AUSTRALIAN PRODUCT INFORMATION
Tecentriq® (atezolizumab)

1 NAME OF THE MEDICINE

Atezolizumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tecentriq 840 mg/14 mL concentrated injection
Each vial of 14 mL contains 840 mg of atezolizumab at a concentration of 60 mg/mL.

Tecentriq 1200 mg/20 mL concentrated injection
Each vial of 20 mL contains 1200 mg of atezolizumab at a concentration of 60 mg/mL.

For the full list of excipients, see section *6.1 List of excipients*.

3 PHARMACEUTICAL FORM

Concentrated injection for intravenous infusion. Tecentriq is supplied as a single-use vial containing either 14 mL or 20 mL preservative-free, colourless to slightly yellow solution, at a concentration of 60 mg/mL.

Tecentriq IV formulation is not intended for subcutaneous administration. For information about the subcutaneous dosage form of Tecentriq please see the separate Tecentriq SC Product Information.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Early-stage non-small cell lung cancer

Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and no progression after platinum-based adjuvant chemotherapy for adult patients with stage II to IIIA (as per 7th edition of the UICC/AJCC staging system) NSCLC whose tumours have PD-L1 expression on ≥ 50% of tumour cells.

Metastatic non-small cell lung cancer

Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (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.

Tecentriq, in combination with nanoparticle albumin-bound paclitaxel (nab-paclitaxel) and carboplatin, is indicated for first-line treatment of patients with metastatic non-squamous NSCLC who do not have tumour EGFR or ALK genomic aberrations.

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.

Small cell lung cancer

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

Urothelial carcinoma

Tecentriq is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are considered cisplatin ineligible and whose tumours express PD-L1 (PD-L1 stained tumour-infiltrating immune cells [IC] covering ≥ 5% of the tumour area), as determined by a validated test.

This indication is approved based on overall response rate and duration of response in a single-arm study. Improvements in overall survival, progression-free survival, or health-related quality of life have not been established.

Hepatocellular carcinoma

Tecentriq, in combination with bevacizumab, is indicated for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

4.2 Dose and method of administration

General

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

Tecentriq must be administered as an intravenous (IV) infusion. Do not administer as an IV push or bolus.

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

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

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 medical record.

Atezolizumab was originally developed using an every-three-weeks monotherapy dosing regimen (see Section *5.1 Pharmacodynamic properties, Clinical Trials*). Subsequent approval of the every-two-weeks and every-four-weeks dosing regimens were based on pharmacokinetic and exposure-response modelling and simulations. Data from randomised controlled trials of every-two-weeks or every-four-weeks versus every-three-weeks dosing of atezolizumab, with sufficient sample size to demonstrate non-inferiority using clinical endpoint data (such as PFS or OS), is not available.

Patients currently receiving subcutaneous Tecentriq

Patients currently receiving subcutaneous Tecentriq can switch to intravenous Tecentriq (or vice versa).

Dose

Tecentriq monotherapy

Patient selection for urothelial carcinoma
Select cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial carcinoma for treatment with Tecentriq based on the PD-L1 expression on tumour infiltrating immune cells confirmed by a validated test (see section *5.1 Pharmacodynamic properties, Clinical Trials*).

Table 1. Recommended Dosage of Tecentriq as Monotherapy

Indication	**Recommended Dosage of Tecentriq**	**Duration of Therapy**
Urothelial carcinoma	• 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks	Until disease progression or unacceptable toxicity
Metastatic NSCLC	• 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks	Until disease progression or unacceptable toxicity
Early Stage NSCLC	• 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks	Patients are treated with Tecentriq for 1 year unless there is disease recurrence or unacceptable toxicity

Tecentriq in combination therapy
Please also refer to the Product Information for the combination products.

Table 2. Recommended Dosage of Tecentriq in Combination Therapy

Tecentriq recommended dosage regimen		
Tecentriq dosage is any one of: • 840 mg every 2 weeks, or • 1200 mg every 3 weeks, or • 1680 mg every 4 weeks		
Recommended dosage in indications with combination therapies		
Indication	**Recommended Dosage**	**Duration of therapy**
NSCLC (in combination with bevacizumab, paclitaxel and carboplatin)	Induction phase: Tecentriq per recommended dosage regimen Tecentriq should be administered first when given on the same day as combination partners Bevacizumab, paclitaxel, then carboplatin every 3 weeks for 4 or 6 cycles Maintenance phase (without chemotherapy): Tecentriq per recommended dosage regimen Bevacizumab every 3 weeks	Until loss of clinical benefit or unmanageable toxicity

NSCLC (in combination with nab-paclitaxel and carboplatin)	Induction phase: Tecentriq per recommended dosage regimen Tecentriq should be administered first when given on the same day as combination partners Nanoparticle albumin-bound paclitaxel (nab-paclitaxel), then carboplatin every 3 weeks for 4 or 6 cycles For each three week cycle: Day 1: Tecentriq, nab-paclitaxel and carboplatin Day 8 and Day 15: nab-paclitaxel Maintenance phase (without chemotherapy): Tecentriq per recommended dosage regimen	Until loss of clinical benefit or unmanageable toxicity
SCLC (in combination with carboplatin and etoposide)	Induction phase: Tecentriq per recommended dosage regimen Tecentriq should be administered first when given on the same day as combination partners Carboplatin then etoposide every 3 weeks for 4 cycles: Day 1: carboplatin then etoposide Day 2 and Day 3: etoposide Maintenance phase (without chemotherapy): Tecentriq per recommended dosage regimen	Until loss of clinical benefit or unmanageable toxicity
HCC (in combination with bevacizumab)	Tecentriq per recommended dosage regimen Tecentriq should be administered first when given on the same day as combination partners Bevacizumab 15 mg/kg once every 3 weeks	Until loss of clinical benefit or unmanageable toxicity

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

Dose reductions of Tecentriq are not recommended.

Dose delay or discontinuation

See also sections *4.4 Special warnings and precautions for use* and *4.8 Adverse effects (Undesirable effects)*.

Table 3. Dose modification advice for Tecentriq

Adverse reaction	Severity	Treatment modification
Immune-mediated 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
Immune-mediated hepatitis in patients without HCC*	Grade 2: (ALT or AST >3 to 5x ULN *or* blood bilirubin >1.5 to 3x 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 >5x ULN *or* blood bilirubin >3x ULN)	Permanently discontinue Tecentriq
Immune-mediated hepatitis in patients with HCC*	If AST/ALT is within normal limits at baseline and increases to >3x to ≤10x ULN *or* If AST/ALT is >1 to ≤3x ULN at baseline and increases to >5x to ≤10x ULN *or* If AST/ALT is >3x to ≤5x ULN at baseline and increases to >8x to ≤10x ULN	Withhold Tecentriq Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤10 mg prednisone or equivalent per day
	If AST/ALT increases to >10x ULN or total bilirubin increases to >3x ULN	Permanently discontinue
Immune-mediated 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;	Permanently discontinue Tecentriq

Adverse reaction	Severity	Treatment modification
	urgent intervention indicated)	
Immune-mediated hypothyroidism or hyperthyroidism	Symptomatic	Withhold[1] 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
Immune-mediated 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 the patient is stable on replacement therapy
Immune-mediated 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 the patient is stable on replacement therapy
	Grade 4	Permanently discontinue Tecentriq
Immune-mediated Type 1 diabetes mellitus	Grade 3 or 4 hyperglycaemia (fasting glucose greater than 13.9 mmol/L)	Withhold[1] Tecentriq Treatment may be resumed when metabolic control is achieved on insulin replacement therapy
Immune-mediated meningitis, encephalitis, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome	All grades	Permanently discontinue Tecentriq
Immune-mediated myelitis	Grade 2, 3 or 4	Permanently discontinue Tecentriq
Immune-mediated facial paresis	Grade 1 or 2	Withhold Tecentriq Treatment may be resumed when symptoms 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
Immune-mediated myocarditis	Grade 2 or above	Permanently discontinue Tecentriq
	Grade 1 pericarditis	Withhold Tecentriq[3]

Adverse reaction	Severity	Treatment modification
Immune-mediated pericardial disorders	Grade 2 or above	Permanently discontinue Tecentriq
Immune-mediated myositis	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
	Grade 4 or grade 3 recurrent myositis	Permanently discontinue Tecentriq
Immune-mediated nephritis	Grade 2: (creatinine level >1.5 to 3x baseline or >1.5 - 3x 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: (creatinine level >3x baseline or >3x ULN) Grade 4: (creatinine level >6x ULN)	Permanently discontinue Tecentriq
Immune-mediated pancreatitis	Grade 3 or 4 serum amylase or lipase levels increased (>2x 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
Infusion-related reactions	Grade 1 or 2	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved Premedication with antipyretic and antihistamines may be considered for subsequent doses
	Grade 3 or 4	Permanently discontinue Tecentriq
Haemophagocytic lymphohistiocytosis	Suspected haemophagocytic lymphohistiocytosis[2]	Permanently discontinue Tecentriq
Rash/Severe cutaneous adverse reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[2]	Withhold Tecentriq Treatment may be resumed when rash 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 or confirmed Stevens-Johnson syndrome (SJS) or toxic	Permanently discontinue Tecentriq

Adverse reaction	Severity	Treatment modification
	epidermal necrolysis (TEN)[2]	
Other immune-mediated adverse reactions	Grade 2 or Grade 3	Withhold Tecentriq until adverse reactions recover to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤10 mg prednisone or equivalent per day
	Grade 4 or recurrent Grade 3	Permanently discontinue Tecentriq (except endocrinopathies controlled with replacement hormones)

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.0 (NCI-CTCAE v.4.).
[*] HCC: hepatocellular carcinoma
[1] Treatment with Tecentriq may be resumed when symptoms are controlled and the patient is clinically stable.
[2] Regardless of severity
[3] Conduct a detailed cardiac evaluation to determine the aetiology and manage appropriately

Patients treated with Tecentriq must be given the Patient Alert Card and be informed about the risks of Tecentriq.

