.1).

4.2 Posology and method of administration

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

PD-L1 testing for patients with UC or NSCLC

Tecentriq monotherapy

Patients with first-line (1L) UC, early-stage NSCLC, and 1L metastatic NSCLC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1).

Tecentriq in combination therapy

Posology

The recommended dose of Tecentriq is either 840 mg administered intravenously every two weeks, or 1 200 mg administered intravenously every three weeks, **or** 1 680 mg administered intravenously every four weeks, as presented in Table 1.

When Tecentriq is administered in combination therapy please also refer to the full prescribing information for the combination products (see also section 5.1).

Table 1: Recommended dose for Tecentriq by intravenous administration

Indication	Recommended dose and schedule	Duration of treatment
Tecentriq monotherapy		
1L UC 1L metastatic NSCLC	• 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks	Until disease progression or unmanageable toxicity
Early-stage NSCLC	• 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks	For 1 year unless disease recurrence or unacceptable toxicity. Treatment duration for more than 1 year was not studied.
2L UC 2L NSCLC	• 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks	Until loss of clinical benefit or unmanageable toxicity

Indication	Recommended dose and schedule	Duration of treatment
Tecentriq combination therapy		
1L non-squamous NSCLC with bevacizumab, paclitaxel, and carboplatin	Induction and maintenance phases: • 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks Tecentriq should be administered first when given on the same day. Induction phase for combination partners (four or six cycles): Bevacizumab, paclitaxel, and then carboplatin are administered every three weeks. Maintenance phase (without chemotherapy): Bevacizumab every 3 weeks.	Until disease progression or unmanageable toxicity. Atypical responses (i.e., an initial disease progression followed by tumour shrinkage) have been observed with continued Tecentriq treatment after disease progression. Treatment beyond disease progression may be considered at the discretion of the physician.
1L non-squamous NSCLC with nab-paclitaxel and carboplatin	Induction and maintenance phases: • 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks Tecentriq should be administered first when given on the same day. Induction phase for combination partners (four or six cycles): Nab-paclitaxel, and carboplatin are administered on day 1; in addition, nab-paclitaxel is administered on days 8 and 15 of each 3-weekly cycle.	Until disease progression or unmanageable toxicity. Atypical responses (i.e., an initial disease progression followed by tumour shrinkage) have been observed with continued Tecentriq treatment after disease progression. Treatment beyond disease progression may be considered at the discretion of the physician.
1L ES-SCLC with carboplatin and etoposide	Induction and maintenance phases: • 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks Tecentriq should be administered first when given on the same day. Induction phase for combination partners (four cycles): Carboplatin, and then etoposide are administered on day 1; etoposide is also administered on days 2 and 3 of each 3-weekly cycle.	Until disease progression or unmanageable toxicity. Atypical responses (i.e., an initial disease progression followed by tumour shrinkage) have been observed with continued Tecentriq treatment after disease progression. Treatment beyond disease progression may be considered at the discretion of the physician.
Advanced or unresectable HCC with bevacizumab	• 840 mg every 2 weeks or • 1 200 mg every 3 weeks or • 1 680 mg every 4 weeks Tecentriq should be administered prior to bevacizumab when given on the same day. Bevacizumab is	Until loss of clinical benefit or unmanageable toxicity.

Indication	Recommended dose and schedule	Duration of treatment
	administered at 15 mg/kg body weight (bw) every 3 weeks.	

Delayed or missed doses

If a planned dose of Tecentriq is missed, it should be administered as soon as possible. The schedule of administration must be adjusted to maintain the appropriate interval between doses.

Dose modifications during treatment

Dose reductions of Tecentriq are not recommended.

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

Table 2: Dose modification advice for Tecentriq

Immune-mediated adverse reaction	**Severity**	**Treatment modification**
Pneumonitis	Grade 2	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4	Permanently discontinue Tecentriq
Hepatitis in patients without HCC	Grade 2: (ALT or AST > 3 to 5 x upper limit of normal [ULN] *or* blood bilirubin > 1.5 to 3 x ULN)	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4: (ALT or AST > 5 x ULN *or* blood bilirubin > 3 x ULN)	Permanently discontinue Tecentriq

Immune-mediated adverse reaction	**Severity**	**Treatment modification**
Hepatitis in patients with HCC	If AST/ALT is within normal limits at baseline and increases to > 3 x to ≤ 10x ULN *or* If AST/ALT is > 1 to ≤ 3 x ULN at baseline and increases to > 5x to ≤ 10x ULN *or* If AST/ALT is > 3 x to ≤ 5 x ULN at baseline and increases to >8 x to ≤ 10x ULN	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	If AST/ALT increases to > 10 x ULN or total bilirubin increases to > 3 x ULN	Permanently discontinue Tecentriq
Colitis	Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) *or* Symptomatic Colitis	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)	Permanently discontinue Tecentriq
Hypothyroidism or hyperthyroidism	Symptomatic	Withhold Tecentriq *Hypothyroidism:* Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing *Hyperthyroidism:* Treatment may be resumed when symptoms are controlled by anti-thyroid medicinal product and thyroid function is improving
Adrenal insufficiency	Symptomatic	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy

Immune-mediated adverse reaction	Severity	Treatment modification
Hypophysitis	Grade 2 or 3	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy
	Grade 4	Permanently discontinue Tecentriq
Type 1 diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L)	Withhold Tecentriq Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Rash/Severe cutaneous adverse reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	Withhold Tecentriq Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[1]	Permanently discontinue Tecentriq
Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis	All Grades	Permanently discontinue Tecentriq
Pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (> 2 x ULN) or Grade 2 or 3 pancreatitis	Withhold Tecentriq Treatment may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue Tecentriq

Immune-mediated adverse reaction	Severity	Treatment modification
Myocarditis	Grade 2 or above	Permanently discontinue Tecentriq
Nephritis	Grade 2: (creatinine level > 1.5 to 3.0 x baseline or > 1.5 to 3.0 x ULN)	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day
	Grade 3 or 4: (creatinine level > 3.0 x baseline or > 3.0 x ULN)	Permanently discontinue Tecentriq
Myositis	Grade 2 or 3	Withhold Tecentriq
	Grade 4 or Grade 3 recurrent myositis	Permanently discontinue Tecentriq
Pericardial disorders	Grade 1 pericarditis	Withhold Tecentriq[2]
	Grade 2 or above	Permanently discontinue Tecentriq
Haemophagocytic lymphohistiocytosis	Suspected haemophagocytic lymphohistiocytosis[1]	Permanently discontinue Tecentriq
Other immune-mediated adverse reactions	Grade 2 or Grade 3	Withhold until adverse reactions recovers to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day.
	Grade 4 or recurrent Grade 3	Permanently discontinue Tecentriq (except endocrinopathies controlled with replacement hormones)
Other adverse reactions	**Severity**	**Treatment modification**
Infusion-related reactions	Grade 1 or 2	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved
	Grade 3 or 4	Permanently discontinue Tecentriq

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.0 (NCI-CTCAE v.4.).
[1] Regardless of severity
[2] Conduct a detailed cardiac evaluation to determine the etiology and manage appropriately

Special populations

Paediatric population

The safety and efficacy of Tecentriq in children and adolescents aged below 18 years have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Elderly

Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq is required in patients ≥ 65 years of age (see sections 4.8 and 5.1).

Asian patients

Due to increased haematologic toxicities observed in Asian patients in IMpower150, it is recommended that the starting dose of paclitaxel should be 175 mg/m^2 every three weeks.

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 or moderate hepatic impairment. Tecentriq has not been studied in patients with 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 NSCLC, ES-SCLC, 2nd line UC and HCC (see sections 4.4 and 5.1).

Method of administration

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

The initial dose of Tecentriq 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

Traceability

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 in the patient file.

Immune-mediated adverse reactions

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

For suspected immune-mediated 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 trials in patients whose immune-mediated 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-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones (see sections 4.2 and 4.8).

Immune-mediated 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 and causes other than immune-mediated pneumonitis should be ruled out.

Treatment with atezolizumab should be withheld for Grade 2 pneumonitis, and 1 to 2 mg/kg body weight (bw)/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-mediated 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.

For patients without HCC, 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 bw/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).

For patients with HCC, treatment with atezolizumab should be withheld if ALT or AST increases to > 3 to ≤ 10 x ULN from normal limits at baseline, or > 5 to ≤ 10 x ULN from > 1 ULN to ≤ 3 x ULN at baseline, or > 8 to ≤ 10 x ULN from > 3 ULN to ≤ 5 x ULN at baseline, and persists for more than 5 to 7 days, and 1 to 2 mg/kg bw/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 if ALT or AST increases to > 10 x ULN or total bilirubin increases > 3 x ULN).

Immune-mediated 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 bw/day prednisone or equivalent should be started. For Grade 3 diarrhoea or colitis, treatment with intravenous corticosteroids (1 to 2 mg/kg bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/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. The potential complication of gastrointestinal perforation associated with colitis should be taken into consideration.

Immune-mediated 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 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 bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/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 bw/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 bw/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-mediated 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 bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/day of prednisone or equivalent should follow.

Immune-mediated 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 bw/day of prednisone or equivalent) should be considered.

Immune-mediated pancreatitis

Pancreatitis, including increases in serum amylase and lipase levels, has 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 bw/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg bw/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-mediated myocarditis

Cases of myocarditis, including fatal cases, have been observed with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of myocarditis. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly.

Patients with cardiac or cardiopulmonary symptoms should be assessed for potential myocarditis, to ensure the initiation of appropriate measures at an early stage. If myocarditis is suspected, treatment with atezolizumab should be withheld, prompt initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg bw/day of prednisone or equivalent should be started, and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of myocarditis is established, treatment with atezolizumab must be permanently discontinued for Grade ≥ 2 myocarditis (see section 4.2).

Immune-mediated 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 2 mg/kg bw/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.

Immune-mediated myositis

Cases of myositis, including fatal cases, have been observed with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of myositis. Patients with possible myositis should be monitored for signs of myocarditis.

If a patient develops signs and symptoms of myositis, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Treatment with atezolizumab should be withheld for Grade 2 or 3 myositis and corticosteroid therapy (1-2 mg/kg bw/day prednisone or equivalent) should be initiated. If symptoms improve to ≤ Grade 1, taper corticosteroids as clinically indicated. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4 or grade 3 recurrent myositis, or when unable to reduce the corticosteroid dose to the equivalent of ≤ 10 mg prednisone per day within 12 weeks after onset.

Immune-mediated severe cutaneous adverse reactions

Immune-mediated severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients receiving atezolizumab. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. For suspected SCARs, patients should be referred to a specialist for further diagnosis and management.

Based on the severity of the adverse reaction, atezolizumab should be withheld for Grade 3 skin reactions and treatment with systemic corticosteroids at a dose of 1-2 mg/kg bw/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 should be permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered.

Atezolizumab should be withheld for patients with suspected SJS or TEN. For confirmed SJS or TEN, atezolizumab should be permanently discontinued.

Caution should be used when considering the use of atezolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Immune-mediated pericardial disorders

Pericardial disorders, including pericarditis, pericardial effusion and cardiac tamponade, some leading to fatal outcomes, have been observed with atezolizumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of pericardial disorders.

For suspected Grade 1 pericarditis, treatment with atezolizumab should be withheld and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. For suspected Grade ≥ 2 pericardial disorders, treatment with atezolizumab should be withheld, prompt treatment with systemic corticosteroids at a dose of 1 to 2 mg/kg bw/day of prednisone or equivalent should be started and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of a pericardial disorder event is established, treatment with atezolizumab must be permanently discontinued for Grade ≥ 2 pericardial disorders (see section 4.2).

Haemophagocytic lymphohistiocytosis

Haemophagocytic lymphohistiocytosis (HLH), including fatal cases, has been reported in patients receiving atezolizumab (see section 4.8). HLH should be considered when the presentation of cytokine release syndrome is atypical or prolonged. Patients should be monitored for clinical signs and symptoms of HLH. For suspected HLH, atezolizumab must be permanently discontinued and patients should be referred to a specialist for further diagnosis and management.

Other immune-mediated adverse reactions

Given the mechanism of action of atezolizumab, other potential immune-mediated adverse reactions may occur, including noninfective cystitis.

Evaluate all suspected immune-mediated adverse reactions to exclude other causes. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions and, based on the severity of the reaction, managed with treatment modifications and corticosteroids as clinically indicated (see section 4.2 and section 4.8).

Infusion-related reactions

Infusion-related reactions have been observed 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.

Disease-specific precautions

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in metastatic non-squamous NSCLC

Physicians should carefully consider the combined risks of the four-drug regimen of atezolizumab bevacizumab, paclitaxel, and carboplatin before initiating treatment (see section 4.8).

Use of atezolizumab in UC for previously untreated patients who are considered cisplatin ineligible

The baseline and prognostic disease characteristics of the IMvigor210 Cohort 1 study population were overall comparable to patients in the clinic who would be considered cisplatin ineligible but would be eligible for a carboplatin-based combination chemotherapy. There are insufficient data for the subgroup of patients that would be unfit for any chemotherapy; therefore atezolizumab should be used with caution in these patients, after careful consideration of the potential balance of risks and benefits on an individual basis.

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin

Patients with NSCLC that had clear tumour infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging, were excluded from the pivotal clinical trial IMpower150 after several cases of fatal pulmonary haemorrhage were observed, which is a known risk factor of treatment with bevacizumab.

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.

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in EGFR+ patients with NSCLC who have progressed on erlotinib+bevacizumab

In study IMpower150, there are no data on the efficacy of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in EGFR+ patients who have progressed previously on erlotinib+bevacizumab.

Use of atezolizumab in combination with bevacizumab in HCC

Data in HCC patients with Child-Pugh B liver disease treated with atezolizumab in combination with bevacizumab are very limited and there are currently no data available in HCC patients with Child-Pugh C liver disease.

Patients treated with bevacizumab have an increased risk of haemorrhage, and cases of severe gastrointestinal haemorrhage, including fatal events, were reported in patients with HCC treated with atezolizumab in combination with bevacizumab. In patients with HCC, screening for and subsequent treatment of oesophageal varices should be performed as per clinical practice prior to starting treatment with the combination of atezolizumab and bevacizumab. Bevacizumab should be permanently discontinued in patients who experience Grade 3 or 4 bleeding with the combination treatment. Please refer to the bevacizumab Summary of Product Characteristics.

Diabetes mellitus can occur during treatment with atezolizumab in combination with bevacizumab. Physicians should monitor blood glucose levels prior to and periodically during treatment with atezolizumab in combination with bevacizumab as clinically indicated.

Use of atezolizumab as monotherapy for first-line treatment in metastatic NSCLC

Physicians should consider the delayed onset of atezolizumab effect before initiating first-line treatment as monotherapy in patients with NSCLC. A higher number of deaths within 2.5 months after randomisation followed by a long-term survival benefit was observed with atezolizumab compared with chemotherapy. No specific factor(s) associated with early deaths could be identified (see section 5.1).

Patients excluded from clinical trials

Patients with the following conditions were excluded from clinical trials: a history of autoimmune disease, history of pneumonitis, active brain metastasis, HIV, hepatitis B or hepatitis C infection (for non-HCC patients), significant cardiovascular disease and patients with inadequate hematologic and end-organ function. 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; therapeutic oral or intravenous antibiotics within 2 weeks prior to initiation of study treatment were excluded from clinical trials.

Patient card

The prescriber must discuss the risks of Tecentriq therapy with the patient. The patient will be provided with the patient 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 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-mediated 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-mediated 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 Tecentriq 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

Tecentriq 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

The safety of atezolizumab as monotherapy is based on pooled data in 4 349 patients across multiple tumour types. The most common adverse reactions (> 10%) were fatigue (30.1%), decreased appetite (21.3%), nausea (20.0%), rash (19.3%), pyrexia (19.0%), cough (18.6%), diarrhoea (18.0%), dyspnoea (17.2%), arthralgia (16.7%), asthenia (13.2%), pruritus (13.2%), back pain (12.8%), vomiting (12.5), urinary tract infection (11.5%) and headache (10.3%).

The safety of atezolizumab given in combination with other medicinal products, has been evaluated in 4 535 patients across multiple tumour types. The most common adverse reactions (≥ 20%) were anaemia (36.8%), neutropenia (36.6%), nausea (35.5%), fatigue (33.1%), alopecia (28.1%), rash (27.8%), diarrhoea (27.6%), thrombocytopenia (27.1%), constipation (25.8%), decreased appetite (24.7%) and peripheral neuropathy (24.4%).

Use of atezolizumab in the adjuvant NSCLC setting

The safety profile of atezolizumab in the adjuvant setting in the non-small cell lung cancer (NSCLC) patient population (IMpower010) was generally consistent with the overall pooled monotherapy safety profile in the advanced setting. Nevertheless, the incidence of immune-mediated adverse reactions of atezolizumab in IMpower010 was 51.7% compared to 38.4% in the pooled monotherapy population with advanced disease. No new immune-mediated adverse reactions were identified in the adjuvant setting.