Special dosage instructions

Paediatric use

The safety and efficacy of Tecentriq in children and adolescents below 18 years of age have not been established. Available safety data are described in section 4.4.

Use in the elderly

Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq is required in patients ≥ 65 years of age (see sections *4.4 Special warnings and precautions for use* and *5.2 Pharmacokinetic properties*).

Use in Asian patients

Due to increased haematologic toxicities observed in Asian patients in study GO29436 (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 sections *4.4 Special warnings and precautions for use* and *5.2 Pharmacokinetic properties*). 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 sections 4.4 *Special warnings and precautions for use* and 5.2 *Pharmacokinetic properties*).

Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2

Patients with ECOG performance status ≥ 2 were excluded from the clinical trials in NSCLC, ES-SCLC and HCC (see sections *4.4 Special warnings and precautions for use* and *5.1 Pharmacodynamic properties*).

Instructions for dilution

Tecentriq does not contain any antimicrobial preservative and should be prepared by a healthcare professional using aseptic technique. Use a sterile needle and syringe to prepare Tecentriq.

Withdraw the required volume of Tecentriq concentrate from the vial and dilute to the required administration volume in a polyvinyl chloride (PVC), polyethylene (PE), polyolefin 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 mg/mL and 16.8 mg/mL. The bag should be gently inverted to mix the solution in order to avoid foaming.

Tecentriq must not be mixed with other medicinal products.

Instructions for administration

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.

The product is for single use in one patient only. Discard any residue.

Tecentriq must not be mixed with other medicinal products.

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

4.3 Contraindications

Tecentriq is contraindicated in patients with a known hypersensitivity to atezolizumab or any of the excipients.

4.4 Special warnings and precautions for use

Assessment of PD-L1 status

When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is chosen to minimise false negative or false positive determinations.

Immune-mediated adverse reactions

Most immune-mediated adverse reactions occurring during treatment with Tecentriq were reversible with interruptions of Tecentriq 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 Tecentriq may occur after the last dose of Tecentriq. For suspected immune-mediated adverse reactions, a thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, Tecentriq should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroids should be tapered over ≥ 1 month. Based on limited data from clinical studies in patients whose immune-mediated adverse reactions could not be controlled with

systemic corticosteroid use, administration of other systemic immunosuppressants may be considered.

Tecentriq must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs; for any Grade 4 immune-mediated adverse reactions(except for endocrinopathies that are controlled with replacement hormones); and for some Grade 2 and 3 immune-mediated adverse reactions (see sections *4.2 Dose and method of administration* and *4.8 Adverse effects (Undesirable effects)*).

Immune-mediated pneumonitis

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

Treatment with Tecentriq should be withheld for Grade 2 pneumonitis, and 1 to 2 mg/kg prednisone or equivalent per day should be started. If symptoms improve to ≤ Grade 1, taper corticosteroids over ≥ 1 month. Treatment with Tecentriq 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 Tecentriq 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 Tecentriq (see section *4.8 Adverse effects (Undesirable effects)*). Patients should be monitored for signs and symptoms of hepatitis. Monitor aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin prior to and periodically during treatment with Tecentriq. Appropriate management of patients with abnormal liver function tests (LFTs) at baseline should be considered.

Treatment with Tecentriq should be withheld if Grade 2 (ALT or AST > 3 to 5 x ULN or blood bilirubin > 1.5 to 3.0 x ULN) persists for more than 5 to 7 days, and 1 to 2 mg/kg prednisone or equivalent per day should be started. If the event improves to ≤ Grade 1, taper corticosteroids over ≥ 1 month.

Treatment with Tecentriq 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 Tecentriq must be permanently discontinued for Grade 3 or Grade 4 events (ALT or AST > 5.0 x ULN or blood bilirubin > 3 x ULN).

Immune-mediated colitis

Cases of diarrhoea or colitis have been observed in clinical trials with Tecentriq (see section *4.8 Adverse effects (Undesirable effects)*). Patients should be monitored for signs and symptoms of colitis. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis.

Treatment with Tecentriq 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, start 1 - 2 mg/kg prednisone or equivalent per day. Treat Grade 3 diarrhoea or colitis with IV corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent). Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, taper corticosteroids over ≥ 1 month. Treatment

with Tecentriq 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 Tecentriq must be permanently discontinued for Grade 4 (life threatening; urgent intervention indicated) diarrhoea or colitis.

Immune-mediated endocrinopathies

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

Patients should be monitored for clinical signs and symptoms of endocrinopathies and for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation). Patients may present with the following: fatigue, headache, mental status changes, heat or cold intolerance, tachycardia or bradycardia, unusual bowel habits, weight change, polyuria/polydipsia, blurred vision. Unless an alternative aetiology has been identified, signs and symptoms of endocrinopathies should be conservatively considered immune-mediated. Appropriate management of patients with abnormal thyroid function tests at baseline should be considered.

Asymptomatic patients with abnormal thyroid function tests can receive Tecentriq. For symptomatic hypothyroidism, Tecentriq 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, Tecentriq should be withheld and an anti-thyroid drug should be initiated as needed. Treatment with a beta blocker may also be considered. Treatment with Tecentriq may be resumed when symptoms are controlled and thyroid function is improving.

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

Treatment with Tecentriq should be withheld for Grade 2 or Grade 3 hypophysitis. Treatment with intravenous corticosteroids (1 to 2 mg/kg per day IV methylprednisolone or equivalent) should be started, and hormone replacement should be initiated as needed. Once symptoms improve, treatment with 1 to 2 mg/kg per 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 per day prednisone or equivalent and the patient is stable on replacement therapy (if required). Treatment with Tecentriq 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 greater than 13.9 mmol/L), Tecentriq should be withheld. Treatment with Tecentriq may be resumed if metabolic control is achieved on insulin replacement therapy.

Immune-mediated meningoencephalitis

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

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

Immune-mediated neuropathies

Myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome, which may be life-threatening, and facial paresis were observed in patients receiving Tecentriq (see section *4.8 Adverse effects (Undesirable effects)*). Patients should be monitored for symptoms of motor and sensory neuropathy.

Treatment with Tecentriq must be permanently discontinued for any grade of myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg oral prednisone or equivalent per day.

Treatment with Tecentriq must be permanently discontinued for Grade 3 or 4 facial paresis. Treatment with Tecentriq should be withheld for Grade 1 or 2 facial paresis, and treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) should be considered. Treatment may be resumed when symptoms improve to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day.

Immune-mediated myelitis

Myelitis has been observed in clinical trials with Tecentriq (see section *4.8 Adverse effects (Undesirable effects)*). Patients should be closely monitored for signs and symptoms that are suggestive of myelitis. Treatment with Tecentriq must be permanently discontinued for Grade 2, 3 or 4 myelitis.

Immune-mediated pancreatitis

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

Treatment with Tecentriq should be withheld for ≥ Grade 3 serum amylase or lipase levels increased (> 2.0 ULN), or Grade 2 or 3 pancreatitis, and treatment with intravenous corticosteroids (1 to 2 mg/kg methylprednisolone or equivalent per day), should be started. Once symptoms improve, follow with 1 to 2 mg/kg oral prednisone or equivalent per day. Treatment with Tecentriq 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 Tecentriq should be permanently discontinued for Grade 4, or any grade of recurrent pancreatitis.

Haemophagocytic lymphohistiocytosis

Haemophagocytic lymphohistiocytosis (HLH), including fatal cases, has been reported in patients receiving Tecentriq (see section *4.8 Adverse effects (Undesirable effects)*). 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. Treatment with

Tecentriq must be permanently discontinued for suspected haemophagocytic lymphohistiocytosis.

Immune-mediated myocarditis

Myocarditis, including fatal cases, has been observed in clinical trials with Tecentriq (see section *4.8 Adverse effects (Undesirable effects)*). Patients should be monitored for signs and symptoms of myocarditis. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly.

Treatment with Tecentriq should be withheld for suspected myocarditis and treatment with systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent should be started. Treatment with Tecentriq must be permanently discontinued for Grade 2 or above myocarditis.

Immune-mediated myositis

Cases of myositis, including fatal cases, have been observed in clinical trials with Tecentriq (see section *4.8 Adverse effects (Undesirable effects)*). Patients should be monitored for signs and symptoms of myositis. Patients with possible myositis should be monitored for signs of myocarditis.

Treatment with Tecentriq should be withheld for Grade 2 or 3 myositis and corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) should be initiated. If symptoms improve to ≤ Grade 1, taper corticosteroids as clinically indicated. Treatment with Tecentriq 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 Tecentriq should be permanently discontinued for Grade 4 or Grade 3 recurrent myositis.

Immune-mediated pericardial disorders

Pericardial disorders, including pericarditis, pericardial effusion and cardiac tamponade, some leading to fatal outcomes, have been observed in clinical trials with Tecentriq (see section *4.8 Adverse effects (Undesirable effects)* and *Postmarketing Experience*). Patients should be monitored for clinical signs and symptoms of pericardial disorders.

For suspected Grade 1 pericarditis, treatment with Tecentriq should be withheld and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. For suspected Grade 2, 3 or 4 pericardial disorders, treatment with Tecentriq should be withheld, prompt treatment with systemic corticosteroids at a dose of 1 to 2 mg/kg/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 Tecentriq must be permanently discontinued for Grade 2, 3 or 4 pericardial disorders.

Immune-mediated nephritis

Nephritis has been observed in clinical trials with Tecentriq (see section *4.8 Adverse effects (Undesirable effects)*). Patients should be monitored for changes in renal function.

Treatment with Tecentriq should be withheld for Grade 2 nephritis. Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) should be initiated. Treatment with Tecentriq may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg prednisone or equivalent per day. Tecentriq must be permanently discontinued for Grade 3 or 4 nephritis.

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 Tecentriq. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, Tecentriq should be withheld for Grade 3 skin reactions and treatment with systemic corticosteroids at a dose of 1-2 mg/kg/day of prednisone or equivalent should be initiated. 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 Tecentriq should be permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered at a dose of 1-2 mg/kg/day of prednisone or equivalent .

For suspected SCARs, patients should be referred to a specialist for further diagnosis and management. Tecentriq should be withheld for patients with suspected SJS or TEN. For confirmed SJS or TEN, Tecentriq should be permanently discontinued.

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

Autoimmune haemolytic anaemia

Tecentriq can cause autoimmune haemolytic anaemia (AIHA). Patients should be monitored for signs and symptoms of drug-induced AIHA, and if this adverse reaction is observed, administration of Tecentriq should be permanently discontinued. Treatment for AIHA should be initiated, as deemed medically appropriate.

Infusion-related reactions

Infusion-related reactions (IRRs), including hypersensitivity and anaphylaxis, have been observed in clinical trials with Tecentriq (see section *4.8 Adverse effects (Undesirable effects)*).

The rate of infusion should be reduced or treatment should be interrupted in patients with Grade 1 or 2 infusion-related reactions. Tecentriq 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 Tecentriq with close monitoring; premedication with an antipyretic and antihistamines may be considered.

Other immune-mediated adverse reactions

The following additional clinically significant, immune-mediated adverse reactions have been reported in clinical studies with Tecentriq: uveitis (see section 4.8). Refer to section 4.2 for recommended dose modifications (follow dose modification recommendations for 'other immune-mediated adverse reactions').

Cases of haemolytic anaemia and aplastic anaemia have been observed during treatment with immune checkpoint inhibitors. Patients should be monitored for signs and symptoms indicative of these immune-mediated adverse reactions.

Patients with pre-existing autoimmune disease (AID)

In patients with pre-existing autoimmune disease (AID), data from observational studies suggest that the risk of immune-mediated adverse reactions following immune checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing

AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.

Disease-specific precautions

Patients excluded from clinical trials

Patients with the following conditions were excluded from clinical trials: history of autoimmune disease, history of pneumonitis, active brain metastasis, HIV, hepatitis B or hepatitis C infection. Patients who were administered a live, attenuated vaccine within 28 days prior to enrolment; systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to study entry were excluded from clinical trials.

Patients with a baseline performance status ≥ 2 were excluded (apart from Study GO29293 [IMvigor210] Cohort 1 that enrolled patients with cisplatin-ineligible urothelial carcinoma and allowed a baseline performance status ≥ 2) (see section *5.1 Pharmacodynamic properties*).

Use of Tecentriq 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 Tecentriq, bevacizumab, paclitaxel, and carboplatin before initiating treatment (see section *4.8 Adverse effects (Undesirable effects)*).
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 study 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, Tecentriq should be used with caution in these populations after careful evaluation of the balance of benefits and risks for the patient.

Use of Tecentriq in urothelial carcinoma 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 Tecentriq 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 Tecentriq in combination with bevacizumab in hepatocellular carcinoma

Bleeding (including fatal events) is a known adverse reaction with bevacizumab. Serious bleeding events, including fatalities, have occurred in hepatocellular cancer patients treated with the combination of Tecentriq and bevacizumab.

There is lack of clinical data to support the combination of Tecentriq and bevacizumab in hepatocellular cancer patients with bleeding varices (including recent bleeds), untreated varices or varices at high risk of bleeding because these patients were excluded from treatment with Tecentriq and bevacizumab in the IMbrave150 pivotal study (see section *5.1 Pharmacodynamic properties; Clinical Trials*).

Carefully consider the risks of Tecentriq plus bevacizumab in patients with HCC before initiating treatment. Patients with HCC should be evaluated for the presence of varices and have

varices treated as indicated within 6 months prior to initiating therapy with the combination of Tecentriq and bevacizumab.

Refer to the bevacizumab Product Information for full prescribing information on the risks of bleeding events.

Use in hepatic impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild or moderate hepatic impairment (see sections *4.2 Dose and method of administration* and *5.2 Pharmacokinetic properties*). There are no data in patients with moderate or severe hepatic impairment.

Use in renal impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with mild or moderate renal impairment (see sections *4.2 Dose and method of administration* and *5.2 Pharmacokinetic properties*). Data from patients with severe renal impairment are too limited to draw conclusions on this population.

Use in the elderly

No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients (see sections *4.2 Dose and method of administration* and *5.2 Pharmacokinetic properties*).

Paediatric use

Tecentriq is not approved for use in patients under the age of 18 years. The safety and efficacy of Tecentriq in the population has not been established. An early phase study conducted in paediatric and young adult patients did not demonstrate clinical benefit of atezolizumab.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

No formal pharmacokinetic drug-drug interaction studies have been conducted with Tecentriq. Since Tecentriq 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.

4.6 Fertility, pregnancy and lactation

Effects on 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. Atezolizumab had an effect on menstrual cycles in all female monkeys in the 50 mg/kg/week dose group characterised by an irregular cycle pattern during the dosing phase and correlated with the lack of fresh corpora lutea in the ovaries at the terminal necropsy; this effect was reversible during the dose-free recovery period. The AUC at the no effect level

(15mg/kg/week) was approximately 3.5 times that anticipated in patients at the clinical dose yielding the highest exposure. There was no effect on the male reproductive organs.

Use in pregnancy - Category D

Based on the mechanism of action, the use of Tecentriq may cause foetal harm. Administration of Tecentriq is expected to have an adverse effect on pregnancy and poses a risk to the human foetus, including embryofoetal lethality. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to an increased risk of immune-mediated rejection of the developing foetus resulting in foetal death.

No dedicated reproductive or teratogenicity studies in animals have been conducted with atezolizumab.

There are no clinical studies of Tecentriq in pregnant women. Tecentriq is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. Pregnant women should be advised of the potential risk to the foetus.

Women of childbearing potential should use highly effective contraception during treatment with Tecentriq and for 5 months after the last dose.

The safety of Tecentriq during labor and delivery has not been established.

Use in lactation

It is not known whether atezolizumab is excreted in human breast milk. No studies have been conducted to assess the impact of atezolizumab on milk production or its presence in breast milk. As the potential for harm to the nursing infant is unknown, a decision must be made to either discontinue breast-feeding or discontinue Tecentriq therapy.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and to use machines have been performed. 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.

4.8 Adverse effects (Undesirable effects)

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 <1/1000), very rare (<1/10,000).

Tecentriq monotherapy

The safety of Tecentriq as a monotherapy is based on pooled data in 3178 patients across multiple tumour types with supporting data from the estimated cumulative exposure in > 13,000 patients across all clinical trials. The most common adverse reactions (> 10%) were fatigue (35.9%), decreased appetite (25.5%), nausea (23.5%), cough (20.8%), dyspnoea (20.5%), pyrexia (20.1%), diarrhoea (19.7%), rash (19.3%), musculoskeletal pain (15.4%), back pain (15.3%), vomiting (15.0%), asthenia (14.5%), arthralgia (13.9%), pruritus (12.6%), headache (11.1%) and urinary tract infection (11.6%).

Table 4 summarises the adverse drug reactions (ADRs) that have been reported in association with the use of Tecentriq monotherapy.

Table 4. Summary of ADRs occurring in patients treated with Tecentriq monotherapy in clinical trials

System Organ Class/ADR (MedDRA preferred term)	Tecentriq (n = 3178)			
	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
Blood and Lymphatic System Disorders				
Thrombocytopenia[n]	116 (3.7%)	27 (0.8%)	0 (0%)	Common
Haemophagocytic lymphohistiocytosis[ff]	1 (<0.1%)	0 (0%)	1 (<0.1%)	Rare
Neutropenia[ll]	49 (1.5%)	21 (0.7%)	1 (0.1%)	Common
Cardiac Disorders				
Myocarditis[a]	-	-	-	Rare
Pericardial disorders[ee, ff]	45 (1.4%)	22 (0.7%)	2 (<0.1%)	Common
Endocrine Disorders				
Hypothyroidism[b]	164 (5.2%)	6 (0.2%)	0 (0%)	Common
Hyperthyroidism[c]	30 (0.9%)	1 (< 0.1%)	0 (0%)	Uncommon
Adrenal insufficiency[d]	11 (0.3%)	2 (< 0.1%)	0 (0%)	Uncommon
Hypophysitis[y]	2 (< 0.1%)	0 (0%)	0 (0%)	Rare
Diabetes mellitus[e]	10 (0.3%)	6 (0.2%)	0 (0%)	Uncommon
Eye Disorders				
Uveitis	3 (< 0.1%)	0 (0%)	0 (0%)	Rare
Gastrointestinal Disorders				
Diarrhoea[o]	626 (19.7%)	36 (1.1%)	0 (0%)	Very Common
Dysphagia	82 (2.6%)	16 (0.5%)	0 (0%)	Common
Colitis[f]	34 (1.1%)	18 (0.6%)	0 (0%)	Common
Nausea	747 (23.5%)	35 (1.1%)	0 (0%)	Very Common
Vomiting	477 (15.0%)	26 (0.8%)	0 (0%)	Very Common
Abdominal pain	268 (8.4%)	34 (1.1%)	0 (0%)	Common
Pancreatitis[g]	18 (0.6%)	13 (0.4%)	0 (0%)	Uncommon
Oropharyngeal pain[q]	131 (4.1%)	0 (0%)	0 (0%)	Common
Dry mouth	154 (4.8%)	0 (0%)	0 (0%)	Common
General Disorders and Administration Site Conditions				
Chills	207 (6.5%)	2 (< 0.1%)	0 (0%)	Common
Fatigue	1142 (35.9%)	109 (3.4%)	0 (0%)	Very Common
Asthenia	461 (14.5%)	63 (2.0%)	0 (0%)	Very Common
Influenza like illness	186 (5.9%)	1 (< 0.1%)	0 (0%)	Common
Pyrexia	638 (20.1%)	17 (0.5%)	0 (0%)	Very Common
Hepatobiliary Disorders				
ALT increased	167 (5.3%)	46 (1.4%)	0 (0%)	Common
AST increased	180 (5.7%)	46 (1.4%)	0 (0%)	Common
Hepatitis[i]	62 (2.0%)	25 (0.8%)	2 (< 0.1%)	Common
Immune System Disorders				
Infusion related reaction[h]	32 (1.0%)	4 (0.1%)	0 (0%)	Common
Hypersensitivity	36 (1.1%)	3 (< 0.1%)	0 (0%)	Common
Sarcoidosis[ii]	-	-	-	Very rare