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin

In the first-line NSCLC study (IMpower150), an overall higher frequency of adverse events was observed in the four-drug regimen of atezolizumab, bevacizumab, paclitaxel, and carboplatin compared to atezolizumab, paclitaxel and carboplatin, including Grade 3 and 4 events (63.6% compared to 57.5%), Grade 5 events (6.1% compared to 2.5%), adverse events of special interest to atezolizumab (52.4% compared to 48.0%), as well as adverse events leading to withdrawal of any study treatment (33.8% compared to 13.3%). Nausea, diarrhoea, stomatitis, fatigue, pyrexia, mucosal inflammation, decreased appetite, weight decreased, hypertension and proteinuria were reported higher (≥5% difference) in patients receiving atezolizumab in combination with bevacizumab, paclitaxel and carboplatin. Other clinically significant adverse events which were observed more frequently in the atezolizumab, bevacizumab, paclitaxel, and carboplatin arm were epistaxis, haemoptysis, cerebrovascular accident, including fatal events.

Further details on serious adverse reactions are provided in section 4.4.

Tabulated list of adverse reactions

The adverse reactions (ARs) are listed by MedDRA system organ class (SOC) and categories of frequency in Table 3 for atezolizumab given as monotherapy or as combination therapy. Adverse reactions known to occur with atezolizumab or chemotherapies given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical trials with combination therapy. 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), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Summary of adverse reactions occurring in patients treated with atezolizumab

Atezolizumab monotherapy		Atezolizumab in combination therapy
Infections and infestations		
Very common	urinary tract infection[a]	lung infection[b]
Common		sepsis[aj]
Blood and lymphatic system disorders		
Very common		anaemia, thrombocytopenia[d], neutropenia[e], leukopenia[f]
Common	thrombocytopenia[d]	lymphopenia[g]
Rare	haemophagocytic lymphohistiocytosis	haemophagocytic lymphohistiocytosis
Immune system disorders		
Common	infusion-related reaction[h]	infusion-related reaction[h]
Endocrine disorders		
Very common		hypothyroidism[i]
Common	hypothyroidism[i], hyperthyroidism[j]	hyperthyroidism[j]
Uncommon	diabetes mellitus[k], adrenal insufficiency[l]	
Rare	hypophysitis[m]	
Metabolism and nutrition disorders		
Very common	decreased appetite	decreased appetite
Common	hypokalaemia[ae], hyponatraemia[af], hyperglycaemia	hypokalaemia[ae], hyponatraemia[af], hypomagnesaemia[n]
Nervous system disorders		
Very Common	headache	peripheral neuropathy[o], headache
Common		syncope, dizziness
Uncommon	Guillain-Barré syndrome[p], meningoencephalitis[q]	
Rare	myasthenic syndrome[r]	
Eye disorders		
Rare	uveitis	
Cardiac disorders		
Rare	myocarditis[s]	
Common	pericardial disorders[ao]	
Uncommon		pericardial disorders[ao]
Vascular disorders		
Very Common		hypertension[ai]
Common	hypotension	
Respiratory, thoracic, and mediastinal disorders		
Very common	dyspnoea, cough	dyspnoea, cough, nasopharyngitis[am]
Common	pneumonitis[t], hypoxia[ag],	dysphonia

Atezolizumab monotherapy		Atezolizumab in combination therapy
	nasopharyngitis[am]	
Gastrointestinal disorders		
Very common	nausea, vomiting, diarrhoea[u]	nausea, vomiting diarrhoea[u], constipation,
Common	colitis[v], abdominal pain, dysphagia, oropharyngeal pain[w]	stomatitis, dysgeusia
Uncommon	pancreatitis[x]	
Hepatobiliary disorders		
Common	AST increased, ALT increased, hepatitis[y]	AST increased, ALT increased
Skin and subcutaneous tissue disorders		
Very common	rash[z], pruritus	rash[z], pruritus, alopecia[ah]
Common	dry skin	
Uncommon	severe cutaneous adverse reactions[ak], psoriasis[an]	severe cutaneous adverse reactions[ak], psoriasis[an]
Rare	pemphigoid	pemphigoid
Musculoskeletal and connective tissue disorders		
Very common	arthralgia, back pain	arthralgia, musculoskeletal pain[aa], back pain
Common	musculoskeletal pain[aa]	
Uncommon	myositis[ab]	
Renal and urinary disorders		
Common	blood creatinine increased[c]	proteinuria[ac], blood creatinine increased[c]
Uncommon	nephritis[ad]	
Not known	cystitis noninfective[al]	
General disorders and administration site conditions		
Very common	pyrexia, fatigue, asthenia	pyrexia, fatigue, asthenia, oedema peripheral
Common	influenza like illness, chills	
Investigations		
Common		blood alkaline phosphatase increased

[a] Includes reports of urinary tract infection, cystitis, pyelonephritis, escherichia urinary tract infection, urinary tract infection bacterial, kidney infection, pyelonephritis acute, pyelonephritis chronic, pyelitis, renal abscess, streptococcal urinary tract infection, urethritis, urinary tract infection fungal, urinary tract infection pseudomonal.
[b] Includes reports of pneumonia, bronchitis, lower respiratory tract infection, infectious pleural effusion, tracheobronchitis, atypical pneumonia, lung abscess, infective exacerbation of chronic obstructive airways disease, paracancerous pneumonia, pyopneumothorax, pleural infection, post procedural pneumonia.
[c] Includes reports of blood creatinine increased, hypercreatininaemia.

[d] Includes reports of thrombocytopenia, platelet count decreased.
[e] Includes reports of neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis, granulocytopenia.
[f] Includes reports of white blood cell count decreased, leukopenia.
[g] Includes reports of lymphopenia, lymphocyte count decreased.
[h] Includes reports of infusion-related reaction, cytokine release syndrome, hypersensitivity, anaphylaxis.
[i] Includes reports of anti-thyroid antibody positive, autoimmune hypothyroidism, autoimmune thyroiditis, blood thyroid stimulating hormone abnormal, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, euthyroid sick syndrome, goitre, hypothyroidism, immune-mediated hypothyroidism, myxoedema, myxoedema coma, primary hypothyroidism, thyroid disorder, thyroid hormones decreased, thyroid function test abnormal, thyroiditis, thyroiditis acute, thyroxine decreased, thyroxine free decreased, thyroxine free increased, thyroxine increased, tri-iodothyronine decreased, tri-iodothyronine free abnormal, tri-iodothyronine free decreased, tri-iodothyronine free increased, silent thyroiditis, thyroiditis chronic.
[j] Includes reports of hyperthyroidism, Basedow's disease, endocrine ophthalmopathy, exophthalmos.
[k] Includes reports of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis, ketoacidosis.
[l] Includes reports of adrenal insufficiency, blood corticotropin decreased, glucocorticoid deficiency, primary adrenal insufficiency secondary adrenocortical insufficiency.
[m] Includes reports of hypophysitis, temperature regulation disorder.
[n] Includes reports of hypomagnesaemia, blood magnesium decreased.
[o] Includes reports of neuropathy peripheral, autoimmune neuropathy, peripheral sensory neuropathy, polyneuropathy, herpes zoster, peripheral motor neuropathy, neuralgic amyotrophy, peripheral sensorimotor neuropathy, toxic neuropathy, axonal neuropathy, lumbosacral plexopathy, neuropathic arthropathy, peripheral nerve infection, neuritis, immune-mediated neuropathy.
[p] Includes reports of Guillain-Barré syndrome, demyelinating polyneuropathy.
[q] Includes reports of encephalitis, encephalitis autoimmune, meningitis, photophobia.
[r] Includes reports of myasthenia gravis.
[s] Includes reports of myocarditis, autoimmune myocarditis, and immune-mediated myocarditis.
[t] Includes reports of pneumonitis, lung infiltration, bronchiolitis, immune-mediated pneumonitis, interstitial lung disease, alveolitis, lung opacity, pulmonary toxicity, radiation pneumonitis.
[u] Includes reports of diarrhoea, defaecation urgency, frequent bowel movements, diarrhoea haemorrhagic, gastrointestinal hypermotility.
[v] Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic, colitis ulcerative, diversion colitis, immune-mediated enterocolitis.
[w] Includes reports of oropharyngeal pain, oropharyngeal discomfort, throat irritation.
[x] Includes reports of autoimmune pancreatitis, pancreatitis, pancreatitis acute, lipase increased, amylase increased.
[y] Includes reports of ascites, autoimmune hepatitis, hepatocellular injury, hepatitis, hepatitis acute, hepatitis toxic, hepatotoxicity, liver disorder, drug-induced liver injury, hepatic failure, hepatic steatosis, hepatic lesion, oesophageal varices haemorrhage, varices oesophageal.
[z] Includes reports of acne, acne pustular, blister, blood blister, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis exfoliative, drug eruption, eczema, eczema infected, erythema, erythema of eyelid, eyelid rash, fixed eruption, folliculitis, furuncle, hand dermatitis, lip blister, oral blood blister, palmar-plantar erythrodysaesthesia syndrome, pemphigoid, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash papulosquamous, rash pruritic, rash pustular, rash vesicular, scrotal dermatitis, seborrhoeic dermatitis, skin exfoliation, skin toxicity, skin ulcer.
[aa] Includes reports of musculoskeletal pain, myalgia, bone pain.
[ab] Includes reports of myositis, rhabdomyolysis, polymyalgia rheumatica, dermatomyositis, muscle abscess, myoglobin urine present.
[ac] Includes reports of proteinuria, protein urine present, haemoglobinurea, urine abnormality, nephrotic syndrome, albuminuria.
[ad] Includes reports of nephritis, autoimmune nephritis, Henoch-Schonlein Purpura nephritis, paraneoplastic glomerulonephritis, tubulointerstitial nephritis.
[ae] Includes reports of hypokalaemia, blood potassium decreased.
[af] Includes reports of hyponatraemia, blood sodium decreased.

[ag] Includes reports of hypoxia, oxygen saturation decreased, pO2 decreased.
[ah] Includes reports of alopecia, madarosis, alopecia areata, alopecia totalis, hypotrichosis.
[ai] Includes reports of hypertension, blood pressure increased, hypertensive crisis, blood pressure systolic increased, diastolic hypertension, blood pressure inadequately controlled, retinopathy hypertensive, hypertensive nephropathy, essential hypertension, orthostatic hypertension.
[aj] Includes reports of sepsis, septic shock, urosepsis, neutropenic sepsis, pulmonary sepsis, bacterial sepsis, klebsiella sepsis, abdominal sepsis, candida sepsis, escherichia sepsis, pseudomonal sepsis, staphylococcal sepsis.
[ak] Includes reports of dermatitis bullous, exfoliative rash, erythema multiforme, dermatitis exfoliative generalised, toxic skin eruption, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis, cutaneous vasculitis.
[al] Includes reports of cystitis noninfective and immune-mediated cystitis.
[am] Includes reports of nasopharyngitis, nasal congestion and rhinorrhoea.
[an] Includes reports of psoriasis, dermatitis psoriasiform, guttate psoriasis.
[ao] Includes reports of pericarditis, pericardial effusion, cardiac tamponade and pericarditis constrictive.

Description of selected adverse reactions

The data below reflect information for significant adverse reactions for atezolizumab as monotherapy in clinical trials (see section 5.1). Details for the significant adverse reactions for atezolizumab when given in combination are presented if clinically relevant differences were noted in comparison to atezolizumab monotherapy. The management guidelines for these adverse reactions are described in sections 4.2 and 4.4.

Immune-mediated pneumonitis

Pneumonitis occurred in 3.0% (130/4,349) of patients who received atezolizumab monotherapy. Of the 130 patients, two experienced fatal events. The median time to onset was 4.0 months (range: 3 days to 29.8 months). The median duration was 1.6 months (range: 1 day to 27.8+ months; + denotes a censored value). Pneumonitis led to discontinuation of atezolizumab in 29 (0.7%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.7% (76/4 349) of patients receiving atezolizumab monotherapy.

Immune-mediated hepatitis

Hepatitis occurred in 1.7% (75/4 349) of patients who received atezolizumab monotherapy. Of the 75 patients, two experienced fatal events. The median time to onset was 1.6 months (range: 7 days to 18.8 months). The median duration was 2.1 months (range: 1 day to 22.0+ months; + denotes a censored value). Hepatitis led to discontinuation of atezolizumab in 13 (0.3%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.5% (22/4 349) of patients receiving atezolizumab monotherapy.

Immune-mediated colitis

Colitis occurred in 1.1 % (50/4 349) of patients who received atezolizumab monotherapy. The median time to onset was 5.1 months (range: 15 days to 17.2 months). The median duration was 1.2 months (range: 1 day to 35.9+ months; + denotes a censored value). Colitis led to discontinuation of atezolizumab in 17 (0.4%) patients. Colitis requiring the use of corticosteroids occurred in 0.6% (24/4 349) of patients receiving atezolizumab monotherapy.

Immune-mediated endocrinopathies

Thyroid disorders

Hypothyroidism occurred in 7.6% (331/4 349) of patients who received atezolizumab monotherapy. The median time to onset was 4.3 months (range: 1 day to 34.5 months). Hypothyroidism occurred in 17.4% (86/495) of patients who received atezolizumab monotherapy in the adjuvant NSCLC setting. The median time to onset was 4.0 months (range: 22 days to 11.8 months).

Hyperthyroidism occurred in 2.1% (93/4 349) of patients who received atezolizumab monotherapy. The median time to onset was 2.6 months (range: 1 days to 24.3 months). Hyperthyroidism occurred in 6.5% (32/495) of patients who received atezolizumab monotherapy in the adjuvant NSCLC setting. The median time to onset was 2.8 months (range: 1 day to 9.9 months).

Adrenal insufficiency

Adrenal insufficiency occurred in 0.5% (21/4 349) of patients who received atezolizumab monotherapy. The median time to onset was 6.1 months (range: 2 days to 21.4 months). Adrenal insufficiency led to discontinuation of atezolizumab in 5 (0.1%) patients. Adrenal insufficiency requiring the use of corticosteroids occurred in 0.4% (17/4 349) of patients receiving atezolizumab monotherapy.

Hypophysitis

Hypophysitis occurred in < 0.1% (4/4 349) of patients who received atezolizumab monotherapy. The median time to onset was 6.1 months (range: 23 days to 13.7 months). Three (< 0.1%) patients required the use of corticosteroids and treatment with atezolizumab was discontinued in 1 (< 0.1%) patient.

Hypophysitis occurred in 0.8% (3/393) of patients who received atezolizumab with bevacizumab, paclitaxel, and carboplatin. The median time to onset was 7.7 months (range: 5.0 to 8.8 months). Two patients required the use of corticosteroids.

Hypophysitis occurred in 0.4% (2/473) of patients who received atezolizumab in combination with nab-paclitaxel and carboplatin. The median time to onset was 5.2 months (range: 5.1 to 5.3 months). Both patients required the use of corticosteroids.

Diabetes mellitus

Diabetes mellitus occurred in 0.5% (20/4 349) of patients who received atezolizumab monotherapy. The median time to onset was 5.5 months (range: 4 days to 29.0 months). Diabetes mellitus led to the discontinuation of atezolizumab in < 0.1% (3/4 349) patients.

Diabetes mellitus occurred in 2.0% (10/493) of HCC patients who received atezolizumab in combination with bevacizumab. The median time to onset was 4.4 months (range: 1.2 months - 8.3 months). No events of diabetes mellitus led to atezolizumab withdrawal.

Immune-mediated meningoencephalitis

Meningoencephalitis occurred in 0.4% (18/4 349) of patients who received atezolizumab monotherapy. The median time to onset was 16 days (range: 1 day to 12.5 months). The median duration was 22 days (range: 6 days to 14.5+ months; + denotes a censored value).

Meningoencephalitis requiring the use of corticosteroids occurred in 0.2% (10/4 349) of patients receiving atezolizumab and eight patients (0.2%) discontinued atezolizumab.

Immune-mediated neuropathies

Guillain-Barré syndrome and demyelinating polyneuropathy occurred in 0.1% (6/4 349) of patients who received atezolizumab monotherapy. The median time to onset was 4.1 months (range: 17 days to 8.1 months). The median duration was 8.0 months (range: 19 days to 24.5+ months; + denotes a censored value). Guillain-Barré syndrome led to discontinuation of atezolizumab in 1 patient (< 0.1%). Guillain-Barré syndrome requiring the use of corticosteroids occurred in < 0.1% (3/4 349) of patients receiving atezolizumab monotherapy.

Myasthenic syndrome

Myasthenia gravis occurred in < 0.1% (1/4 349) of patients who received atezolizumab monotherapy. The time to onset was 1.2 months.

Immune-mediated pancreatitis

Pancreatitis, including amylase increased and lipase increased, occurred in 0.7% (32/4 349) of patients who received atezolizumab monotherapy. The median time to onset was 5.5 months (range: 1 day to 24.8 months). The median duration was 24 days (range: 3 days to 22.4+ months; + denotes a censored value). Pancreatitis led to the discontinuation of atezolizumab in 3 (< 0.1%) patients. Pancreatitis requiring the use of corticosteroids occurred in 0.1% (5/4 349) of patients receiving atezolizumab monotherapy.

Immune-mediated myocarditis

Myocarditis occurred in < 0.1% (3/4 349) of patients who received atezolizumab monotherapy. Of the 3 patients, one experienced a fatal event in the adjuvant NSCLC setting. The median time to onset was 2.1 months (range: 1.5 to 4.9 months). The median duration was 14 days (range: 14 days to 2.8 months). Myocarditis led to the discontinuation of atezolizumab in 2 (< 0.1%) patients. Two (<0.1%) patients required the use of corticosteroids.