System Organ Class/ADR (MedDRA preferred term)	Tecentriq (n = 3178)			
	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
Infections and Infestations				
Urinary tract infection[p]	368 (11.6%)	86 (2.7%)	0 (0%)	Very Common
Cytomegalovirus infection	1 (<0.1%)	0 (0%)	0 (0%)	Rare
Investigations				
Blood creatine phosphokinase increased	6 (0.2%)	3 (<0.1%)	0 (0%)	Uncommon
Metabolism and Nutrition Disorders				
Decreased appetite	810 (25.5%)	35 (1.1%)	0 (0%)	Very Common
Hypokalemia[v]	142 (4.5%)	33 (1.0%)	0 (0%)	Common
Hyponatremia[w]	171 (5.4%)	98 (3.1%)	0 (0%)	Common
Hyperglycaemia	103 (3.2%)	32 (1.0%)	0 (0%)	Common
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	441 (13.9%)	23 (0.7%)	0 (0%)	Very Common
Back pain	487 (15.3%)	52 (1.6%)	0 (0%)	Very Common
Musculoskeletal pain[r]	489 (15.4%)	36 (1.1%)	0 (0%)	Common
Arthritis[kk]	64 (2.0%)	8 (0.3%)	0(0%)	Common
Myositis [t, u]	13 (0.4%)	5 (0.2%)	0 (0%)	Uncommon
Tenosynovitis[ij]	10 (0.3%)	1 (<0.1%)	0 (0%)	Uncommon
Nervous System Disorders				
Headache	352 (11.1%)	10 (0.3%)	0 (0%)	Very Common
Peripheral neuropathy[hh]	156 (4.9%)	5 (0.2%)	0 (0%)	Common
Guillain-Barré syndrome[j]	5 (0.2%)	4 (0.1%)	0 (0%)	Uncommon
Meningoencephalitis[k]	14 (0.4%)	6 (0.2%)	0 (0%)	Uncommon
Myasthenic syndrome[z]	1 (< 0.1%)	0 (0%)	0 (0%)	Rare
Facial paresis[ff]	1 (<0.1%)	0 (0%)	0 (0%)	Rare
Myelitis[ff]	1 (<0.1%)	1 (<0.1%)	0 (0%)	Rare
Renal and Urinary Disorders				
Blood creatinine increased[aa]	171 (5.4%)	14 (0.4%)	0 (0%)	Common
Nephritis[s]	3 (< 0.1%)	1 (< 0.1%)	0 (0%)	Rare
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	660 (20.8%)	9 (0.3%)	0 (0%)	Very Common
Dyspnoea	651 (20.5%)	117 (3.7%)	1 (< 0.1%)	Very Common
Hypoxia[x]	75 (2.4%)	36 (1.1%)	0 (0%)	Common
Pneumonitis[l]	87 (2.7%)	27 (0.8%)	1 (< 0.1%)	Common
Nasopharyngitis[bb]	280 (8.8%)	0 (0%)	0 (0%)	Common
Skin and Subcutaneous Tissue Disorders				
Rash[m]	613 (19.3%)	33 (1.0%)	0 (0%)	Very Common
Pruritus	400 (12.6%)	7 (0.2%)	0 (0%)	Very Common
Dry skin[gg]	199 (6.3%)	2 (< 0.1%)	0 (0%)	Common
Psoriatic conditions[cc]	19 (0.6%)	2 (< 0.1%)	0 (0%)	Uncommon
Severe cutaneous adverse reactions[dd]	22 (0.7%)	3 (<0.1%)	1 (<0.1%)	Uncommon
Vascular Disorders				

System Organ Class/ADR (MedDRA preferred term)	Tecentriq (n = 3178)			
	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
Hypotension	102 (3.2%)	20 (0.6%)	0 (0%)	Common

[a.] Reported in studies outside the pooled dataset. The frequency is based on the program-wide exposure. Includes reports of autoimmune myocarditis, immune-mediated myocarditis

[b.] Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, blood thyroid stimulating hormone decreased, autoimmune thyroiditis (cases of autoimmune thyroiditis have been reported in studies outside the pooled dataset), thyroiditis, autoimmune hypothyroidism, euthyroid sick syndrome, myxoedema, thyroid function test abnormal, thyroiditis acute, thyroxine decreased

[c.] Includes reports of hyperthyroidism, Basedow's disease, endocrine ophthalmopathy, exophthalmos

[d.] Includes reports of adrenal insufficiency, primary adrenal insufficiency

[e.] Includes reports of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis and ketoacidosis

[f.] Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic, colitis ulcerative, immune-mediated enterocolitis (cases of immune-mediated enterocolitis have been reported in studies outside the pooled dataset)

[g.] Includes reports of pancreatitis, autoimmune pancreatitis, pancreatitis acute, lipase increased, amylase increased

[h.] includes infusion related reaction, cytokine release syndrome and anaphylaxis (anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock), where anaphylaxis was reported outside the pooled dataset.

[i.] Includes reports of ascites, autoimmune hepatitis, hepatocellular injury, hepatitis, hepatitis acute, hepatotoxicity, liver disorder, drug-induced liver injury, hepatic failure, hepatic steatosis, hepatic lesion, oesophageal varices haemorrhage, varices oesophageal

[j.] Includes reports of Guillain-Barré syndrome, demyelinating polyneuropathy

[k.] Includes reports of encephalitis, meningitis, photophobia

[l.] Includes reports of pneumonitis, lung infiltration, bronchiolitis, interstitial lung disease, radiation pneumonitis.

[m.] Includes reports of rash, rash maculo-papular, erythema, rash pruritic, dermatitis acneiform, eczema, dermatitis, rash erythematous, skin ulcer, rash papular, folliculitis, rash macular, skin exfoliation, rash pustular, , furuncle, acne, drug eruption, palmar-plantar erythrodysaesthesia syndrome, seborrhoeic dermatitis, dermatitis allergic, erythema of eyelid, skin toxicity, eyelid rash, fixed eruption, rash papulosquamous, rash vesicular, blister, lip blister, pemphigoid, oral blood blister, scrotal dermatitis (cases of scrotal dermatitis have been reported in studies outside the pooled dataset)

[n.] Includes reports of immune thrombocytopenia (reported in studies outside the pooled dataset), thrombocytopenia and platelet count decreased

[o.] Includes reports of diarrhoea, frequent bowel movements, and gastrointestinal hypermotility

[p.] Includes reports of urinary tract infection, cystitis, pyelonephritis, Escherichia urinary tract infection, pyelonephritis acute, urinary tract infection bacterial, kidney infection, urinary tract infection fungal, urinary tract infection pseudomonal

[q.] Includes reports of oropharyngeal pain, throat irritation, oropharyngeal discomfort

[r.] Includes reports of musculoskeletal pain, myalgia, bone pain

[s.] Includes reports of nephritis, Henoch-Scholein Purpura nephritis

[t.] Includes reports of myositis, rhabdomyolysis, polymyalgia rheumatica, dermatomyositis, muscle abscess, myoglobin urine present

[u.] Fatal cases have been reported in studies outside the pooled dataset

[v.] Includes reports of hypokalaemia and blood potassium decreased

[w.] Includes reports of hyponatraemia and blood sodium decreased

[x.] Includes reports of hypoxia, oxygen saturation decreased, PO_2 decreased

[y.] Includes reports of hypophysitis and temperature regulation disorder

[z.] Includes report of myasthenia gravis

[aa.] Includes reports of blood creatinine increased and hypercreatininaemia

[bb] Includes reports of nasopharyngitis, nasal congestion and rhinorrhoea

[cc] Includes reports of dermatitis psoriasiform and psoriasis

[dd] Includes reports of dermatitis bullous, exfoliative rash, erythema multiforme, dermatitis exfoliative generalised, toxic skin eruption, toxic epidermal necrolysis

[ee] Includes reports of pericarditis, pericardial effusion, cardiac tamponade and pericarditis constrictive

[ff] Reported from postmarketing experience outside the pooled dataset. The frequency is based on the program-wide exposure

[gg] Includes reports of dry skin, xerosis

[hh] Includes reports of neuropathy peripheral, peripheral sensory neuropathy, polyneuropathy, peripheral motor neuropathy, toxic neuropathy, peripheral sensorimotor neuropathy, autoimmune neuropathy, axonal neuropathy, brachial plexopathy, lumbosacral plexopathy, neuralgic amyotrophy, and neuritis

[ii] Reported in studies outside the pooled dataset. The frequency is based on the program-wide exposure

[jj] Includes reports of tenosynovitis, tendonitis, tendon pain and synovitis

[kk] Includes reports of joint swelling, osteoarthritis, spinal osteoarthritis, polyarthritis, rheumatoid arthritis, joint effusion, spondylitis, autoimmune arthritis, arthropathy, immune-mediated arthritis and rheumatic disorder

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

Tecentriq combination therapy

The safety of Tecentriq given in combination with other medicinal products is based on pooled data in 4,371 patients in clinical trials across multiple tumour types. Additional ADRs associated with the use of Tecentriq in combination therapy (not reported in monotherapy trials) are summarised in Table 5. ADRs with a clinically relevant difference when compared to monotherapy (refer to Table 4) are also presented. The most common adverse reactions (≥ 10%) were anaemia (36.8%), neutropenia (35.8%), thrombocytopenia (27.7%), alopecia (26.4%), constipation (25.7%), peripheral neuropathy (23.0%), hypertension (14.0%), hypothyroidism (13.4%), leucopenia (13.1%), lung infection (12.9%), peripheral oedema (10.3%) and nasopharyngitis (10.1%).

Table 5. Summary of ADRs occurring in patients treated with Tecentriq combination therapy in clinical trials

System Organ Class/ADR (MedDRA preferred term)	Tecentriq + Combination Treatments (n = 4371)			
	All Grades (%)	Grade 3-4 (%)	Grade 5 (%)	Frequency (All Grades)
Blood and Lymphatic System Disorders				
Anaemia[*]	1608 (36.8%)	631 (14.4%)	0 (0%)	Very Common
Lymphopenia[*, k]	145 (3.3%)	63 (1.4%)	0 (0%)	Common
Neutropenia[*, a]	1565 (35.8%)	1070 (24.5%)	6 (0.1%)	Very Common
Thrombocytopenia[*, ‡, b]	1211 (27.7%)	479 (11.0%)	1 (< 0.1%)	Very Common
Leucopenia[*, i]	571 (13.1%)	245 (5.6%)	0 (0%)	Very Common
Endocrine Disorders				
Hypothyroidism[*, ‡ ,c]	586 (13.4)	9 (0.2%)	0 (0%)	Very Common
Hyperthyroidism[‡]	193 (4.4%)	7 (0.2%)	0 (0%)	Common
Adrenal insufficiency[‡, d]	40 (0.9%)	8 (0.2%)	1 (< 0.1%)	Uncommon
Hypophysitis[‡, e]	13 (0.3%)	5 (0.1%)	0 (0%)	Uncommon
Eye Disorders				
Uveitis[q]	2 (<0.1%)	0 (0%)	0 (0%)	Rare
Gastrointestinal Disorders				
Constipation[*]	1123 (25.7%)	24 (0.5%)	0 (0%)	Very Common

System Organ Class/ADR (MedDRA preferred term)	Tecentriq + Combination Treatments (n = 4371)			
	All Grades (%)	Grade 3-4 (%)	Grade 5 (%)	Frequency (All Grades)
Stomatitis*	351 (8.0%)	23 (0.5%)	0 (0%)	Common
General Disorders and Administration Site Conditions				
Peripheral oedema*	451 (10.3%)	11 (0.3%)	0 (0%)	Very Common
Infections and Infestations				
Lung infection*, h	564 (12.9%)	226 (5.2%)	26 (0.6%)	Very Common
Investigations				
Blood alkaline phosphatase increased	200 (4.6%)	26 (0.6%)	0 (0%)	Common
Metabolism and Nutrition Disorders				
Hypomagnesemia*, j	403 (9.2%)	22 (0.5%)	0 (0%)	Common
Nervous System Disorders				
Dizziness*	408 (9.3%)	9 (0.2%)	0 (0%)	Common
Dysgeusia*	269 (6.2%)	0 (0.0%)	0 (0%)	Common
Peripheral neuropathy*, f	976 (22.3%)	104 (2.4%)	0 (0%)	Very Common
Syncope*	68 (1.6%)	36 (0.8%)	0 (0%)	Common
Renal and Urinary Disorders				
Nephritis‡, l	23 (0.5%)	15 (0.3%)	0 (0%)	Uncommon
Proteinuria*, g	359 (8.2%)	61 (1.4%)	0 (0%)	Common
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia*	236 (5.4%)	4 (< 0.1%)	0 (0%)	Common
Nasopharyngitis°	442 (10.1%)	1 (< 0.1%)	0 (0%)	Very Common
Skin and Subcutaneous Tissue Disorders				
Alopecia[n]	1152 (26.4%)	3 (< 0.1%)	0 (0%)	Very Common
Severe cutaneous adverse reactions[p]	27 (0.6%)	8 (0.2%)	0 (0)%	Uncommon
Vascular Disorders				
Hypertension*, m	611 (14.0%)	258 (5.9%)	0 (0%)	Very Common

* ADR occurring at a frequency difference of ≥ 5% (All grades) or ≥ 2% (Grades 3-4) compared to the control arm

‡ Observed rate in the combination represents a clinically relevant difference in comparison to Tecentriq monotherapy

a. Includes reports of neutropenia, decreased neutrophil count, febrile neutropenia, neutropenic sepsis, granulocytopenia. Fatal cases of febrile neutropenia have been observed when Tecentriq is given in combination with bevacizumab, paclitaxel and carboplatin.

[b.] Includes reports of immune thrombocytopenia, thrombocytopenia, decreased platelet count
[c.] Includes reports of hypothyroidism, increased blood thyroid stimulating hormone, decreased blood thyroid stimulating hormone, autoimmune thyroiditis, goitre, thyroiditis, decreased free thyroxine, decreased free tri-iodothyronine, thyroid disorder, increased free thyroxine, increased thyroxine, decreased tri-iodothyronine, increased free tri-iodothyronine, abnormal blood thyroid stimulating hormone, euthyroid sick syndrome, myxoedema coma, abnormal thyroid function test, decreased thyroxine, abnormal tri-iodothyronine, silent thyroiditis, chronic thyroiditis
[d.] Includes reports of adrenal insufficiency, decreased cortisol, acute adrenocortical insufficiency, secondary adrenocortical insufficiency, abnormal adrenocorticotropic hormone stimulation test, Addison's disease, adrenalitis, adrenocorticotropic hormone deficiency
[e.] Includes reports of hypophysitis, hypopituitarism and temperature regulation disorder
[f.] Includes reports of peripheral neuropathy, peripheral sensory neuropathy, polyneuropathy, peripheral motor neuropathy, toxic neuropathy, autoimmune neuropathy, neuralgic amyotrophy, peripheral sensorimotor neuropathy, axonal neuropathy, brachial plexopathy, lumbosacral plexopathy and neuritis
[g.] Includes reports of proteinuria, protein urine present, haemoglobinuria, nephrotic syndrome, urine abnormality, albuminuria
[h.] Includes reports of pneumonia, bronchitis, lower respiratory tract infection, tracheobronchitis, infective exacerbation of chronic obstructive airways disease, infectious pleural effusion, paracancerous pneumonia, atypical pneumonia, lung abscess, pleural infection, pyopneumothorax
[i.] Includes reports of decreased white blood cell count, leucopenia
[j.] Includes reports of hypomagnesaemia, decreased blood magnesium
[k.] Includes reports of lymphopenia, decreased lymphocyte count
[l.] Includes reports of nephritis, tubulointerstitial nephritis, autoimmune nephritis, allergic nephritis, glomerulonephritis, nephrotic syndrome, mesangioproliferative glomerulonephritis
[m.] Includes reports of hypertension, increased blood pressure, hypertensive crisis, increased blood pressure systolic, diastolic hypertension, blood pressure inadequately controlled, hypertensive retinopathy
[n.] Includes reports of alopecia, madarosis, alopecia areata, alopecia totalis, hypotrichosis
[o.] Includes reports of nasopharyngitis, nasal congestion and rhinorrhoea
[p.] Includes reports of dermatitis bullous, exfoliative rash, erythema multiforme, dermatitis exfoliative generalised, toxic skin eruption, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), and cutaneous vasculitis (cases of SJS and DRESS have been reported in studies outside the pooled dataset)
[q.] Includes reports of uveitis and iritis

One patient treated with Tecentriq in combination with carboplatin and etoposide in Study GO30081 (IMpower133) experienced Grade 3 anaphylaxis and discontinued treatment with Tecentriq.

Additional information for selected adverse reactions

The data below reflect information for significant adverse reactions for Tecentriq monotherapy. Details for the significant adverse reactions for Tecentriq when given in combination are presented if clinically relevant differences were noted in comparison to Tecentriq monotherapy. See sections *4.2 Dose and method of administration* and *4.4 Special warnings and precautions for use* for management of the following:

Immune-mediated pneumonitis

Pneumonitis occurred in 2.7% (87/3178) of patients who received Tecentriq monotherapy. Of the 87 patients, one event was fatal. The median time to onset was 3.4 months (range: 0.1 to 24.8 months). The median duration was 1.4 months (range 0 to 21.2^{+} months; $^{+}$ denotes a censored value). Pneumonitis led to discontinuation of Tecentriq in 12 (0.4%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.6% (51/3178) of patients receiving Tecentriq.

Immune-mediated hepatitis

Hepatitis occurred in 2.0% (62/3178) of patients who received Tecentriq monotherapy. Of the 62 patients, two events were fatal. The median time to onset was 1.5 months (range 0.2 to 18.8

months). The median duration was 2.1 months (range 0 to 22.0^{+} months; $^{+}$ denotes a censored value). Hepatitis led to discontinuation of Tecentriq in 6 (0.2%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.6% (18/3178) of patients receiving Tecentriq.

Immune-mediated colitis

Colitis occurred in 1.1% (34/3178) of patients who received Tecentriq. The median time to onset was 4.7 months (range 0.5 to 17.2 months). The median duration was 1.2 months (range 0.1 to 17.8^{+} months; $^{+}$ denotes a censored value). Colitis led to discontinuation of Tecentriq in 8 (0.3%) patients. Colitis requiring the use of corticosteroids occurred in 0.6% (19/3178) of patients receiving Tecentriq.

Immune-mediated endocrinopathies

Thyroid disorders

Hypothyroidism occurred in 5.2% (164/3178) of patients who received Tecentriq monotherapy. The median time to onset was 4.9 months (range 0 to 31.3 months).

Hyperthyroidism occurred in 0.9% (30/3178) of patients who received Tecentriq monotherapy. The median time to onset was 2.1 months (range 0.7 to 15.7 months). The median duration was 2.6 months (range: 0^{+} to 17.1^{+} months; $^{+}$ denotes a censored value).