Immune-mediated nephritis

Nephritis occurred in 0.2% (10/4 349) of patients who received atezolizumab. The median time to onset was 5.0 months (range: 2 days to 17.5 months). Nephritis led to discontinuation of atezolizumab in 5 (0.1%) patients. Four (< 0.1%) patients required the use of corticosteroids.

Immune-mediated myositis

Myositis occurred in 0.5% (20/4 349) of patients who received atezolizumab monotherapy. The median time to onset was 3.3 months (range: 12 days to 11.0 months). The median duration was 5.7 months (range: 2 days to 36.9+ months; + denotes a censored value). Myositis led to discontinuation of atezolizumab in 2 (< 0.1%) patients. Seven (0.2%) patients required the use of corticosteroids.

Immune-mediated severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) occurred in 0.6% (28/4 349) of patients who received atezolizumab monotherapy. Of the 28 patients, one experienced a fatal event. The median time to onset was 5.2 months (range: 4 days to 15.5 months). The median duration was 2.4 months (range: 1 day to 37.5+ months; + denotes a censored value). SCARs led to discontinuation of atezolizumab in 3 (< 0.1%) patients. SCARs requiring the use of systemic corticosteroids occurred in 0.2% (9/4 349) of patients receiving atezolizumab monotherapy.

Immune-mediated pericardial disorders

Pericardial disorders occurred in 1.1% (47/4 349) of patients who received Tecentriq monotherapy. The median time to onset was 1.4 months (range: 6 days to 17.5 months). The median duration was 1.4 months (range: 0 to 19.3+ months; + denotes a censored value). Pericardial disorders led to discontinuation of Tecentriq in 3 (< 0.1%) patients. Pericardial disorders requiring the use of corticosteroids occurred in 0.2% (7/4 349) of patients.

Immunogenicity

Across multiple phase II and III studies, 13.1% to 54.1% of patients developed treatment-emergent anti-drug antibodies (ADAs). Patients who developed treatment-emergent ADAs tended to have overall poorer health and disease characteristics at baseline. Those imbalances in health and disease characteristics at baseline can confound the interpretation of pharmacokinetic (PK), efficacy and safety analyses. Exploratory analyses adjusting for imbalances in baseline health and disease characteristics were conducted to assess the effect of ADA on efficacy. These analyses did not exclude possible attenuation of efficacy benefit in patients who developed ADA compared to patients who did not develop ADA. The median time to ADA onset ranged from 3 weeks to 5 weeks.

Across pooled datasets for patients treated with atezolizumab monotherapy (N=3 460) and with combination therapies (N= 2 285), the following rates of adverse events (AEs) have been observed for the ADA-positive population compared to the ADA-negative population, respectively: Grade 3-4 AEs 46.2% vs. 39.4%, Serious Adverse Events (SAEs) 39.6% vs. 33.3%, AEs leading to treatment withdrawal 8.5% vs 7.8% (for monotherapy); Grade 3-4 AEs 63.9% vs. 60.9%, SAEs 43.9% vs. 35.6%, AEs leading to treatment withdrawal 22.8% vs 18.4% (for combination therapy). However, available data do not allow firm conclusions to be drawn on possible patterns of adverse reactions.

Paediatric population

The safety of atezolizumab in children and adolescents has not been established. No new safety signals were observed in a clinical trial with 69 paediatric patients (< 18 years) and the safety profile was comparable to adults.

Elderly

No overall differences in safety were observed between patients ≥ 65 years of age and younger patients receiving atezolizumab 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.

In studies IMpower150, IMpower133 and IMpower110, data for patients ≥ 75 years of age are too limited to draw conclusions on this population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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: L01FF05

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

Urothelial carcinoma

IMvigor211 (GO29294): Randomised trial in locally advanced or metastatic UC patients previously treated with chemotherapy

A phase III, open-label, multi-centre, international, randomised study, (IMvigor211), was conducted to evaluate the efficacy and safety of atezolizumab compared with chemotherapy (investigator’s choice of vinflunine, docetaxel, or paclitaxel) in patients with locally advanced or metastatic UC who progressed during or following a platinum-containing regimen. This study excluded patients who had a history of autoimmune disease; active or corticosteroid-dependent brain metastases; administration of a live, attenuated vaccine within 28 days prior to enrolment; and administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal product within 2 weeks prior to enrolment. Tumour assessments were conducted every 9 weeks for the first 54 weeks, and every 12 weeks thereafter. Tumour specimens were evaluated prospectively for PD-L1 expression on tumour-infiltrating immune cells (IC) and the results were used to define the PD-L1 expression subgroups for the analyses described below.

A total of 931 patients were enrolled. Patients were randomised (1:1) to receive either atezolizumab or chemotherapy. Randomisation was stratified by chemotherapy (vinflunine vs. taxane), PD-L1 expression status on IC (< 5% vs. ≥ 5%), number of prognostic risk factors (0 vs. 1-3), and liver metastases (yes vs. no). Prognostic risk factors included time from prior chemotherapy of < 3 months, ECOG performance status > 0 and haemoglobin < 10 g/dL.

Atezolizumab was administered as a fixed dose of 1 200 mg by intravenous infusion every 3 weeks. No dose reduction of atezolizumab was allowed. Patients were treated until loss of clinical benefit as assessed by the investigator or unacceptable toxicity. Vinflunine was administered 320 mg/m^2 by intravenous infusion on day 1 of each 3-week cycle until disease progression or unacceptable toxicity. Paclitaxel was administered 175 mg/m^2 by intravenous infusion over 3 hours on day 1 of each 3-week cycle until disease progression or unacceptable toxicity. Docetaxel was administered 75 mg/m^2 by intravenous infusion on day 1 of each 3-week cycle until disease progression or unacceptable toxicity. For all treated patients, the median duration of treatment was 2.8 months for the atezolizumab arm, 2.1 months for the vinflunine and paclitaxel arms and 1.6 months for the docetaxel arm.

The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 67 years (range: 31 to 88), and 77.1% of patients were male. The majority of patients were white (72.1%), 53.9% of patients within the chemotherapy arm received vinflunine, 71.4% of patients had at least one poor prognostic risk factor and 28.8% had liver metastases at baseline. Baseline ECOG performance status was 0 (45.6%) or 1 (54.4%). Bladder was the primary tumour site for 71.1% of patients and 25.4% of patients had upper tract UC. There were 24.2% of patients who received only prior platinum-containing adjuvant or neoadjuvant therapy and progressed within 12 months.

The primary efficacy endpoint for IMvigor211 is overall survival (OS). Secondary efficacy endpoints evaluated per investigator-assessed Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 are objective response rate (ORR), progression-free survival (PFS), and duration of response (DOR). Comparisons with respect to OS between the treatment arm and control arm within the IC2/3, IC1/2/3, and ITT (Intention-to-treat, i.e. all comers) populations were tested using a hierarchical fixed-sequence procedure based on a stratified log-rank test at two-sided level of 5% as follows: step 1) IC2/3 population; step 2) IC1/2/3 population; step 3) all comers population. OS results for each of steps 2 and 3 could be formally tested for statistical significance only if the result in the preceding step was statistically significant.

The median survival follow-up is 17 months. The primary analysis of study IMvigor211 did not meet its primary endpoint of OS. Atezolizumab did not demonstrate a statistically significant survival benefit compared to chemotherapy in patients with previously treated, locally advanced or metastatic UC. Per the pre-specified hierarchical testing order, the IC2/3 population was tested first, with an OS HR of 0.87 (95% CI: 0.63, 1.21; median OS of 11.1 vs. 10.6 months for atezolizumab and chemotherapy respectively). The stratified log-rank p-value was 0.41 and therefore the results are considered not statistically significant in this population. As a consequence, no formal tests of statistical significance could be performed for OS in the IC1/2/3 or all comer populations, and results of those analyses would be considered exploratory. The key results in the all comer population are summarised in Table 4. The Kaplan-Meier curve for OS in the all comer population is presented in Figure 1.

An exploratory updated survival analysis was performed with a median duration of survival follow up of 34 months in the ITT population. The median OS was 8.6 months (95% CI: 7.8, 9.6) in the atezolizumab arm and 8.0 months (95% CI: 7.2, 8.6) in the chemotherapy arm with a hazard ratio of 0.82 (95% CI: 0.71, 0.94). Consistent with the trend observed at primary analysis for 12-month OS rates, numerically higher 24-month and 30-month OS rates were observed for patients in the atezolizumab arm compared with the chemotherapy arm in the ITT population. The percentage of patients alive at 24 months (KM estimate) was 12.7% in the chemotherapy arm and 22.5% in the atezolizumab arm; and at 30 months (KM estimate) was 9.8% in the chemotherapy arm and 18.1% in the atezolizumab arm.

Table 4: Summary of efficacy in all comers (IMvigor211)

Efficacy endpoint	Atezolizumab (n = 467)	Chemotherapy (n = 464)
Primary efficacy endpoint		
OS*		
No. of deaths (%)	324 (69.4%)	350 (75.4%)
Median time to events (months)	8.6	8.0
95% CI	7.8, 9.6	7.2, 8.6
Stratified‡ hazard ratio (95% CI)	0.85 (0.73, 0.99)	
12-month OS (%)**	39.2%	32.4%
Secondary and exploratory endpoints		
Investigator-assessed PFS (RECIST v1.1)		
No. of events (%)	407 (87.2%)	410 (88.4%)
Median duration of PFS (months)	2.1	4.0
95% CI	2.1, 2.2	3.4, 4.2
Stratified hazard ratio (95% CI)	1.10 (0.95, 1.26)	
Investigator-assessed ORR (RECIST v1.1)	n = 462	n = 461
No. of confirmed responders (%)	62 (13.4%)	62 (13.4%)
95% CI	10.45, 16.87	10.47, 16.91
No. of complete response (%)	16 (3.5%)	16 (3.5%)
No. of partial response (%)	46 (10.0%)	46 (10.0%)
No. of stable disease (%)	92 (19.9%)	162 (35.1%)
Investigator-assessed DOR (RECIST v1.1)	n = 62	n = 62
Median in months ***	21.7	7.4
95% CI	13.0, 21.7	6.1, 10.3

CI = confidence interval; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

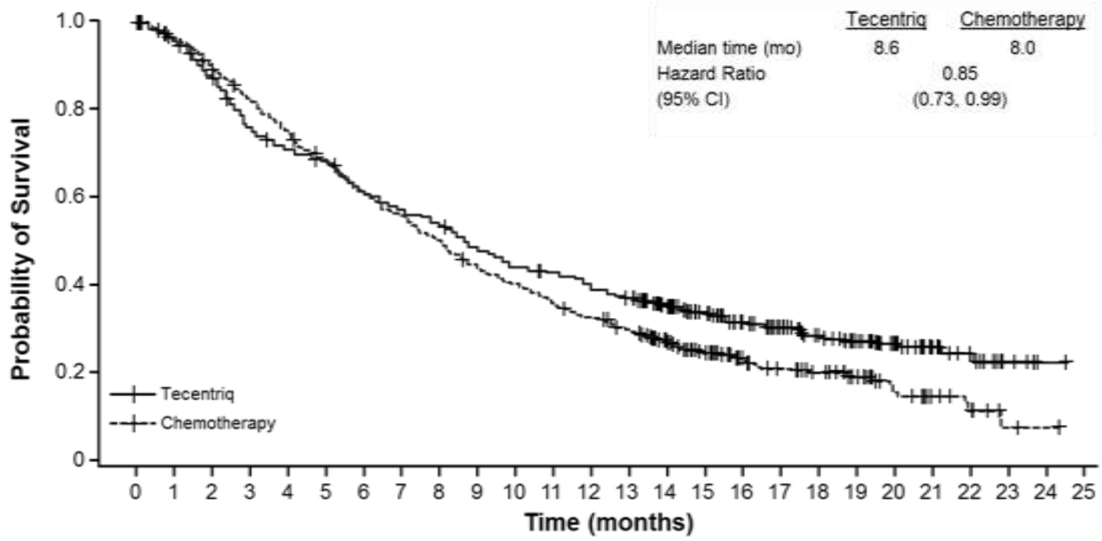
* An analysis of OS in the all comer population was performed based on the stratified log-rank test and the result is provided for descriptive purposes only (p = 0.0378); according to the pre-specified analysis hierarchy, the p-value for the OS analysis in the all comer population cannot be considered statistically significant.

‡ Stratified by chemotherapy (vinflunine vs. taxane), status on IC (< 5% vs. ≥ 5%), number of prognostic risk factors (0 vs. 1-3), and liver metastases (yes vs. no).

** Based on Kaplan-Meier estimate

*** Responses were ongoing in 63% of responders in the atezolizumab arm and in 21% of responders in the chemotherapy arm.

Figure 1: Kaplan-Meier curve for overall survival (IMvigor211)



No. of Patients at Risk

Tecentriq	467	443	405	348	327	309	280	259	245	218	201	192	177	166	138	113	90	76	59	47	34	20	13	5	1
Chemotherapy	464	428	397	364	330	299	268	244	219	191	175	156	140	126	99	78	60	49	42	30	17	11	7	2	1

IMvigor210 (GO29293): Single-arm trial in previously untreated urothelial carcinoma patients who are ineligible for cisplatin therapy and in urothelial carcinoma patients previously treated with chemotherapy

A phase II, multi-centre, international, two-cohort, single-arm clinical trial, IMvigor210, was conducted in patients with locally advanced or metastatic UC (also known as urothelial bladder cancer).

The study enrolled a total of 438 patients and had two patient cohorts. Cohort 1 included previously untreated patients with locally advanced or metastatic UC who were ineligible or unfit for cisplatin-based chemotherapy or had disease progression at least 12 months after treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. Cohort 2 included patients who received at least one platinum-based chemotherapy regimen for locally advanced or metastatic UC or had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen.

In Cohort 1, 119 patients were treated with atezolizumab 1 200 mg by intravenous infusion every 3 weeks until disease progression. The median age was 73 years. Most patients were male (81%), and the majority of patients were White (91%).

Cohort 1 included 45 patients (38%) with ECOG performance status of 0, 50 patients (42%) with ECOG performance status of 1 and 24 patients (20%) with ECOG performance status of 2, 35 patients (29%) with no Bajorin risk factors (ECOG performance status ≥ 2 and visceral metastasis), 66 patients (56%) with one Bajorin risk factor and 18 patients (15 %) with two Bajorin risk factors, 84 patients (71%) with impaired renal function (glomerular filtration rate [GFR] < 60 mL/min), and 25 patients (21%) with liver metastasis.

The primary efficacy endpoint for Cohort 1 was confirmed objective response rate (ORR) as assessed by an independent review facility (IRF) using RECIST v1.1.

The primary analysis was performed when all patients had at least 24 weeks of follow-up. Median duration of treatment was 15.0 weeks and median duration of survival follow-up was 8.5 months in all comers. Clinically relevant IRF-assessed ORRs per RECIST v1.1 were shown; however, when compared to a pre-specified historical control response rate of 10%, statistical significance was not reached for the primary endpoint. The confirmed ORRs per IRF-RECIST v1.1 were 21.9% (95% CI:

9.3, 40.0) in patients with PD-L1 expression ≥ 5%, 18.8% (95% CI: 10.9, 29.0) in patients with PD-L1 expression ≥ 1%, and 19.3% (95% CI: 12.7, 27.6) in all comers. The median duration of response (DOR) was not reached in any PD-L1 expression subgroup or in all comers. OS was not mature with an event patient ratio of approximately 40%. Median OS for all patient subgroups (PD-L1 expression ≥ 5 % and ≥ 1 %) and in all comers was 10.6 months.

An updated analysis was performed with a median duration of survival follow-up of 17.2 months for Cohort 1 and is summarised in Table 5. The median DOR was not reached in any PD-L1 expression subgroup or in all comers.

Table 5: Summary of updated efficacy (IMvigor210 Cohort 1)

Efficacy endpoint	**PD-L1 expression of ≥ 5% in IC**	**PD-L1 expression of ≥ 1% in IC**	**All Comers**
ORR (IRF-assessed; RECIST v1.1)	n = 32	n = 80	n = 119
No. of Responders (%)	9 (28.1%)	19 (23.8%)	27 (22.7%)
95% CI	13.8, 46.8	15.0, 34.6	15.5, 31.3
No. of complete response (%)	4 (12.5%)	8 (10.0%)	11 (9.2%)
95% CI	(3.5, 29.0)	(4.4, 18.8)	(4.7, 15.9)
No. of partial response (%)	5 (15.6%)	11 (13.8%)	16 (13.4%)
95% CI	(5.3, 32.8)	(7.1, 23.3)	(7.9, 20.9)
DOR (IRF-assessed; RECIST v1.1)	n = 9	n = 19	n = 27
Patients with event (%)	3 (33.3%)	5 (26.3%)	8 (29.6%)
Median (months) (95% CI)	NE (11.1, NE)	NE (NE)	NE (14.1, NE)
PFS (IRF-assessed; RECIST v1.1)	n = 32	n = 80	n = 119
Patients with event (%)	24 (75.0%)	59 (73.8%)	88 (73.9%)
Median (months) (95% CI)	4.1 (2.3, 11.8)	2.9 (2.1, 5.4)	2.7 (2.1, 4.2)
OS	n = 32	n = 80	n = 119
Patients with event (%)	18 (56.3%)	42 (52.5%)	59 (49.6%)
Median (months) (95% CI)	12.3 (6.0, NE)	14.1 (9.2, NE)	15.9 (10.4, NE)
1-year OS rate (%)	52.4%	54.8%	57.2%

CI = confidence interval; DOR=duration of response; IC = tumour-infiltrating immune cells; IRF = independent review facility; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

In Cohort 2, the co-primary efficacy endpoints were confirmed ORR as assessed by an IRF using RECIST v1.1 and investigator-assessed ORR according to Modified RECIST (mRECIST) criteria. There were 310 patients treated with atezolizumab 1 200 mg by intravenous infusion every 3 weeks until loss of clinical benefit. The primary analysis of Cohort 2 was performed when all patients had at least 24 weeks of follow-up. The study met its co-primary endpoints in Cohort 2, demonstrating statistically significant ORRs per IRF-assessed RECIST v1.1 and investigator-assessed mRECIST compared to a pre-specified historical control response rate of 10%.