Hyperthyroidism occurred in 4.9% (23/473) of patients who received Tecentriq in combination with carboplatin and nab-paclitaxel. Hyperthyroidism led to discontinuation in 1 (0.2%) patient.

Adrenal insufficiency

Adrenal insufficiency occurred in 0.3% (11/3178) of patients who received Tecentriq monotherapy. The median time to onset was 5.5 months (range 0.1 to 19.0 months). The median duration was 16.8 months (range 0 to 16.8 months). Adrenal insufficiency led to discontinuation of Tecentriq in 1 (< 0.1%) patient. Adrenal insufficiency requiring the use of corticosteroids occurred in 0.3% (9/3178) of patients receiving Tecentriq.

Adrenal insufficiency occurred in 1.5% (7/473) of patients who received Tecentriq in combination with carboplatin and nab-paclitaxel. Adrenal insufficiency requiring the use of corticosteroids occurred in 0.8% (4/473) of patients receiving Tecentriq in combination with carboplatin and nab-paclitaxel.

Hypophysitis

Hypophysitis occurred in < 0.1% (2/3178) of patients who received Tecentriq monotherapy. The median time to onset was 7.2 months (range: 0.8 to 13.7 months). One patient required the use of corticosteroids and treatment with Tecentriq was discontinued.

Hypophysitis occurred in 0.8% (3/393) of patients who received Tecentriq 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 led to the discontinuation of treatment in one patient.

Diabetes mellitus

Diabetes mellitus occurred in 0.3% (10/3178) of patients who received Tecentriq monotherapy. The median time to onset was 4.2 months (range 0.1 to 9.9 months). The median duration was 1.6 months (range: 0.1 to 15.2^{+} months; $^{+}$ denotes a censored value). Diabetes mellitus led to the discontinuation of Tecentriq in 3 (< 0.1%) patients.

Immune-mediated meningoencephalitis

Meningoencephalitis occurred in 0.4% (14/3178) of patients who received Tecentriq monotherapy. The median time to onset was 0.5 months (range 0 to 12.5 months). The median duration was 0.7 months (range 0.2 to 14.5^{+} months; $^{+}$ denotes a censored value). Meningoencephalitis requiring the use of corticosteroids occurred in 0.2% (6/3178) of patients receiving Tecentriq and led to discontinuation of Tecentriq in 4 (0.1%) patients.

Immune-mediated neuropathies

Guillain-Barré syndrome and demyelinating polyneuropathy

Guillain-Barré syndrome and demyelinating polyneuropathy, occurred in 0.2% (5/3178) of patients who received Tecentriq monotherapy. The median time to onset was 7.0 months (range: 0.6 to 8.1 months). The median duration was 8.0 months (0.6 to 8.3^{+} months; $^{+}$ denotes a censored value). Guillain-Barré syndrome led to the discontinuation of Tecentriq in 1 (< 0.1%) patient. Guillain-Barré syndrome requiring the use of corticosteroids occurred in < 0.1% (2/3178) of patients receiving Tecentriq.

Facial paresis

Facial paresis occurred in <0.1% (1/3178) of patients who received Tecentriq monotherapy. The time to onset was 0.95 months. The duration was 1.1 months. The event did not require the use of corticosteroids and the event did not lead to the discontinuation of Tecentriq.

Immune-mediated myelitis

Myelitis occurred in <0.1% (1/3178) of patients who received Tecentriq monotherapy. The time to onset was 0.76 months. The event required the use of corticosteroids but did not lead to the discontinuation of Tecentriq.

Immune-mediated pancreatitis

Pancreatitis, including amylase increased and lipase increased, occurred in 0.6% (18/3178) of patients who received Tecentriq monotherapy. The median time to onset was 5.0 months (range 0.3 to 16.9 months). The median duration was 0.8 months (range 0.1 to 12.0^{+} months; $^{+}$ denotes a censored value). Pancreatitis led to discontinuation of Tecentriq in 3 (< 0.1%) patients. Pancreatitis requiring the use of corticosteroids occurred in 0.1% (4/3178) of patients receiving Tecentriq.

Haemophagocytic lymphohistiocytosis

Haemophagocytic lymphohistiocytosis (HLH) occurred in <0.1% (1/3178) of patients who received Tecentriq monotherapy. The time to onset was 1.6 months. The duration was 1.4 months. HLH led to discontinuation of Tecentriq in 1 (<0.1%) patient. The patient did not require the use of corticosteroids.

Immune-mediated myocarditis

Myocarditis occurred in < 0.1% (2/8000) of patients across all Tecentriq clinical trials in multiple tumour types and treatment combinations. The time to onset was 18 and 33 days. Both patients required corticosteroids and discontinued Tecentriq.

Immune-mediated pericardial disorders

Pericardial disorders occurred in 1.4% (45/3178) of patients who received Tecentriq monotherapy. The median time to onset was 1.4 months (range 0.2 to 17.5 months). The median duration was 1.4 months (range 0 to 19.3 months). Pericardial disorders led to discontinuation of Tecentriq in 3 (<0.1%) patients. Pericardial disorders requiring the use of corticosteroids occurred in 0.2% (7/3178) of patients.

Immune-mediated myositis

Myositis occurred in 0.4% (13/3178) of patients who received Tecentriq monotherapy. The median time to onset was 5.1 months (range 0.7 to 11.0 months). The median duration was 5.0 months (range 0.7 to 22.6^{+} months, $^{+}$ denotes a censored value). Myositis led to discontinuation of Tecentriq in 1 (< 0.1%) patient. Seven (0.2%) patients required the use of corticosteroids.

Immune-mediated nephritis

Nephritis occurred in < 0.1% (3/3178) of patients who received Tecentriq monotherapy. The median time to onset was 13.1 months (range 9.0 to 17.5 months). The median duration was 2.8 months (range 0.5 to 9.5^{+} months, $^{+}$ denotes a censored value). Nephritis led to discontinuation of Tecentriq in 2 (< 0.1%) of patients. One patient required the use of corticosteroids.

Immune-mediated severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) occurred in 0.7% (22/3178) of patients who received Tecentriq monotherapy. The median time to onset was 5.9 months (range 0.1 to 15.5 months). The median duration was 1.6 months (range 0 to 22.1^{+} months; $^{+}$ denotes a censored value). SCARs led to discontinuation of Tecentriq in 3 (<0.1%) patients. SCARs requiring the use of systemic corticosteroids occurred in 0.2% (6/3178) of patients receiving Tecentriq monotherapy.

Use of Tecentriq in combination with bevacizumab, paclitaxel and carboplatin

In Study GO29436 (IMpower150), an overall higher frequency of adverse events was observed in the four-drug regimen of Tecentriq, bevacizumab, paclitaxel, and carboplatin compared to Tecentriq, 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 Tecentriq (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 Tecentriq in combination with bevacizumab, paclitaxel and carboplatin. Other clinically significant adverse events which were observed more frequently in the Tecentriq, bevacizumab, paclitaxel, and carboplatin arm were epistaxis, haemoptysis, cerebrovascular accident, including fatal events.

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reaction(s) reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with atezolizumab: pancreatic exocrine insufficiency.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to atezolizumab with the incidence of antibodies to other products may be misleading.

Across multiple phase II and III studies, 13.1% to 54.1% of patients developed treatment-emergent anti-drug antibodies (ADAs) and 4.3% to 27.5% of patients developed neutralising antibodies (NAbs). The median time to ADA onset ranged from 3 weeks to 5 weeks.

A decrease in exposure (9% increase in clearance) was observed in ADA-positive patients compared to ADA-negative patients; however, this effect on exposure is not expected to be clinically meaningful given the flat exposure-response relationship and adequate target exposure achieved regardless of ADA status.

Patients who developed treatment emergent ADAs tended to have overall poorer health and disease characteristics at baseline. 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 develop ADA compared to patients who did not develop ADA.

Across pooled datasets for patients treated with atezolizumab monotherapy and with combination therapies, the rates of adverse events (AEs) which have been observed for the ADA-positive population compared to the ADA-negative population is presented in Table 6. Available data do not allow conclusions to be drawn on possible patterns of adverse drug reactions or their causal relationship with ADAs.

Table 6. Overview of Safety by ADA Status in Atezolizumab Monotherapy and Combination Therapy Pooled Populations

	Atezolizumab monotherapy pooled population (n=2972)		Atezolizumab combination therapy pooled population (n=2285)	
Total number of patients with:	ADA-negative (n=1905)	ADA-positive (n=1067)	ADA-negative (n=1681)	ADA-positive (n=604)
Grade 3-4 AEs	42.6%	48.6%	60.9%	63.9%
Serious Adverse Events (SAEs)	36.0%	42.2%	35.6%	43.9%
AEs leading to treatment withdrawal	6.5%	6.2%	18.4%	22.8%

Laboratory abnormalities

All identified laboratory abnormalities were reported as ADRs. See section *4.4 Special warnings and precautions for use*, *Immune-mediated hepatitis* and *Immune-mediated endocrinopathies* for management of the following:

- AST, ALT, bilirubin
- thyroid function.

Postmarketing experience

The following adverse reactions have been identified during post-approval use of Tecentriq (see Table 7). Because reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Table 7. Adverse Drug Reactions from Postmarketing Surveillance

System Organ Class/ ADR (MedDRA Preferred Term)	**Frequency**
Blood and Lymphatic System Disorders	
Haemophagocytic lymphohistiocytosis[a]	Rare
Autoimmune haemolytic anaemia (AIHA)	Unknown
Cardiac Disorders	

Pericardial disorders[a,b]	Common
General disorders and administration site conditions	
Systemic inflammatory response syndrome (SIRS)	Unknown
Gastrointestinal Disorders	
Coeliac disease	Rare
Musculoskeletal and connective tissue disorders	
Arthritis (including immune-mediated arthritis)	Unknown
Sjögrens syndrome	Unknown
Tenosynovitis	Unknown
Neoplasms benign, malignant and unspecified	
Sarcoidosis	Unknown
Nervous System Disorders	
Facial paresis[a]	Rare
Myelitis[a]	Rare
Renal and Urinary Disorders	
Renal failure	Unknown

[a]Reported from postmarketing experience outside the pooled dataset. The frequency is based on the program-wide exposure.
[b]Includes reports of pericarditis, pericardial effusion, cardiac tamponade and pericarditis constrictive

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

There is no information on overdose with Tecentriq.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: L01FF05

Mechanism of action

Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells suppresses cytotoxic T-cell activity through the inhibition of T-cell proliferation and cytokine production. PD-L1 may be expressed on tumour cells (TC) and tumour-infiltrating immune cells (IC), and can contribute to the inhibition of the anti-tumour immune response in the microenvironment.