An analysis was also performed with a median duration of survival follow-up of 21.1 months for Cohort 2. The confirmed ORRs per IRF-RECIST v1.1 were 28.0% (95% CI: 19.5, 37.9) in patients with PD-L1 expression ≥ 5%, 19.3% (95% CI: 14.2, 25.4) in patients with PD-L1 expression ≥ 1%, and 15.8% (95% CI: 11.9, 20.4) in all comers. The confirmed ORR per investigator-assessed mRECIST was 29.0% (95% CI: 20.4, 38.9) in patients with PD-L1 expression ≥ 5%, 23.7% (95% CI:

18.1, 30.1) in patients with PD-L1 expression ≥ 1%, and 19.7% (95% CI: 15.4, 24.6) in all comers. The rate of complete response per IRF-RECIST v1.1 in the all comer population was 6.1% (95% CI: 3.7, 9.4). For Cohort 2, median DOR was not reached in any PD-L1 expression subgroup or in all comers, however was reached in patients with PD-L1 expression < 1% (13.3 months; 95% CI 4.2, NE). The OS rate at 12 months was 37% in all comers.

IMvigor130 (WO30070): Phase III multi-centre, randomised, placebo-controlled study of atezolizumab as monotherapy and in combination with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma

Based on an independent Data Monitoring Committee (iDMC) recommendation following an early review of survival data, accrual of patients on the atezolizumab monotherapy treatment arm whose tumours have a low PD-L1 expression (less than 5% of immune cells staining positive for PD-L1 by immunohistochemistry) was stopped after observing decreased overall survival for this subgroup. The iDMC did not recommend any change of therapy for patients who had already been randomised to and were receiving treatment in the monotherapy arm. No other changes were recommended.

<u>*Non-small cell lung cancer*</u>

Adjuvant treatment of early-stage NSCLC

IMpower010 (GO29527): Randomised phase III trial in patients with resected NSCLC after cisplatin-based chemotherapy

A phase III, open label, multi-centre, randomised study, GO29527 (IMpower010), was conducted to evaluate the efficacy and safety of atezolizumab for the adjuvant treatment of patients with stage IB (tumours ≥ 4 cm) – IIIA NSCLC (per the Union for International Cancer Control/American Joint Committee on Cancer staging system, 7th edition).

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of the patient population with stage II – IIIA according to the 7th edition staging system:

Tumour size ≥ 5 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that are invasive of thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus < 2 cm distal to the carina but without involvement of the carina; or tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary.

The study did not include patients who had N2 status with tumours invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodule(s) in a different ipsilateral lobe.

A total of 1 280 enrolled patients had complete tumour resection and were eligible to receive up to 4 cycles of cisplatin-based chemotherapy. The cisplatin-based chemotherapy regimens are described in Table 6.

Table 6: Adjuvant chemotherapy regimens (IMpower010)

Adjuvant cisplatin-based chemotherapy: Cisplatin 75 mg/m^2 intravenous on Day 1 of each 21 day cycle with one of the following treatment regimens	Vinorelbine 30 mg/m^2 intravenous, Days 1 and 8
	Docetaxel 75 mg/m^2 intravenous, Day 1
	Gemcitabine 1 250 mg/m^2 intravenous, Days 1 and 8
	Pemetrexed 500 mg/m^2 intravenous, Day 1(non-squamous)

After completion of cisplatin-based chemotherapy (up to four cycles), a total of 1 005 patients were randomised in a 1:1 ratio to receive atezolizumab (Arm A) or best supportive care (BSC) (Arm B). Atezolizumab was administered as a fixed dose of 1 200 mg by IV infusion every 3 weeks for 16 cycles unless there was disease recurrence or unacceptable toxicity. Randomisation was stratified by sex, stage of disease, histology, and PD-L1 expression.

Patients were excluded if they had a history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomisation; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomisation. Tumour assessments were conducted at baseline of the randomisation phase and every 4 months for the first year following Cycle 1, Day 1 and then every 6 months until year five, then annually thereafter.

The demographics and baseline disease characteristics in the ITT population were well balanced between the treatment arms. The median age was 62 years (range: 26 to 84), and 67% of patients were male. The majority of patients were White (73%), and 24% were Asian. Most patients were current or previous smokers (78%) and baseline ECOG performance status in patients was 0 (55%) or 1 (44%). Overall, 12% of patients had stage IB, 47% had stage II and 41% had stage IIIA disease. The percentage of patients who had tumours with PD-L1 expression ≥ 1% and ≥ 50% on TC as measured by the VENTANA PD-L1 (SP263) Assay was 55% and 26%, respectively.

The primary efficacy outcome measure was disease-free survival (DFS) as assessed by the investigator. DFS was defined as the time from the date of randomisation to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC, or death due to any cause, whichever occurred first. The primary efficacy objective was to evaluate DFS in the PD-L1 ≥ 1% TC stage II – IIIA patient population. Key secondary efficacy objectives were to evaluate DFS in the PD-L1 ≥ 50% TC stage II – IIIA patient population and overall survival (OS) in the ITT population.

At the time of the interim DFS analysis, the study met its primary endpoint. The median follow-up time was approximately 32 months. In the analysis of patients with PD-L1 ≥ 50% TC stage II – IIIA without EGFR mutations or ALK rearrangements (n = 209), a clinically meaningful improvement in DFS in the atezolizumab arm was observed compared to the BSC arm (Table 7). The OS data were immature at the time of the DFS interim analysis with approximately 16.3 % of deaths overall reported in the PD-L1 ≥ 50% TC stage II – IIIA patient population, without EGFR mutations and ALK rearrangements. An exploratory analysis of OS suggested a trend in favor of atezolizumab over BSC, with a stratified HR of 0.39 (95% CI: 0.18, 0.82) in this patient population.

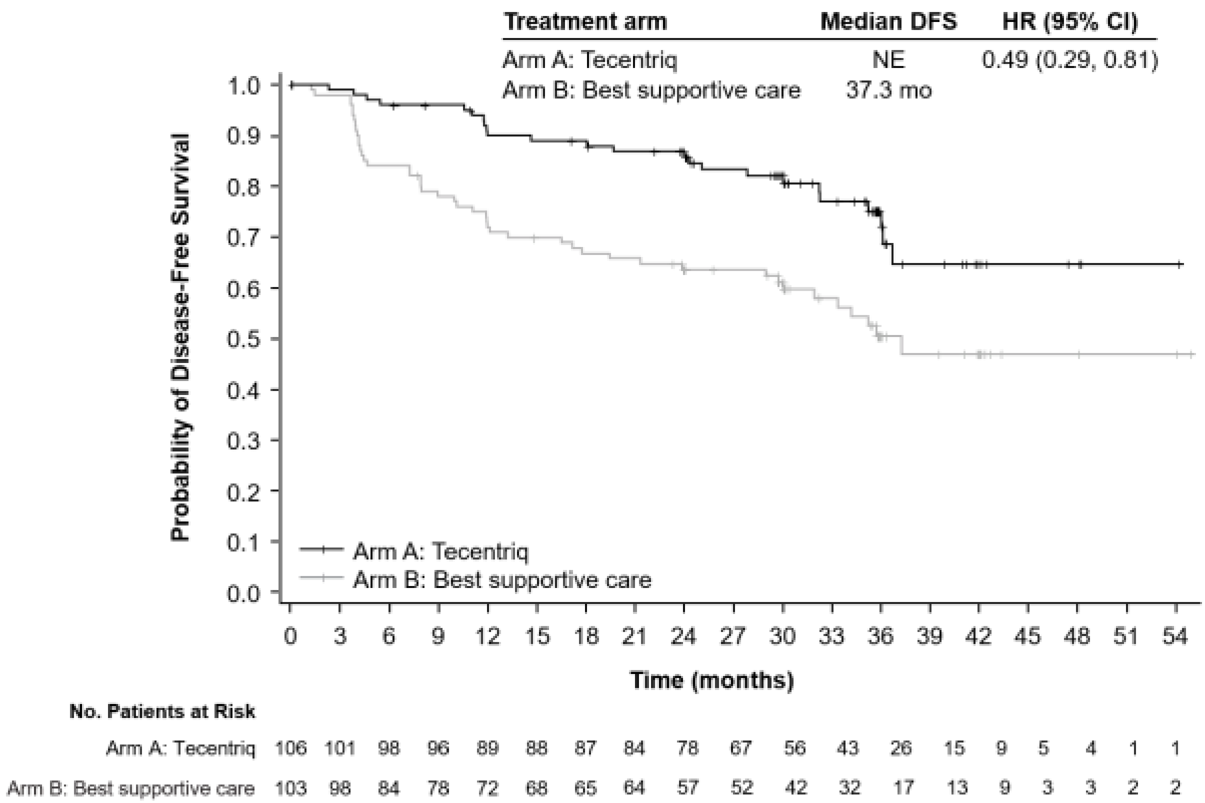
The key efficacy results for the PD-L1 ≥ 50% TC stage II – IIIA patient population, without EGFR mutations and ALK rearrangements, are summarised in Table 7. The Kaplan-Meier curve for DFS is presented in Figure 2.

Table 7: Summary of efficacy in the PD-L1 expression ≥ 50% TC stage II – IIIA patient population without EGFR mutations or ALK rearrangements (IMpower010)

Efficacy endpoint	Arm A (Atezolizumab)	Arm B (Best supportive care)
Investigator-assessed DFS	n = 106	n = 103
No. of events (%)	24 (22.6%)	45 (43.7%)
Median duration of DFS (months)	NE	37.3
95% CI	NE, NE	30.1, NE
Stratified hazard ratio (95% CI)	0.49 (0.29, 0.81)	
3-year DFS rate (%)	75.1	50.4

DFS = Disease-free survival; CI = confidence interval; NE = not estimable

Figure 2: Kaplan-Meier curve for disease-free survival in the PD-L1 expression ≥ 50% TC stage II – IIIA patient population without EGFR mutations or ALK rearrangements (IMpower010)



The observed DFS improvement in the atezolizumab arm compared with the BSC arm was consistently shown across the majority of pre-specified subgroups in the PD-L1 ≥ 50% TC stage II – IIIA patient population without EGFR mutations or ALK rearrangements, including both non-squamous NSCLC patients (unstratified HR of 0.35, 95% CI: 0.18, 0.69; median DFS NE vs. 35.7 months) and squamous NSCLC patients (unstratified HR of 0.60, 95% CI: 0.29, 1.26; median DFS 36.7 vs. NE months).

First-line treatment of metastatic NSCLC

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, multi-centre, 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.

Patients were excluded if they had history of autoimmune disease, administration of a live, attenuated vaccine within 28 days prior to randomisation, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal product within 2 weeks prior to randomisation, active or untreated CNS metastases, clear tumour infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging. 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.

A total of 1 202 patients were enrolled and were randomised (1:1:1) to receive one of the treatment regimens described in Table 8. Randomisation was stratified by sex, presence of liver metastases and PD-L1 tumour expression on TC and IC.

Table 8: 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 bw) + paclitaxel (200 mg/m^2)[b,c] + carboplatin[c] (AUC 6)	Atezolizumab[a] (1 200 mg) + bevacizumab[d] (15 mg/kg bw)
C	Bevacizumab[d] (15 mg/kg bw) + paclitaxel (200 mg/m^2)[b,c] + carboplatin[c] (AUC 6)	Bevacizumab[d] (15 mg/kg bw)

[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, or unacceptable toxicity whichever occurs first
[d.] Bevacizumab is administered until progressive disease or unacceptable toxicity

The demographics and baseline disease characteristics of the study population were well balanced between the treatment arms. The median age was 63 years (range: 31 to 90), and 60% of patients were male. The majority of patients were white (82%). Approximately 10% of patients had known EGFR mutation, 4% had known ALK rearrangements, 14% had liver metastasis at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%). 51% of patients' tumours had PD-L1 expression of ≥ 1% TC or ≥ 1% IC and 49% of patients' tumours had PD-L1 expression of < 1% TC and < 1% IC.

At the time of the final analysis for PFS, patients had a median follow up time of 15.3 months. The ITT population, including patients with EGFR mutations or ALK rearrangements who should have been previously treated with tyrosine kinase inhibitors, demonstrated clinically meaningful PFS improvement in Arm B as compared to Arm C (HR of 0.61, 95% CI: 0.52, 0.72; median PFS 8.3 vs. 6.8 months).

At the time of the interim OS analysis, patients had a median follow-up of 19.7 months. The key results from this analysis as well as from the updated PFS analysis in the ITT population are summarised in Tables 9 and 10. The Kaplan-Meier curve for OS in the ITT population is presented in Figure 3. Figure 4 summarises the results of OS in the ITT and PD-L1 subgroups. Updated PFS results are also presented in Figures 5 and 6.

Table 9: Summary of updated efficacy in the ITT population (IMpower150)

Efficacy endpoint	Arm A (Atezolizumab + Paclitaxel + Carboplatin)	Arm B (Atezolizumab + Bevacizumab + Paclitaxel + Carboplatin)	Arm C (Bevacizumab + Paclitaxel + Carboplatin)
Secondary Endpoints[#]			
Investigator-assessed PFS (RECIST v1.1)*	n = 402	n = 400	n = 400
No. of events (%)	330 (82.1%)	291 (72.8%)	355 (88.8%)
Median duration of PFS (months)	6.7	8.4	6.8
95% CI	(5.7, 6.9)	(8.0, 9.9)	(6.0, 7.0)
Stratified hazard ratio[‡^] (95% CI)	0.91 (0.78, 1.06)	0.59 (0.50, 0.69)	---
p-value[1,2]	0.2194	< 0.0001	
12-month PFS (%)	24	38	20
OS interim analysis*	n = 402	n = 400	n = 400
No. of deaths (%)	206 (51.2%)	192 (48.0%)	230 (57.5%)
Median time to events (months)	19.5	19.8	14.9
95% CI	(16.3, 21.3)	(17.4, 24.2)	(13.4, 17.1)
Stratified hazard ratio[‡^] (95% CI)	0.85 (0.71, 1.03)	0.76 (0.63, 0.93)	---
p-value[1,2]	0.0983	0.006	
6-month OS (%)	84	85	81
12-month OS (%)	66	68	61
Investigator-assessed Overall Best Response[3]* (RECIST 1.1)	n = 401	n = 397	n = 393
No. of responders (%)	163 (40.6%)	224 (56.4%)	158 (40.2%)
95% CI	(35.8, 45.6)	(51.4, 61.4)	(35.3, 45.2)
No. of complete response (%)	8 (2.0%)	11 (2.8%)	3 (0.8%)
No. of partial response (%)	155 (38.7%)	213 (53.7%)	155 (39.4%)
Investigator-assessed DOR* (RECIST v1.1)	n = 163	n = 224	n = 158
Median in months	8.3	11.5	6.0
95% CI	(7.1, 11.8)	(8.9, 15.7)	(5.5, 6.9)

[#] Primary efficacy endpoints were PFS and OS and they were analysed in the ITT-wild-type (WT) population, i.e. excluding patients with EGFR mutations or ALK rearrangements.

[1] Based on the stratified log-rank test

[2] For informational purposes; in the ITT population, comparisons between Arm B and Arm C as well as between Arm A and Arm C were not formally tested yet as per the pre-specified analysis hierarchy

[3] Overall best response for complete response and partial response

[‡] Stratified by sex, presence of liver metastases and PD-L1 tumour expression on TC and IC

^ The Arm C is the comparison group for all hazard ratios

* Updated PFS analysis and interim OS analysis at clinical cut-off 22 January 2018

PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.
CI = confidence interval; DOR = duration of response; OS = overall survival.

Table 10: Summary of updated efficacy for Arm A vs. Arm B in the ITT population (IMpower150)

Efficacy endpoint	Arm A (Atezolizumab + Paclitaxel + Carboplatin)	Arm B (Atezolizumab + Bevacizumab + Paclitaxel + Carboplatin)
Investigator-assessed PFS (RECIST v1.1)*	n = 402	n = 400
No. of events (%)	330 (82.1%)	291 (72.8%)
Median duration of PFS (months)	6.7	8.4
95% CI	(5.7, 6.9)	(8.0, 9.9)
Stratified hazard ratio‡^ (95% CI)	0.67 (0.57, 0.79)	
p-value[1,2]	< 0.0001	
OS interim analysis*	n = 402	n = 400
No. of deaths (%)	206 (51.2%)	192 (48.0%)
Median time to events (months)	19.5	19.8
95% CI	(16.3, 21.3)	(17.4, 24.2)
Stratified hazard ratio‡^ (95% CI)	0.90 (0.74, 1.10)	
p-value[1,2]	0.3000	

[1] Based on the stratified log-rank test

[2] For informational purposes; in the ITT population, comparisons between Arm A and Arm B were not included in the pre-specified analysis hierarchy

‡ Stratified by sex, presence of liver metastases and PD-L1 expression on TC and IC

* Updated PFS analysis and interim OS analysis at clinical cut-off 22 January 2018

^ The Arm A is the comparison group for all hazard ratios

Figure 3: Kaplan-Meier curve for overall survival in the ITT population (IMpower150)

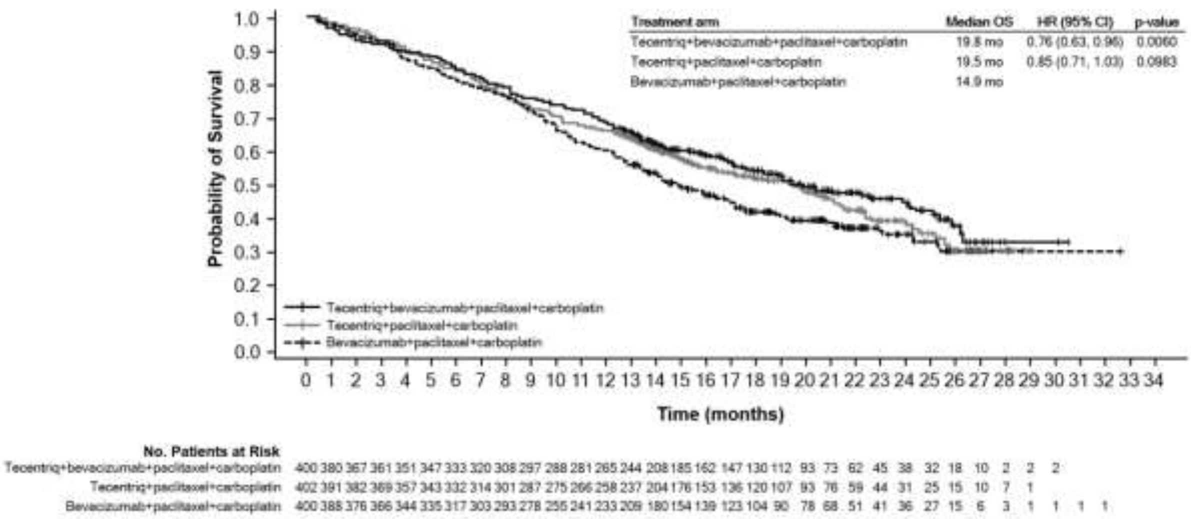


Figure 4: Forest plot of overall survival by PD-L1 expression in the ITT population, Arm B vs. C (IMpower150)

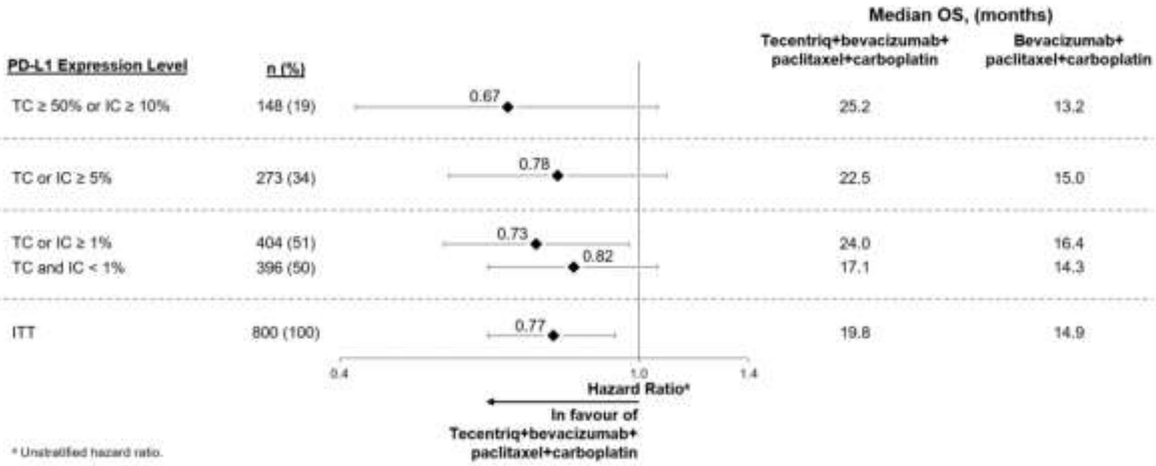


Figure 5: Kaplan-Meier curve for PFS in the ITT population (IMpower150)

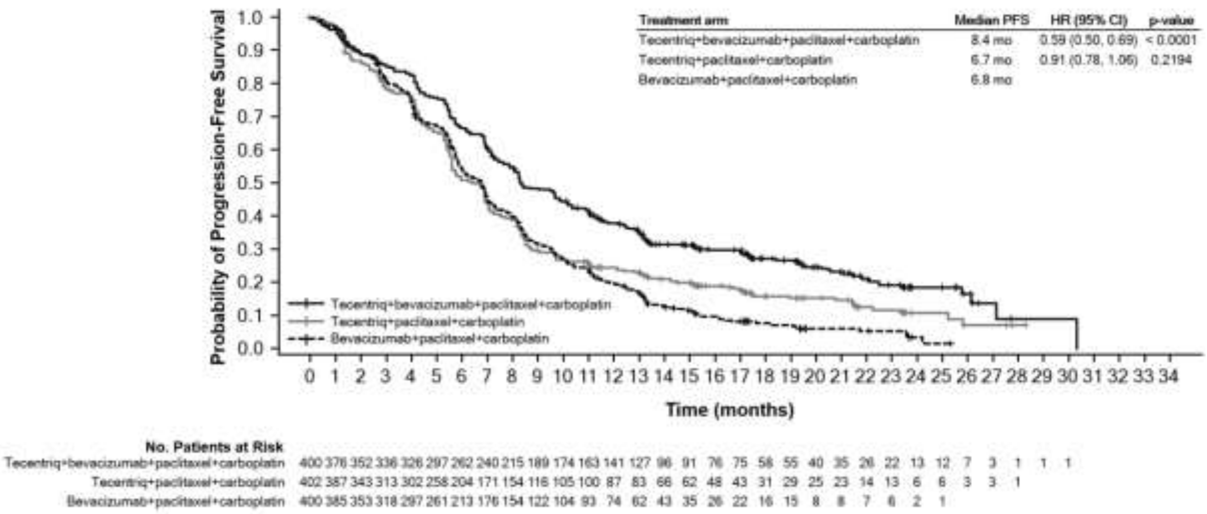
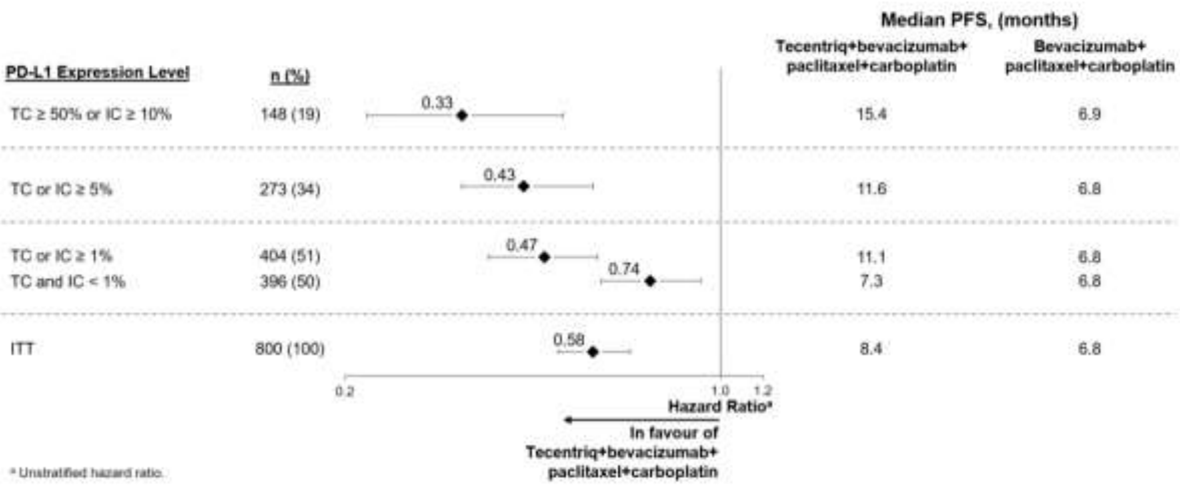


Figure 6: Forest plot of progression free survival by PD-L1 expression in the ITT population, Arm B vs. C (IMpower150)



In Arm B as compared to Arm C, pre-specified subgroup analyses from the interim OS analysis showed an OS improvement for patients with EGFR mutations or ALK rearrangements (hazard ratio [HR] of 0.54, 95% CI: 0.29, 1.03; median OS not reached vs. 17.5 months), and liver metastases (HR of 0.52, 95% CI: 0.33, 0.82; median OS 13.3 vs. 9.4 months). PFS improvements were also shown in patients with EGFR mutations or ALK rearrangements (HR of 0.55, 95% CI: 0.35, 0.87; median PFS 10.0 vs. 6.1 months) and liver metastases (HR of 0.41, 95% CI: 0.26, 0.62; median PFS 8.2 vs. 5.4 months). OS results were similar for patients aged < 65 and ≥ 65 subgroups, respectively. Data for patients ≥ 75 years of age are too limited to draw conclusions on this population. For all subgroup analyses, formal statistical testing was not planned.

IMpower130 (GO29537): Randomised phase III trial in chemotherapy-naïve patients with metastatic non-squamous NSCLC, in combination with nab-paclitaxel and carboplatin

A phase III, open-label, randomised study, GO29537 (IMpower130), was conducted to evaluate the efficacy and safety of atezolizumab in combination with nab-paclitaxel and carboplatin, in chemotherapy-naïve patients with metastatic non-squamous NSCLC. Patients with EGFR mutations or ALK rearrangements should have been previously treated with tyrosine kinase inhibitors.

Patients were staged according to the American Joint Committee on Cancer (AJCC) 7th edition. Patients were excluded if they had a history of autoimmune disease, administration of live, attenuated vaccine within 28 days prior to randomisation, administration of immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to randomisation, and active or untreated CNS metastases. Patients who had prior treatment with CD137 agonists or immune checkpoint blockade therapies (anti-PD-1, and anti-PD-L1 therapeutic antibodies) were not eligible. However, patients who had prior anti-CTLA-4 treatment could be enrolled, as long as the last dose was received at least 6 weeks prior to randomisation, and there was no history of severe immune-mediated adverse events from anti-CTLA-4 (NCI CTCAE Grades 3 and 4). Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, 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.

Patients, including those with EGFR mutations or ALK rearrangements, were enrolled and were randomised in a 2:1 ratio to receive one of the treatment regimens described in Table 11. Randomisation was stratified by sex, presence of liver metastases and PD-L1 expression on TC and IC. Patients receiving treatment regimen B were able to crossover and receive atezolizumab monotherapy following disease progression.

Table 11: Intravenous treatment regimens (IMpower130)

Treatment Regimen	Induction (Four or six 21-day cycles)	Maintenance (21-day cycles)
A	Atezolizumab (1 200 mg)[a] + nab-paclitaxel (100 mg/m^2)[b,c] + carboplatin (AUC 6)[c]	Atezolizumab (1 200 mg)[a]
B	Nab-paclitaxel (100 mg/m^2)[b,c] + carboplatin (AUC 6)[c]	Best supportive care or pemetrexed

[a] Atezolizumab is administered until loss of clinical benefit as assessed by investigator
[b] Nab-paclitaxel is administered on days 1, 8, and 15 of each cycle
[c] Nab-paclitaxel and carboplatin are administered until completion of 4-6 cycles, or progressive disease or unacceptable toxicity whichever occurs first

The demographics and baseline disease characteristics of the study population defined as ITT-WT (n=679) were well balanced between the treatment arms. The median age was 64 years (range: 18 to 86 years). The majority of the patients were male (59%) and white (90%). Fourteen point seven percent of patients had liver metastases at baseline, and most patients were current or previous smokers (90%). The majority of patients had a baseline ECOG performance status of 1 (59%) and PD-L1 expression < 1% (approximately 52%). Among 107 Arm B patients who had a response status of stable disease, partial response, or complete response after induction therapy, 40 received pemetrexed switch maintenance therapy.

The primary analysis was conducted in all patients, excluding those with EGFR mutations or ALK rearrangements, defined as ITT-WT population (n=679). Patients had a median survival follow up time of 18.6 months and showed improved OS and PFS with atezolizumab, nab-paclitaxel and carboplatin as compared to the control. The key results are summarised in Table 12 and Kaplan-Meier curves for OS and PFS are presented in Figures 7 and 9, respectively. The exploratory results of OS and PFS by PD-L1 expression are summarised in Figures 8 and 10, respectively. Patients with liver metastases did not show improved PFS or OS with atezolizumab, nab-paclitaxel and carboplatin, compared to nab-paclitaxel and carboplatin (HR of 0.93, 95% CI: 0.59, 1.47 for PFS and HR of 1.04, 95% CI: 0.63, 1.72 for OS, respectively).

Fifty-nine percent of patients in the nab-paclitaxel and carboplatin arm received any cancer immunotherapy after disease progression, which includes atezolizumab as crossover treatment (41% of all patients), compared to 7.3% of patients in the atezolizumab, nab paclitaxel and carboplatin arm.

In an exploratory analysis with longer follow up (median: 24.1 months), the median OS for both arms was unchanged relative to the primary analysis, with HR = 0.82 (95% CI: 0.67, 1.01).

Table 12: Summary of efficacy from IMpower130 in the primary analysis (ITT-WT population)

Efficacy endpoints	**Arm A** **Atezolizumab + nab-paclitaxel + carboplatin**	**Arm B** **Nab-paclitaxel + carboplatin**
Co-primary endpoints		
OS	n=451	n=228
No. of deaths (%)	226 (50.1%)	131 (57.5%)
Median time to events (months)	18.6	13.9
95% CI	(16.0, 21.2)	(12.0, 18.7)
Stratified hazard ratio‡ (95% CI)	0.79 (0.64, 0.98)	
p-value	0.033	
12-month OS (%)	63	56
Investigator-assessed PFS (RECIST v1.1)	n=451	n=228
No. of events (%)	347 (76.9%)	198 (86.8%)
Median duration of PFS (months)	7.0	5.5
95% CI	(6.2, 7.3)	(4.4, 5.9)
Stratified hazard ratio‡ (95% CI)	0.64 (0.54, 0.77)	
p-value	< 0.0001	
12-month PFS (%)	29%	14%
Other endpoints		
Investigator-assessed ORR (RECIST v1.1)^	n=447	n=226
No. of confirmed responders (%)	220 (49.2%)	72 (31.9%)
95% CI	(44.5, 54.0)	(25.8, 38.4)
No. of complete response (%)	11 (2.5%)	3 (1.3%)
No. of partial response (%)	209 (46.8%)	69 (30.5%)
Investigator-assessed confirmed DOR (RECIST 1.1)^	n=220	n=72
Median in months	8.4	6.1
95% CI	(6.9, 11.8)	(5.5, 7.9)

‡ Stratified by sex and PD-L1 expression on TC and IC
^ Confirmed ORR and DoR are exploratory endpoints
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

Figure 7: Kaplan-Meier curves for overall survival (IMpower130)

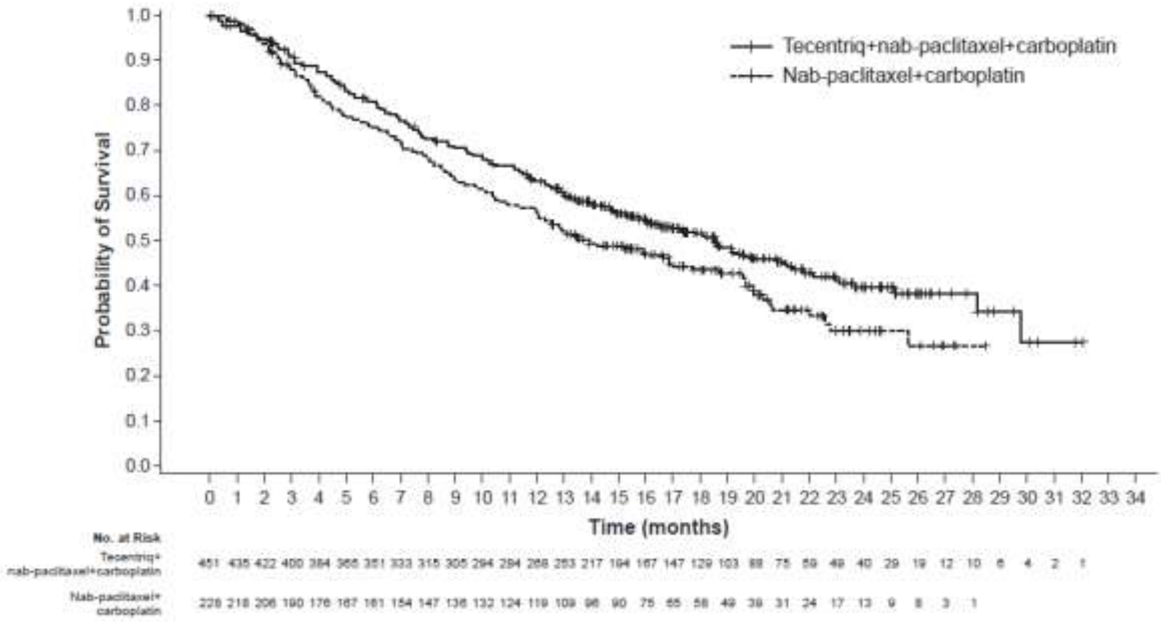


Figure 8: Forest plot of overall survival by PD-L1 expression (IMpower130)