Atezolizumab is an Fc-engineered humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 pathway-mediated inhibition of the immune response, including reactivating the anti-tumour immune response. Atezolizumab leaves the PD-L2/PD-1 interaction intact,

allowing PD-L2/PD-1 mediated inhibitory signals to persist. In syngeneic mouse tumour models, blocking PD-L1 activity resulted in decreased tumour growth.

PD-L1 expression by immunohistochemistry

In certain clinical studies with atezolizumab (see "Clinical trials," below), the VENTANA PD-L1 (SP263) Assay or the VENTANA PD-L1 (SP142) Assay was used in accordance with validated usage to detect PD-L1 expression: either in tumour cells (TC) only (SP263) or in both tumour-infiltrating immune cells (IC) and TC (SP142) (see section *5.1 Pharmacodynamic properties*).

Clinical trials

Non-small cell lung cancer

Early-stage NSCLC

IMpower010 (GO29527)

A phase III, open-label, multi-centre, randomised study, GO29527 (IMpower010), was conducted to evaluate the efficacy and safety of Tecentriq 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). A total of 1280 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 8.

Table 8. Chemotherapy Intravenous Treatment Regimens in Study IMpower010

Adjuvant cisplatin-based chemotherapy Cisplatin 75 mg/m^2 IV on Day 1 of each 21 day cycle with one of the following treatment regimens:	Vinorelbine 30 mg/m^2 IV, Day 1 and 8
	Docetaxel 75 mg/m^2 IV, Day 1
	Gemcitabine 1250 mg/m^2 IV, Day 1 and 8
	Pemetrexed 500 mg/m^2 IV, Day 1

After completion of cisplatin-based chemotherapy (up to four cycles), a total of 1005 patients were randomised in a 1:1 ratio to receive Tecentriq (Arm A) or best supportive care (BSC) (Arm B). Tecentriq was administered as a fixed dose of 1200 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 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. As

measured by the VENTANA PD-L1 (SP263) Assay, 55% of patients had tumours with PD-L1 expression ≥ 1% on TC and 26% of patients had tumours with PD-L1 expression ≥ 50% on TC. 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. DFS was assessed hierarchically in the following patient populations: stage II-IIIA NSCLC with PD-L1 expression ≥1% TC, all randomised patients with stage II-IIIA NSCLC, and all randomised ITT patients. DFS in the PD-L1 ≥ 50% TC stage II-IIIA population and OS in the ITT population were pre-specified key secondary objectives.

At the time of the interim DFS analysis, the study met its primary endpoint and demonstrated a statistically significant improvement in DFS in the Tecentriq arm compared to the BSC arm in the PD-L1 ≥ 1% TC stage II - IIIA patient population. The median follow-up time was approximately 32 months.

In the secondary objective analysis of stage II-IIIA patients with PD-L1 TC ≥ 50%, a clinically meaningful improvement in DFS was shown in the Tecentriq arm compared to the BSC arm with an unstratified HR of 0.43 (95% CI: 0.27, 0.68). Results were consistent at the time of the final DFS analysis, with median follow up time of 65 months. The OS data were immature at the time of the DFS final analysis.

The key efficacy results are summarised in Table 9. The Kaplan-Meier curve for DFS for the PD-L1 ≥ 50% TC stage II-IIIA patient population is presented in Figure 1.

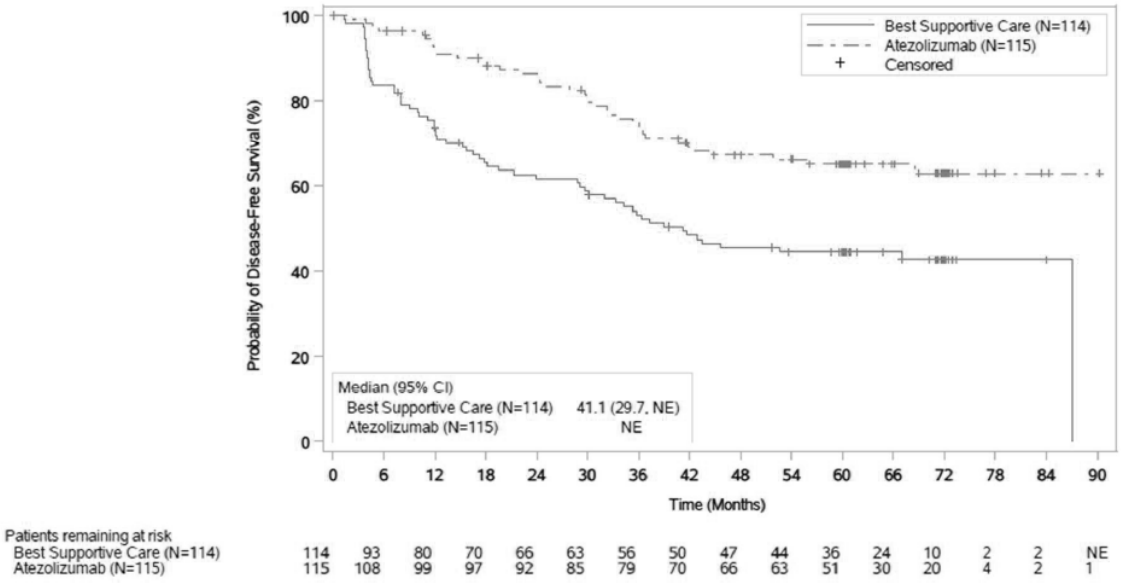
Table 9. Summary of efficacy from GO29527 (IMpower010) in PD-L1 expression ≥ 1% TC, ≥ 50% TC, and 1 – 49% TC stage II-IIIA patient populations

Efficacy endpoints **Investigator-assessed DFS**	**Arm A** (Tecentriq)	**Arm B** (Best Supportive Care)
Primary Endpoint		
DFS in PD-L1 ≥1% TC Stage II-IIIA	n = 248	n = 228
No. of events (%)	113 (45.6)	127 (55.7)
Median duration of DFS (months)	68.5	37.3
95% CI	51.8, NE	30.1, 57.8
Stratified* hazard ratio (95% CI)	0.70 (0.55, 0.91)	
p-value	0.007	
Secondary Endpoint		
DFS in PD-L1 ≥50% TC Stage II-IIIA	n = 115	n = 114
No. of events (%)	38 (33.0%)	62 (54.4%)
Median duration of DFS (months)	NE	41.1
95% CI	NE, NE	29.7, NE
Unstratified hazard ratio (95% CI)	0.48 (0.32, 0.72)	

Efficacy endpoints **Investigator-assessed DFS**	**Arm A** (Tecentriq)	**Arm B** (Best Supportive Care)
Exploratory Endpoint		
DFS in PD-L1 1-49% TC Stage II-IIIA	n = 133	n = 114
No. of events (%)	75 (56.4%)	65 (57.0%)
Median duration of DFS (months)	41.7	36.0
95% CI	30.0, 65.6	24.0, 60.6
Unstratified hazard ratio (95% CI)	0.91 (0.65, 1.27)	

DFS = Disease-free survival; CI = confidence interval; NE = not estimable
Updated DFS data analysis from 26 January 2024 clinical cut-off
* Stratified by stage of disease, sex, and histology

Figure 1. Kaplan-Meier Plot of Disease-Free Survival in the PD-L1 expression ≥ 50% TC stage II - IIIA patient population at final DFS analysis



1L metastatic non-squamous NSCLC

IMpower150 (GO29436)

A phase III, open-label, multicentre, international, randomised study, IMpower150 (GO29436), was conducted to evaluate the efficacy and safety of Tecentriq 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 medications 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) using the

VENTANA PD-L1 (SP142) Assay and the results were used to define the PD-L1 expression subgroups for the analyses described below.

A total of 1202 patients were enrolled and were randomised (1:1:1) to receive one of the treatment regimens described in Table 10. Randomisation was stratified by sex, presence of liver metastases and PD-L1 tumour expression on TC and IC.

Table 10. Intravenous treatment regimens (IMpower150)

Treatment regimen	Induction (Four or Six 21-day cycles)	Maintenance (21-day cycles)
A	Tecentriq[a] (1200 mg) + paclitaxel (200 mg/m^2)[b,c] + carboplatin[c] (AUC 6)	Tecentriq[a] (1,200 mg)
B	Tecentriq[a] (1200 mg) + bevacizumab[d] (15 mg/kg) + paclitaxel (200 mg/m^2)[b,c] + carboplatin[c] (AUC 6)	Tecentriq[a] (1,200 mg) + bevacizumab[d] (15 mg/kg)
C	Bevacizumab[d] (15 mg/kg) + paclitaxel (200 mg/m^2)[b,c] + carboplatin[c] (AUC 6)	Bevacizumab[d] (15 mg/kg)

[a] Tecentriq 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 Eastern Cooperative Oncology Group (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 11 and 12. The Kaplan-Meier curve for OS in the ITT population is presented in Figure 2. Figure 3 summarises the results of OS in the ITT and PD-L1 subgroups. Updated PFS results are also presented in Figures 4 and 5.