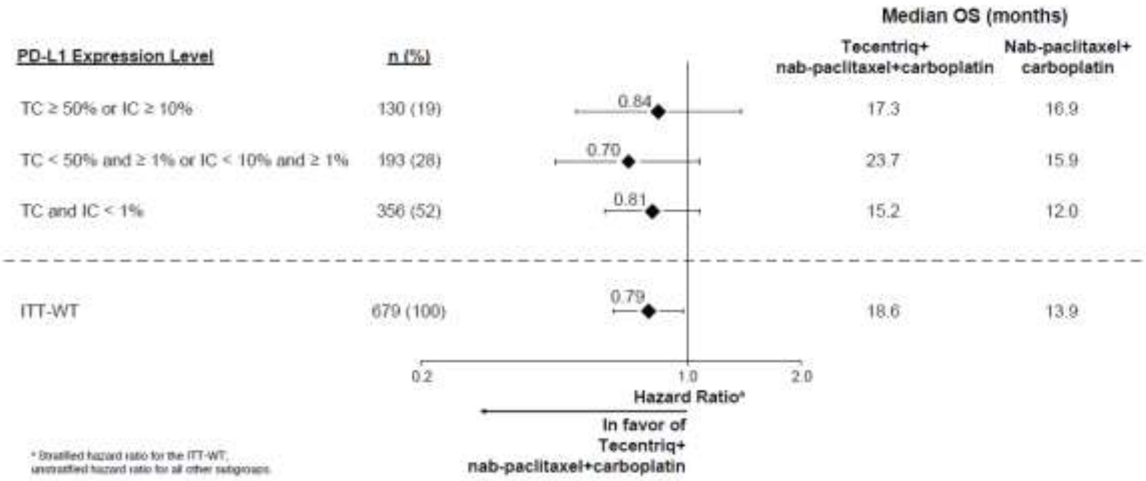


Figure 9: Kaplan-Meier curves for progression free survival (IMpower130)

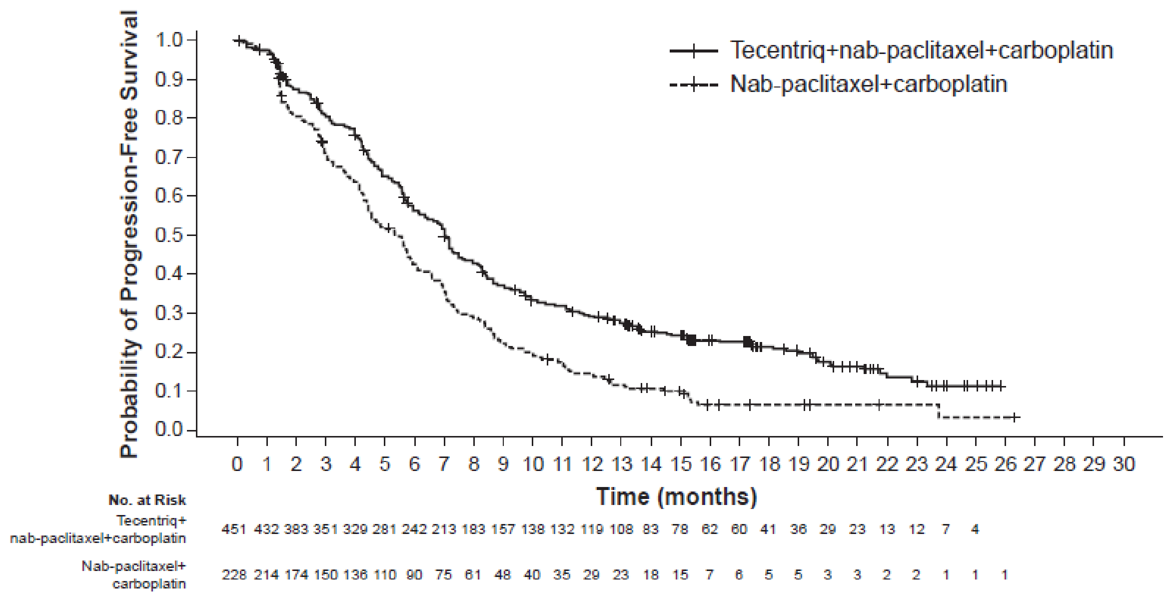
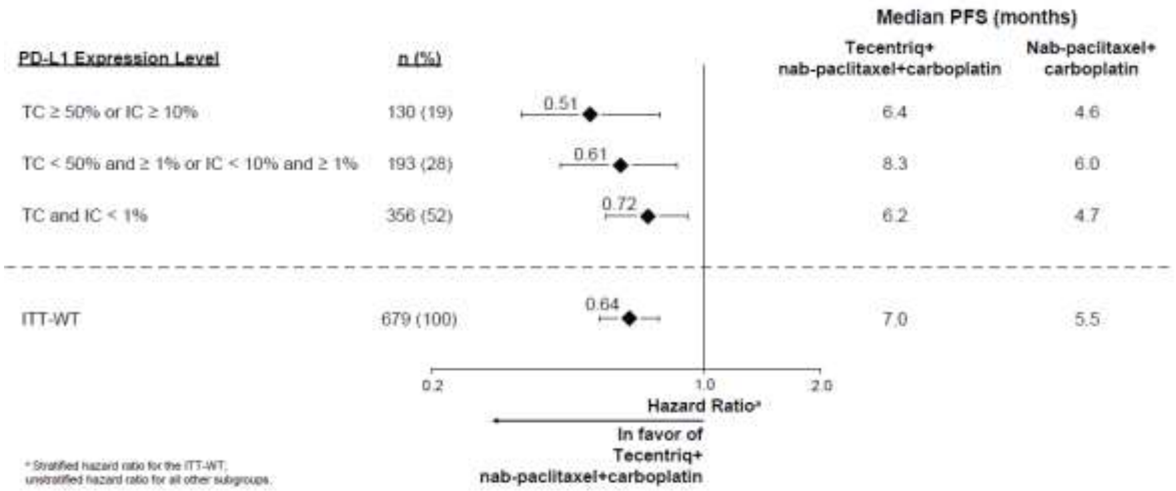


Figure 10: Forest plot of progression free survival by PD-L1 expression (IMpower130)



IMpower110 (GO29431): Randomised phase III trial in chemotherapy-naïve patients with metastatic NSCLC

A phase III, open-label, multi-centre, randomised study, IMpower110, was conducted to evaluate the efficacy and safety of atezolizumab in chemotherapy-naïve patients with metastatic NSCLC. Patients had PD-L1 expression ≥ 1% TC (PD-L1 stained ≥ 1% of tumour cells) or ≥ 1% IC (PD-L1 stained tumour-infiltrating immune cells covering ≥ 1% of the tumour area) based on the VENTANA PD-L1 (SP142) Assay.

A total of 572 patients were randomised in a 1:1 ratio to receive atezolizumab (Arm A) or chemotherapy (Arm B). Atezolizumab was administered as a fixed dose of 1 200 mg by intravenous infusion every 3 weeks until loss of clinical benefit as assessed by the investigator or unacceptable toxicity. The chemotherapy regimens are described in Table 13. Randomisation was stratified by sex, ECOG performance status, histology, and PD-L1 tumour expression on TC and IC.

Table 13: Chemotherapy intravenous treatment regimens (IMpower110)

Treatment regimen	Induction (Four or Six 21-day cycles)	Maintenance (21-day cycles)
B (Non-squamous)	Cisplatin[a] (75 mg/m²) + pemetrexed[a] (500 mg/m²) OR carboplatin[a](AUC 6) + pemetrexed[a] (500 mg/m²)	Pemetrexed[b,d] (500 mg/m²)
B (Squamous)	Cisplatin[a] (75 mg/m²) + gemcitabine[a,c] (1 250 mg/m²) OR carboplatin[a] (AUC 5) + gemcitabine[a,c] (1 000 mg/m²)	Best supportive care[d]

[a] Cisplatin, carboplatin, pemetrexed and gemcitabine are administered until completion of 4 or 6 cycles, or progressive disease, or unacceptable toxicity
[b] Pemetrexed is administered as maintenance regimen every 21 days until progressive disease or unacceptable toxicity
[c] Gemcitabine is administered on days 1 and 8 of each cycle
[d] No crossover was allowed from the control arm (platinum-based chemotherapy) to the atezolizumab arm (Arm A)

Patients were excluded if they had a history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomisation, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to randomisation, active or untreated CNS metastases. Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter.

The demographics and baseline disease characteristics in patients with PD-L1 expression ≥ 1% TC or ≥ 1% IC who do not have EGFR mutations or ALK rearrangements (n=554) were well balanced between the treatment arms. The median age was 64.5 years (range: 30 to 87), and 70% of patients were male. The majority of patients were white (84%) and Asian (14%). Most patients were current or previous smokers (87%) and baseline ECOG performance status in patients was 0 (36%) or 1 (64%). Overall, 69% of patients had non-squamous disease and 31% of patients had squamous disease. The demographics and baseline disease characteristics in patients with high PD-L1 expression (PD-L1 ≥ 50% TC or ≥ 10% IC) who do not have with EGFR mutations or ALK rearrangements (n=205) were generally representative of the broader study population and were balanced between the treatment arms.

The primary endpoint was overall survival (OS). At the time of the interim OS analysis, patients with high PD-L1 expression excluding those with EGFR mutations or ALK rearrangements (n=205) showed statistically significant improvement in OS for the patients randomised to atezolizumab (Arm A) as compared with chemotherapy (Arm B) (HR of 0.59, 95% CI: 0.40, 0.89; median OS of 20.2 months vs 13.1 months) with a two-sided p-value of 0.0106. The median survival follow-up time in patients with high PD-L1 expression was 15.7 months.

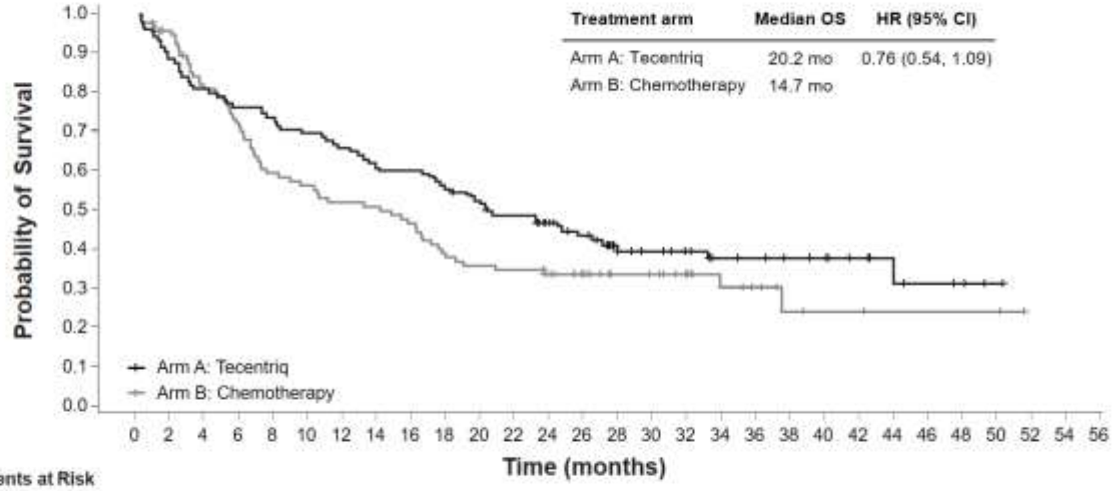
In an exploratory OS analysis with longer follow up (median: 31.3 months) for these patients, the median OS for the atezolizumab arm was unchanged relative to the primary OS interim analysis (20.2 months) and was 14.7 months for the chemotherapy arm (HR of 0.76, 95% CI: 0.54, 1.09). The key results at the exploratory analysis are summarised in Table 14. The Kaplan-Meier curves for OS and PFS in patients with high PD-L1 expression are presented in Figures 11 and 12. A higher proportion of patients experienced death within the first 2.5 months in the atezolizumab arm (16/107, 15.0%) as compared to the chemotherapy arm (10/98, 10.2%). No specific factor(s) associated with early deaths could be identified.

Table 14: Summary of efficacy in patients with high PD-L1 expression ≥ 50% TC or ≥ 10% IC (IMpower110)

Efficacy endpoints	**Arm A** (Atezolizumab)	**Arm B** (Chemotherapy)
Primary endpoint		
Overall survival	n = 107	n = 98
No. of deaths (%)	64 (59.8%)	64 (65.3%)
Median time to events (months)	20.2	14.7
95% CI	(17.2, 27.9)	(7.4, 17.7)
Stratified hazard ratio‡ (95% CI)	0.76 (0.54, 1.09)	
12-month OS (%)	66.1	52.3
Secondary endpoints		
Investigator-assessed PFS (RECIST v1.1)	n = 107	n = 98
No. of events (%)	82 (76.6%)	87 (88.8%)
Median duration of PFS (months)	8.2	5.0
95% CI	(6.8, 11.4)	(4.2, 5.7)
Stratified hazard ratio‡ (95% CI)	0.59 (0.43, 0.81)	
12-month PFS (%)	39.2	19.2
Investigator-assessed ORR (RECIST 1.1)	n = 107	n = 98
No. of responders (%)	43 (40.2%)	28 (28.6%)
95% CI	(30.8, 50.1)	(19.9, 38.6)
No. of complete response (%)	1 (0.9%)	2 (2.0%)
No. of partial response (%)	42 (39.3%)	26 (26.5%)
Investigator-assessed DOR (RECIST 1.1)	n = 43	n = 28
Median in months	38.9	8.3
95% CI	(16.1, NE)	(5.6, 11.0)

‡ Stratified by sex and ECOG performance status (0 vs. 1)
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; NE = not estimable.

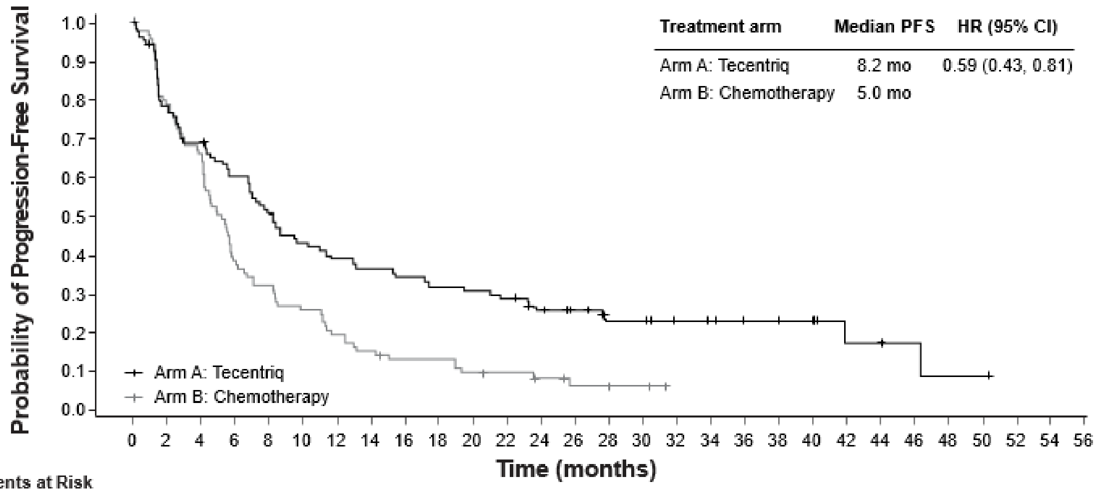
Figure 11: Kaplan-Meier curve for overall survival in patients with high PD-L1 expression ≥ 50% TC or ≥ 10% IC (IMpower110)



No. Patients at Risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56
Arm A: Tecentriq	107	95	86	81	77	74	70	64	64	59	54	51	43	38	27	25	22	18	16	14	13	8	5	4	3	1	0	0	0
Arm B: Chemotherapy	98	90	76	66	56	53	49	48	44	36	34	33	30	24	19	18	14	9	7	4	3	3	2	2	2	2	0	0	0

Figure 12: Kaplan-Meier curve for progression free survival in patients with high PD-L1 expression ≥ 50% TC or ≥ 10% IC (IMpower110)



No. Patients at Risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56
Arm A: Tecentriq	107	83	73	63	54	45	41	38	36	33	32	30	25	21	15	15	12	11	8	7	7	3	3	2	1	1	0	0	0
Arm B: Chemotherapy	98	74	62	36	30	24	18	14	11	11	8	7	5	3	3	2	0	0	0	0	0	0	0	0	0	0	0	0	0

The observed OS improvement in the atezolizumab arm compared with the chemotherapy arm was consistently shown across subgroups in patients with high PD-L1 expression including both non-squamous NSCLC patients (hazard ratio [HR] of 0.62, 95% CI: 0.40, 0.96; median OS 20.2 vs. 10.5 months) and squamous NSCLC patients (HR of 0.56, 95% CI: 0.23, 1.37; median OS not reached vs. 15.3 months). Data for patients ≥ 75 years of age and patients who were never smokers are too limited to draw conclusions in these subgroups.

Second-line treatment of NSCLC

OAK (GO28915): Randomised phase III trial in locally advanced or metastatic NSCLC patients previously treated with chemotherapy

A phase III, open-label, multi-centre, international, randomised study, OAK, was conducted to evaluate the efficacy and safety of atezolizumab compared with docetaxel in patients with locally advanced or metastatic NSCLC who progressed during or following a platinum-containing regimen. This study excluded patients who had a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrolment, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal product within 2 weeks prior to enrolment. Tumour assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter. Tumour specimens were evaluated prospectively for PD-L1 expression on tumour cells (TC) and tumour-infiltrating immune cells (IC).

A total of 1 225 patients were enrolled and per the analysis plan the first 850 randomised patients were included in the primary efficacy analysis. Randomisation was stratified by PD-L1 expression status on IC, by the number of prior chemotherapy regimens, and by histology. Patients were randomised (1:1) to receive either atezolizumab or docetaxel.

Atezolizumab was administered as a fixed dose of 1 200 mg by intravenous infusion every 3 weeks. No dose reduction was allowed. Patients were treated until loss of clinical benefit as assessed by the investigator. Docetaxel was administered 75 mg/m^2 by intravenous infusion on day 1 of each 3-week cycle until disease progression. For all treated patients, the median duration of treatment was 2.1 months for the docetaxel arm and 3.4 months for the atezolizumab arm.

The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 64 years (range: 33 to 85), and 61% of patients were male. The majority of patients were white (70%). Approximately three-quarters of patients had non-squamous histology (74%), 10% had known EGFR mutation, 0.2% had known ALK rearrangements, 10% had CNS metastases at baseline, and most patients were current or previous smokers (82%). Baseline ECOG performance status was 0 (37%) or 1 (63%). Seventy-five percent of patients received only one prior platinum-based therapeutic regimen.

The primary efficacy endpoint was OS. The key results of this study with a median survival follow-up of 21 months are summarised in Table 15. Kaplan-Meier curves for OS in the ITT population are presented in Figure 13. Figure 14 summarises the results of OS in the ITT and PD-L1 subgroups, demonstrating OS benefit with atezolizumab in all subgroups, including those with PD-L1 expression < 1% in TC and IC.

Table 15: Summary of efficacy in the primary analysis population (all comers)* (OAK)

Efficacy endpoint	Atezolizumab (n = 425)	Docetaxel (n = 425)
Primary efficacy endpoint		
OS		
No. of deaths (%)	271 (64%)	298 (70%)
Median time to events (months)	13.8	9.6
95% CI	(11.8, 15.7)	(8.6, 11.2)
Stratified‡ hazard ratio (95% CI)	0.73 (0.62, 0.87)	
p-value**	0.0003	
12-month OS (%)***	218 (55%)	151 (41%)
18-month OS (%)***	157 (40%)	98 (27%)
Secondary endpoints		
Investigator-assessed PFS (RECIST v1.1)		
No. of events (%)	380 (89%)	375 (88%)
Median duration of PFS (months)	2.8	4.0
95% CI	(2.6, 3.0)	(3.3, 4.2)
Stratified hazard ratio (95% CI)	0.95 (0.82, 1.10)	
Investigator-assessed ORR (RECIST v1.1)		
No. of responders (%)	58 (14%)	57 (13%)
95% CI	(10.5, 17.3)	(10.3, 17.0)
Investigator-assessed DOR (RECIST v1.1)	n = 58	n = 57
Median in months	16.3	6.2
95% CI	(10.0, NE)	(4.9, 7.6)

CI = confidence interval; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

* The primary analysis population consists of the first 850 randomised patients

‡ Stratified by PD-L1 expression in tumour infiltrating immune cells, the number of prior chemotherapy regimens, and histology

** Based on the stratified log-rank test

*** Based on Kaplan-Meier estimates

Figure 13: Kaplan-Meier curve for overall survival in the primary analysis population (all comers) (OAK)

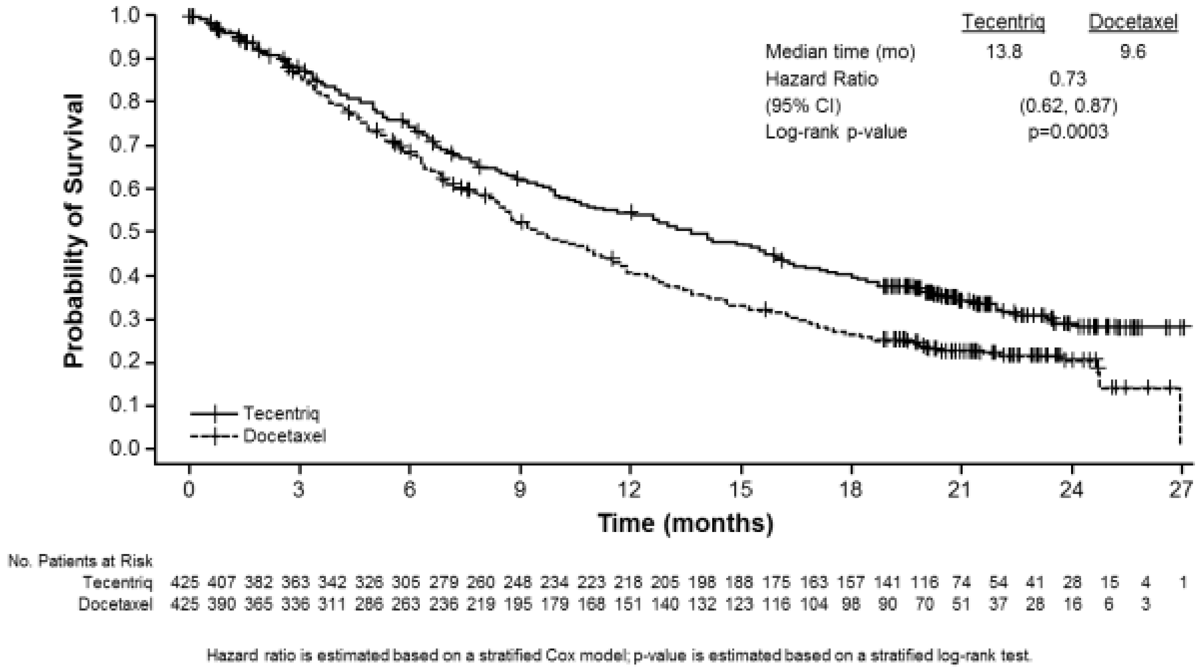
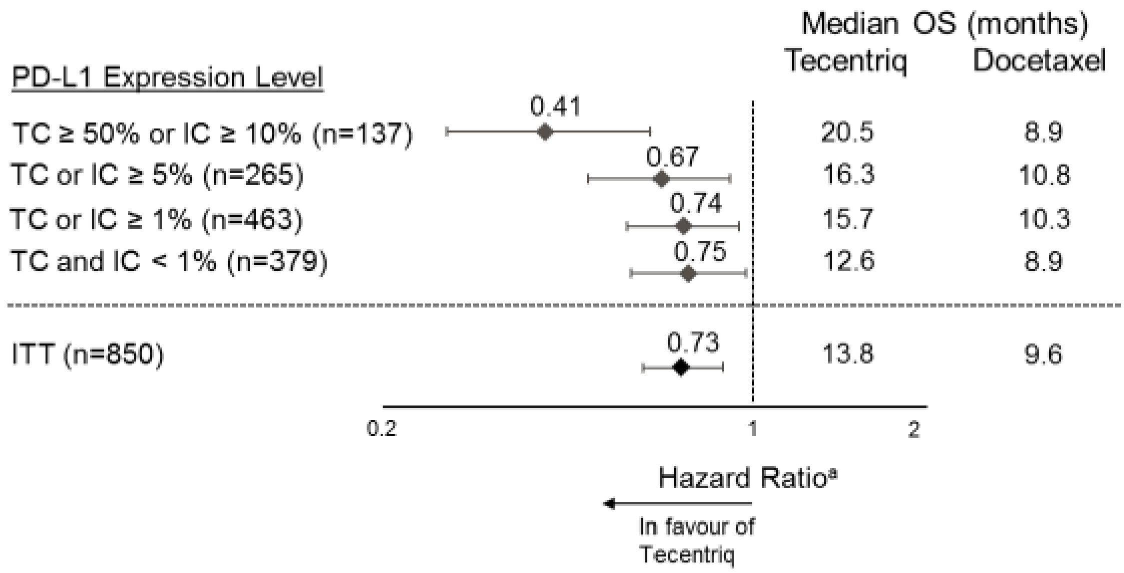


Figure 14: Forest plot of overall survival by PD-L1 expression in the primary analysis population (OAK)



[a] Stratified HR for ITT and TC or IC ≥ 1%. Unstratified HR for other exploratory subgroups.

An improvement in OS was observed with atezolizumab compared to docetaxel in both non-squamous NSCLC patients (hazard ratio [HR] of 0.73, 95% CI: 0.60, 0.89; median OS of 15.6 vs. 11.2 months for atezolizumab and docetaxel, respectively) and squamous NSCLC patients (HR of 0.73, 95% CI: 0.54, 0.98; median OS of 8.9 vs. 7.7 months for atezolizumab and docetaxel, respectively). The observed OS improvement was consistently demonstrated across subgroups of patients including those with brain metastases at baseline (HR of 0.54, 95% CI: 0.31, 0.94; median OS of 20.1 vs. 11.9 months for atezolizumab and docetaxel respectively) and patients who were never smokers (HR of 0.71, 95% CI: 0.47, 1.08; median OS of 16.3 vs. 12.6 months for atezolizumab and docetaxel, respectively). However, patients with EGFR mutations did not show improved OS with atezolizumab compared to docetaxel (HR of 1.24, 95% CI: 0.71, 2.18; median OS of 10.5 vs. 16.2 months for atezolizumab and docetaxel, respectively).

Prolonged time to deterioration of patient-reported pain in chest as measured by the EORTC QLQ-LC13 was observed with atezolizumab compared to docetaxel (HR of 0.71, 95% CI: 0.49, 1.05; median not reached in either arm). The time to deterioration in other lung cancer symptoms (i.e. cough, dyspnoea, and arm/shoulder pain) as measured by the EORTC QLQ-LC13 was similar between atezolizumab and docetaxel. These results should be interpreted with caution due to the open-label design of the study.

POPLAR (GO28753): Randomised phase II trial in locally advanced or metastatic NSCLC patients previously treated with chemotherapy

A phase II, multi-centre, international, randomised, open-label, controlled study, POPLAR, was conducted in patients with locally advanced or metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression. The primary efficacy outcome was overall survival. A total of 287 patients were randomised 1:1 to receive either atezolizumab (1 200 mg by intravenous infusion every 3 weeks until loss of clinical benefit) or docetaxel (75 mg/m^2 by intravenous infusion on day 1 of each 3-week cycle until disease progression). Randomisation was stratified by PD-L1 expression status on IC, by the number of prior chemotherapy regimens and by histology. An updated analysis with a total of 200 deaths observed and a median survival follow-up of 22 months showed a median OS of 12.6 months in patients treated with atezolizumab, vs. 9.7 months in patients treated with docetaxel (HR of 0.69, 95% CI: 0.52, 0.92). ORR was 15.3% vs. 14.7% and median DOR was 18.6 months vs. 7.2 months for atezolizumab vs. docetaxel, respectively.

<u>*Small cell lung cancer*</u>

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 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 medicinal products 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 who met established criteria and who agreed to be treated beyond disease progression had tumour assessments 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 16. Randomisation was stratified by sex, ECOG performance status, and presence of brain metastases.

Table 16: Intravenous treatment regimens (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

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) with 10% of patients ≥ 75 years of age. 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. A statistically significant improvement in OS was observed with atezolizumab in combination with carboplatin and etoposide compared to the control arm (HR of 0.70, 95% CI: 0.54, 0.91; median OS of 12.3 months vs. 10.3 months). In the exploratory OS final analysis with longer follow up (median: 22.9 months), the median OS for both arms was unchanged relative to the primary OS interim analysis. The PFS, ORR and DOR results from the primary analysis as well as the exploratory OS final analysis results are summarised in Table 17. Kaplan-Meier curves for OS and PFS are presented in Figures 15 and 16. Data for patients with brain metastases are too limited to draw conclusions on this population.

Table 17: 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 (%)	142 (70.6%)	160 (79.2%)
Median time to events (months)	12.3	10.3
95% CI	(10.8, 15.8)	(9.3, 11.3)
Stratified hazard ratio‡ (95% CI)	0.76 (0.60, 0.95)	
p-value	0.0154***	
12-month OS (%)	51.9	39.0
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
Other 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

* Exploratory OS final analysis at clinical cut-off 24 January 2019

** PFS, ORR and DOR analyses at clinical cut-off 24 April 2018

*** For descriptive purposes only

^ Confirmed ORR and DoR are exploratory endpoints

Figure 15: Kaplan-Meier curve for overall survival (IMpower133)

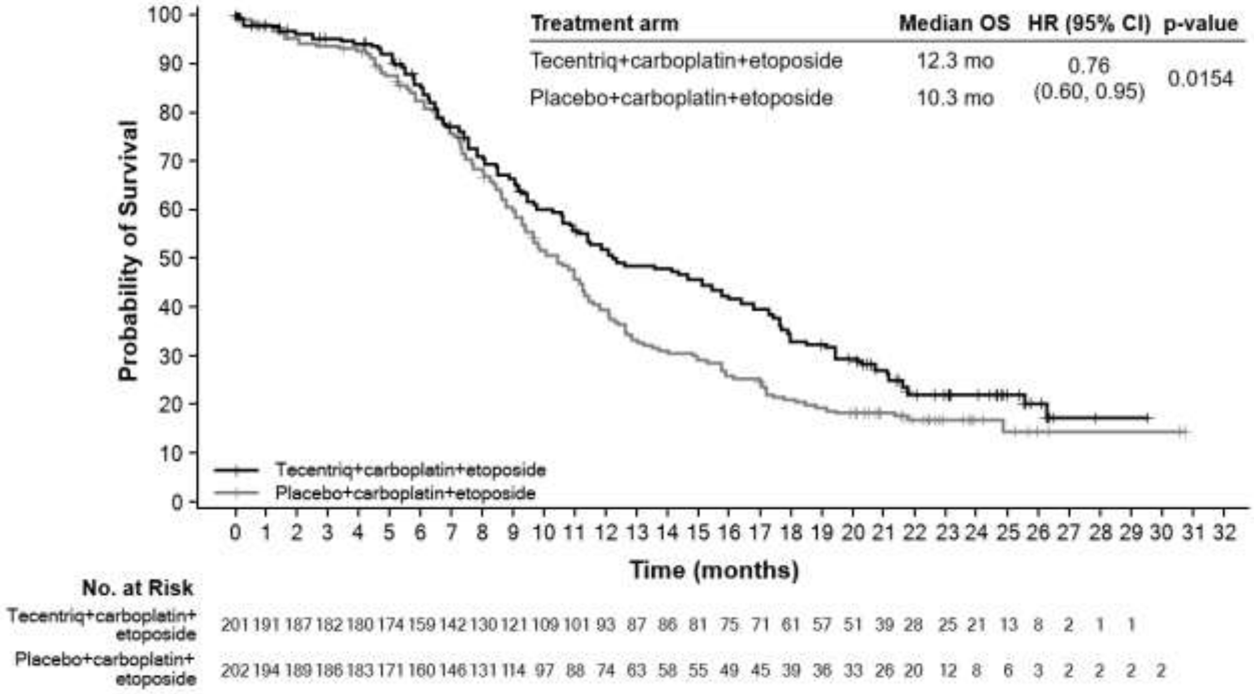
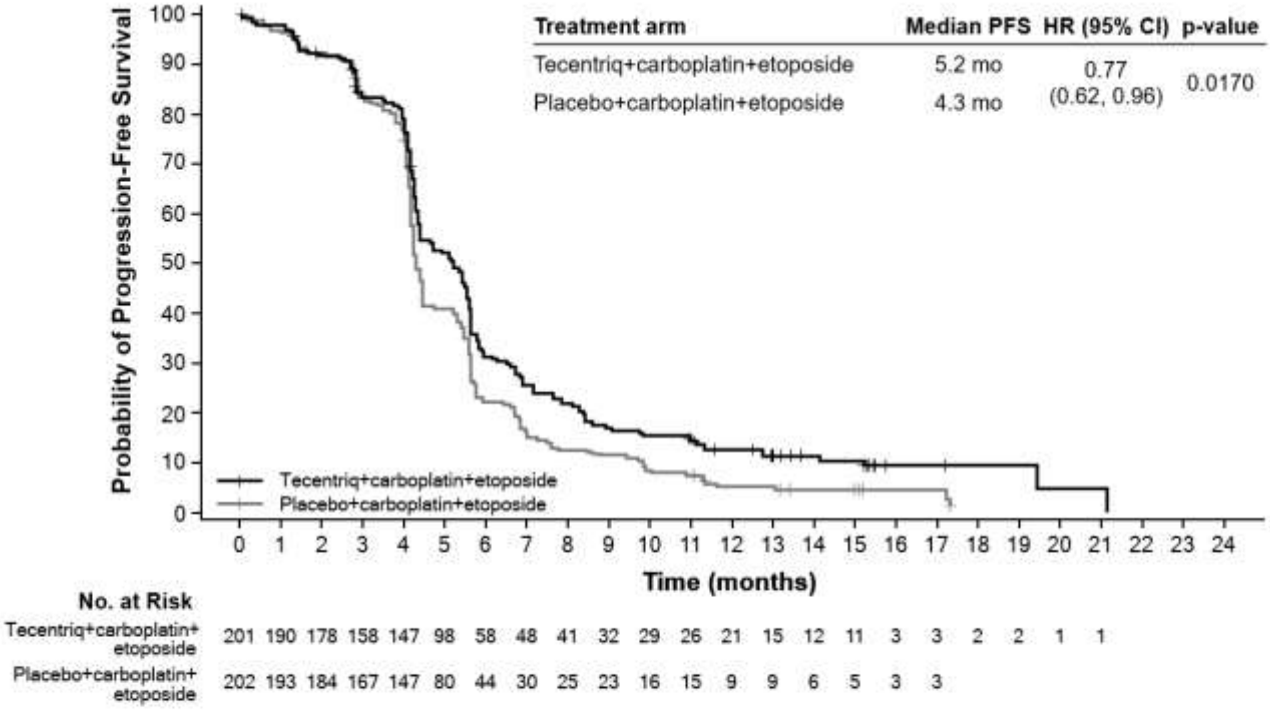


Figure 16: Kaplan-Meier curve for progression-free survival (IMpower133)



Hepatocellular carcinoma

IMbrave150 (YO40245): Randomised phase III trial in patients with unresectable HCC who have not received prior systemic therapy, in combination with bevacizumab

A phase III, randomized, multi-centre, international, open-label study, IMbrave150, was conducted to evaluate the efficacy and safety of atezolizumab in combination with bevacizumab, in patients with locally advanced or metastatic and/or unresectable HCC, who have not received prior systemic treatment. A total of 501 patients were randomized (2:1) to receive either atezolizumab (1 200 mg) and 15 mg/kg bw of bevacizumab every 3 weeks administered by intravenous infusion, or sorafenib 400 mg orally twice per day. Randomization was stratified by geographic region, macrovascular invasion and/or extrahepatic spread, baseline α-fetoprotein (AFP) and ECOG performance status. Patients in both arms received treatment until loss of clinical benefit, or unacceptable toxicity. Patients could discontinue either atezolizumab or bevacizumab (e.g., due to adverse events) and continue on single-agent therapy until loss of clinical benefit or unacceptable toxicity associated with the single-agent.

The study enrolled adults whose disease was not amenable to or progressed after surgical and/or locoregional therapies, were Child-Pugh A, ECOG 0/1, and who had not received prior systemic treatment. Bleeding (including fatal events) is a known adverse reaction with bevacizumab and upper gastrointestinal bleeding is a common and life threatening complication in patients with HCC. Hence, patients were required to be evaluated for the presence of varices within 6 months prior to treatment, and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding or high risk of bleeding. For patients with active hepatitis B, HBV DNA < 500 IU/mL was required within 28 days prior to initiation of study treatment, and standard anti-HBV treatment for a minimum of 14 days prior to study entry and for the length of study.

Patients were also excluded if they had moderate or severe ascites; history of hepatic encephalopathy; known fibrolamellar HCC; sarcomatoid HCC, mixed cholangiocarcinoma and HCC; active co-infection of HBV and HCV; history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to randomization; untreated or corticosteroid-dependent brain metastases. Tumour assessments were performed every 6 weeks for the first 54 weeks following Cycle 1, Day 1, then every 9 weeks thereafter.

The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. The median age was 65 years (range: 26 to 88 years) and 83% were male. The majority of patients were Asian (57%) and white (35%). 40% were from Asia (excluding Japan), while 60% were from rest of world. Approximately 75% of patients presented with macrovascular invasion and/or extrahepatic spread and 37% had a baseline AFP ≥ 400 ng/mL. Baseline ECOG performance status was 0 (62%) or 1 (38%). The primary risk factors for the development of HCC were Hepatitis B virus infection in 48% of patients, Hepatitis C virus infection in 22% of patients, and non-viral disease in 31% of patients. HCC was categorized as Barcelona Clinic Liver Cancer (BCLC) stage C in 82% of patients, stage B in 16% of patients, and stage A in 3% of patients.

The co-primary efficacy endpoints were OS and IRF-assessed PFS according to RECIST v1.1. At the time of the primary analysis, patients had a median survival follow up time of 8.6 months. The data demonstrated a statistically significant improvement in OS and PFS as assessed by IRF per RECIST v1.1 with atezolizumab + bevacizumab compared to sorafenib. A statistically significant improvement was also observed in confirmed objective response rate (ORR) by IRF per RECIST v1.1 and HCC modified RECIST (mRECIST). The key efficacy results from the primary analysis are summarized in Table 19.

A descriptive updated efficacy analysis was performed with a median survival follow up time of 15.6 months. The median OS was 19.2 months (95% CI: 17.0, 23.7) in the atezolizumab + bevacizumab arm versus 13.4 months (95% CI: 11.4, 16.9) in the sorafenib arm with a HR of 0.66 (95% CI: 0.52, 0.85). The median PFS by IRF-assessment per RECIST v1.1 was 6.9 months (95% CI: 5.8, 8.6) in the atezolizumab + bevacizumab arm versus 4.3 months (95% CI: 4.0, 5.6) in the sorafenib arm with a HR of 0.65 (95% CI: 0.53, 0.81).

The IRF-assessed ORR per RECIST v1.1 was 29.8% (95% CI: 24.8, 35.0) in the atezolizumab + bevacizumab arm and 11.3% (95% CI: 6.9, 17.3) in the sorafenib arm. The median duration of response (DOR) by IRF-assessment per RECIST v1.1 in confirmed responders was 18.1 months (95% CI: 14.6, NE) in the atezolizumab + bevacizumab arm compared to 14.9 months (95% CI: 4.9, 17.0) in the sorafenib arm.

Kaplan-Meier curves for OS (updated analysis) and PFS (primary analysis) are presented in Figures 19 and 20, respectively.

Table 19: Summary of efficacy (IMbrave150 primary analysis)

Key efficacy endpoints	Atezolizumab + Bevacizumab		Sorafenib
OS	n=336		n=165
No. of deaths (%)	96 (28.6%)		65 (39.4%)
Median time to event (months)	NE		13.2
95% CI	(NE, NE)		(10.4, NE)
Stratified hazard ratio‡ (95% CI)		0.58 (0.42, 0.79)	
p-value[1]		0.0006	
6-month OS (%)	84.8%		72.3%
IRF-assessed PFS, RECIST 1.1	n=336		n=165
No. of events (%)	197 (58.6%)		109 (66.1%)
Median duration of PFS (months)	6.8		4.3
95% CI	(5.8, 8.3)		(4.0, 5.6)
Stratified hazard ratio‡ (95% CI)		0.59 (0.47, 0.76)	
p-value[1]		<0.0001	
6-month PFS	54.5%		37.2%
IRF-assessed ORR, RECIST 1.1	n=326		n=159
No. of confirmed responders (%)	89 (27.3%)		19 (11.9%)
95% CI	(22.5, 32.5)		(7.4, 18.0)
p-value[2]		<0.0001	
No. of complete responses (%)	18 (5.5%)		0
No. of partial responses (%)	71 (21.8%)		19 (11.9%)
No. of stable disease (%)	151 (46.3%)		69 (43.4%)
IRF-assessed DOR, RECIST 1.1	n=89		n=19
Median in months	NE		6.3
95% CI	(NE, NE)		(4.7, NE)
Range (months)	(1.3+, 13.4+)		(1.4+, 9.1+)

Key efficacy endpoints	Atezolizumab + Bevacizumab		Sorafenib
IRF-assessed ORR, HCC mRECIST	n=325		n=158
No. of confirmed responders (%)	108 (33.2%)		21 (13.3%)
95% CI	(28.1, 38.6)		(8.4, 19.6)
p-value[2]		<0.0001	
No. of complete responses (%)	33 (10.2%)		3 (1.9%)
No. of partial responses (%)	75 (23.1%)		18 (11.4%)
No. of stable disease (%)	127 (39.1%)		66 (41.8%)
IRF-assessed DOR, HCC mRECIST	n=108		n=21
Median in months	NE		6.3
95% CI	(NE, NE)		(4.9, NE)
Range (months)	(1.3+, 13.4+)		(1.4+, 9.1+)

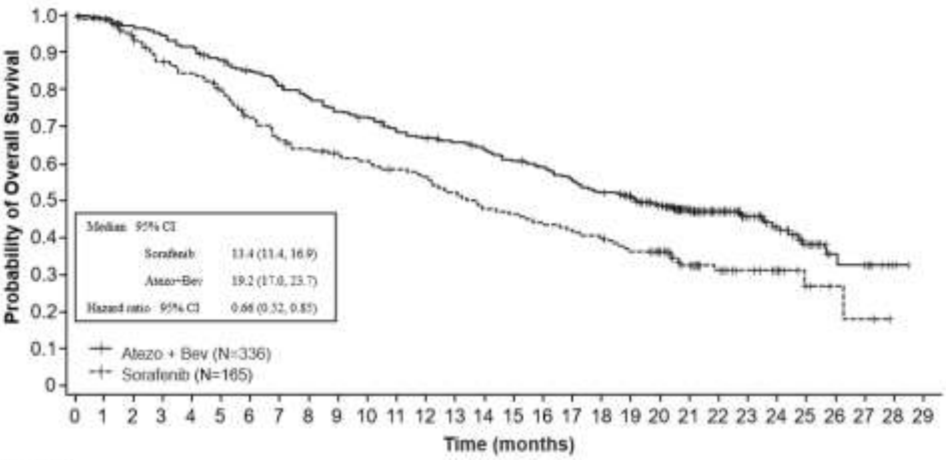
‡ Stratified by geographic region (Asia excluding Japan vs rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥400 ng/mL)

1. Based on two-sided stratified log-rank test
2. Nominal p-values based on two-sided Cochran-Mantel-Haenszel test

+ Denotes a censored value

PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1; HCC mRECIST = Modified RECIST Assessment for Hepatocellular Carcinoma ; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival; NE=not estimable

Figure 19: Kaplan-Meier curve for OS in the ITT population (IMbrave150 updated analysis)

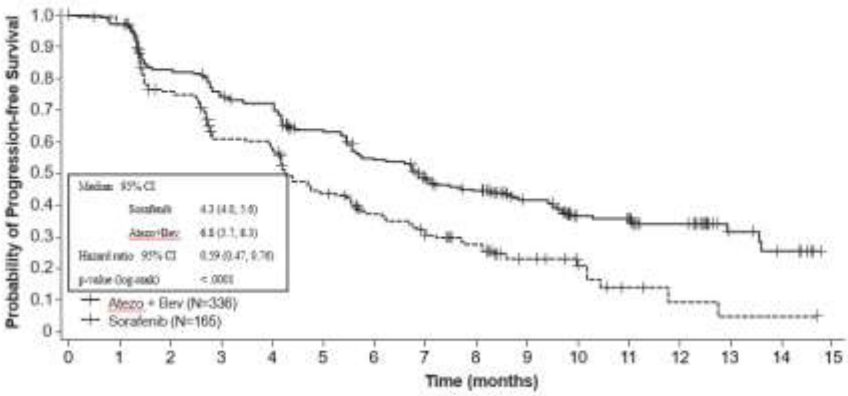


No. of Patients at Risk

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

Hazard ratio is from stratified analysis. Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs absence) and AFP (<400 vs >=400 ng/ml) at screening per IxRS.

Figure 20: Kaplan-Meier curve for IRF-PFS per RECIST v1.1 in the ITT population (IMbrave150 primary analysis)



No. of Patients at Risk

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Atezo + Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE

Hazard ratio and p-value are from stratified analysis.
Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs absence) and AFP (<400 vs >=400 ng/ml) at screening per IxRS

Efficacy in elderly

No overall differences in efficacy were observed between patients ≥ 65 years of age and younger patients receiving atezolizumab monotherapy. In study IMpower150, age ≥ 65 was associated with a diminished effect of atezolizumab in patients receiving atezolizumab in combination with carboplatin and paclitaxel.

In studies IMpower150, IMpower133 and IMpower110, data for patients ≥ 75 years of age are too limited to draw conclusions on this population.

Paediatric population

An early phase, multi-centre open-label study was conducted in paediatric (< 18 years, n=69) and young adult patients (18-30 years, n=18) with relapsed or progressive solid tumours as well as with Hodgkin’s and non-Hodgkin’s lymphoma, to evaluate the safety and pharmacokinetics of atezolizumab. Patients were treated with 15 mg/kg bw atezolizumab intravenously every 3 weeks (see section 5.2).

5.2 Pharmacokinetic properties

Exposure to atezolizumab increased dose proportionally over the dose range 1 mg/kg bw to 20 mg/kg bw 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 bw with a linear two-compartment disposition model with first-order elimination. The pharmacokinetic properties of 840 mg intravenous atezolizumab administered every 2 weeks, 1200 mg administered every 3 weeks, and 1680 mg administered every 4 weeks are the same; comparable total exposures are expected to be achieved with these three dosing regimens. A population pharmacokinetic analysis suggests that steady-state is obtained after 6 to 9 weeks of multiple 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

The pharmacokinetic results from one early-phase, multi-centre open-label study that was conducted in paediatric (< 18 years, n=69) and young adult patients (18-30 years, n=18), show that the clearance and volume of distribution of atezolizumab were comparable between paediatric patients receiving 15 mg/kg bw and young adult patients receiving 1 200 mg of atezolizumab every 3 weeks when normalized by body weight, with exposure trending lower in paediatric patients as body weight decreased. These differences were not associated with a decrease in atezolizumab concentrations below the therapeutic target exposure. Data for children < 2 years is limited thus no definitive conclusions can be made.

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 observed in patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 × to 1.5 × ULN and any AST) or moderate hepatic impairment (bilirubin > 1.5 to 3x ULN and any AST) in comparison to patients with normal hepatic function (bilirubin ≤ ULN and AST ≤ ULN). No data are available in patients with severe hepatic impairment (bilirubin > 3 X ULN and any AST). Hepatic impairment was defined by the National Cancer Institute-Organ Dysfunction Working Group (NCI-ODWG) criteria of hepatic dysfunction (see section 4.2). The effect of severe hepatic impairment (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-mediated 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

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 up to 24 hours at ≤ 30 °C and for up to 30 days at 2 °C to 8 °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) unless dilution has taken place in controlled and validated aseptic conditions.

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 and an aluminium seal with a plastic grey or aqua flip-off cap containing 14 mL or 20 mL of concentrate solution for infusion.

Pack of one vial.

6.6 Special precautions for disposal and other handling

Tecentriq does not contain any antimicrobial preservative or bacteriostatic agents and should be prepared by a healthcare professional using aseptic technique to ensure the sterility of prepared solutions. Use a sterile needle and syringe to prepare Tecentriq.

<u>Aseptic preparation, handling and storage</u>

Aseptic handling must be ensured when preparing the infusion. Preparation should be:

- performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.
- prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.
- followed by adequate storage of the prepared solution for intravenous infusion to ensure maintenance of the aseptic conditions.

Do not shake.

<u>Instructions for dilution</u>

For the recommended dose of 840 mg: fourteen mL of Tecentriq concentrate should be withdrawn from the vial and diluted into a polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), or polypropylene (PP) infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection.

For the recommended dose of 1 200 mg: twenty mL of Tecentriq concentrate should be withdrawn from the vial and diluted into a polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE) or polypropylene (PP) infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection.

For the recommended dose of 1 680 mg: twenty-eight mL of Tecentriq concentrate should be withdrawn from two vials of Tecentriq 840 mg and diluted into a polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), or polypropylene (PP) infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection.

After dilution, the final concentration of the diluted solution should be between 3.2 and 16.8 mg/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 Tecentriq and intravenous bags with product-contacting surfaces of PVC, PO, PE, or PP. 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.

Do not co-administer other medicinal products through the same infusion line.

<u>Disposal</u>

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

7. MARKETING AUTHORISATION HOLDER

F. Hoffmann-La Roche Ltd
124 Grenzacherstrasse
CH-4070 Basel
Switzerland