Table 11. Summary of updated efficacy in the ITT population (IMpower150)

Efficacy endpoint	Arm A (Tecentriq + Paclitaxel + Carboplatin)	Arm B (Tecentriq + 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 12. Summary of updated efficacy for Arm A vs Arm B in the ITT population (IMpower150)

Efficacy endpoint	Arm A (Tecentriq + paclitaxel + carboplatin)	Arm B (Tecentriq + 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

Efficacy endpoint	Arm A (Tecentriq + paclitaxel + carboplatin)	Arm B (Tecentriq + bevacizumab + paclitaxel + carboplatin)
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 2. Kaplan-Meier curve for overall survival in the ITT population (IMpower150)

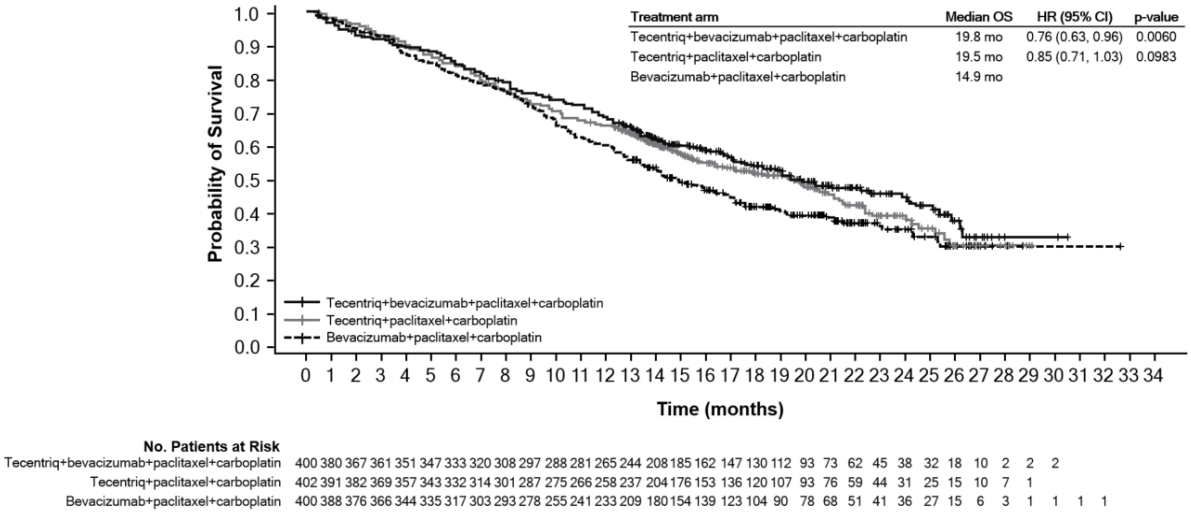


Figure 3. Forest plot of overall survival by PD-L1 expression in the ITT population, Arm B vs C (IMpower150)

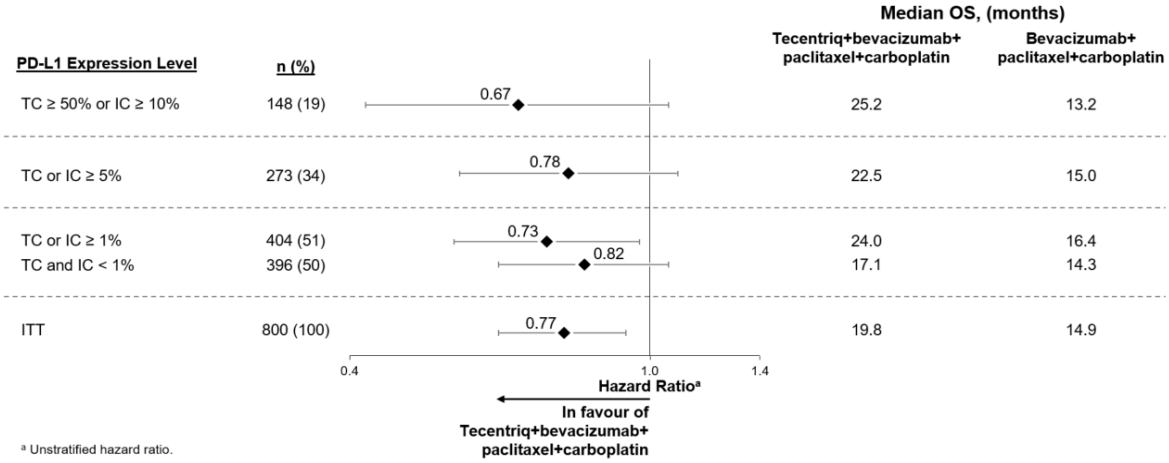
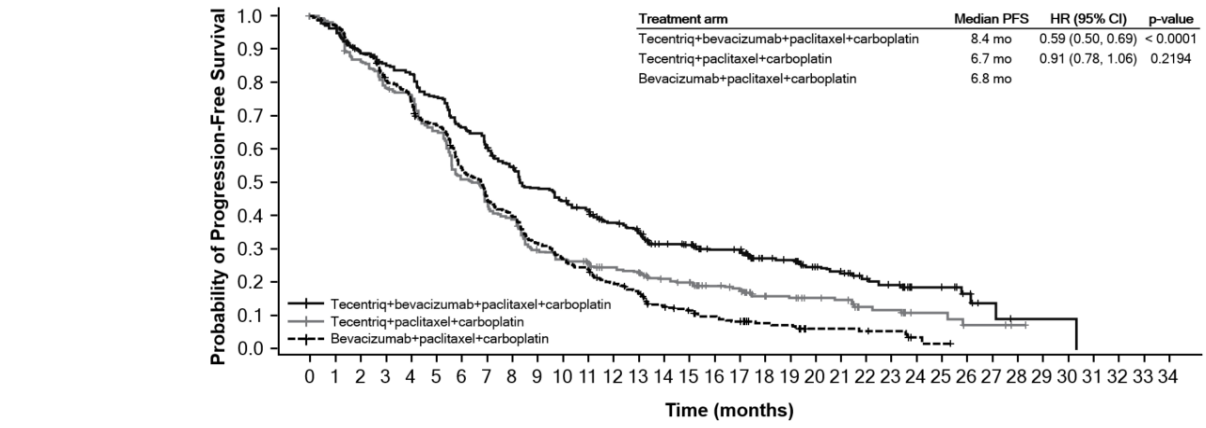


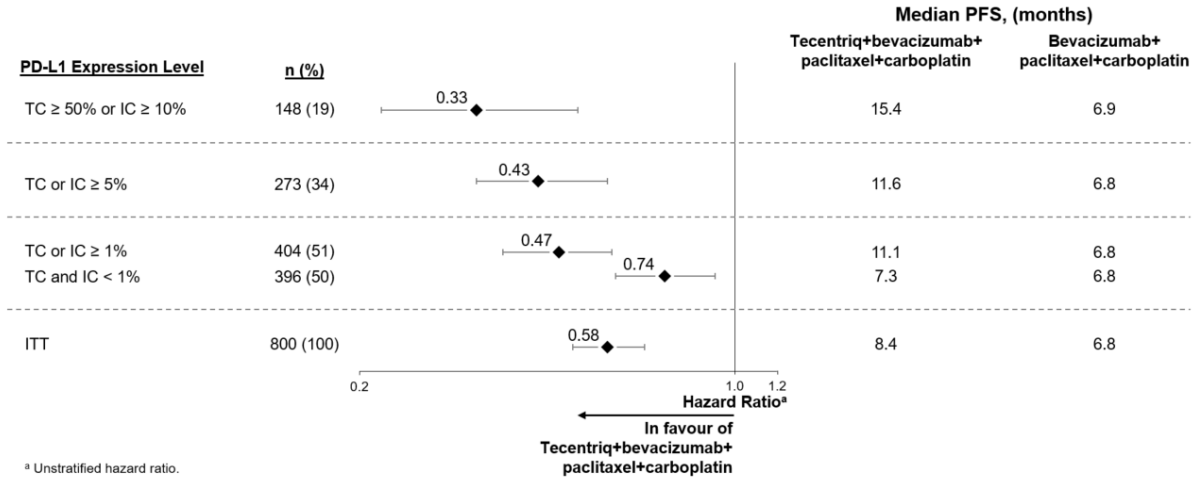
Figure 4. Kaplan-Meier curve for PFS in the ITT population (IMpower150)



No. Patients at Risk

Tecentriq+bevacizumab+paclitaxel+carboplatin	400	376	352	336	326	297	262	240	215	189	174	163	141	127	96	91	76	75	58	55	40	35	26	22	13	12	7	3	1	1	1
Tecentriq+paclitaxel+carboplatin	402	387	343	313	302	258	204	171	154	116	105	100	87	83	66	62	48	43	31	29	25	23	14	13	6	6	3	3	1		
Bevacizumab+paclitaxel+carboplatin	400	385	353	318	297	261	213	176	154	122	104	93	74	62	43	35	26	22	16	15	8	8	7	6	2	1					

Figure 5. 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)

A Phase III, open-label, randomised study, IMpower130 (GO29537) was conducted to evaluate the efficacy and safety of Tecentriq in combination with nab-paclitaxel and carboplatin, in chemotherapy-naïve patients with metastatic non-squamous NSCLC. Patients including those with EGFR or ALK genomic tumour aberrations, were enrolled and were randomised in a 2:1 ratio to receive one of the treatment regimens described in Table 13. Randomisation was stratified by sex, presence of liver metastases and PD-L1 tumour expression on tumour cells (TC) and tumour infiltrating cells (IC) according to the VENTANA PD-L1 (SP142) Assay. Patients in treatment regimen B were able to crossover and receive Tecentriq monotherapy following disease progression.

Table 13. Intravenous treatment regimens in IMpower130

Treatment Regimen	Induction (four or six 21-Day Cycles)	Maintenance (21-Day Cycles)
A	Tecentriq (1200 mg) [a] + nab-paclitaxel (100mg/m^2) [b,c] + carboplatin (AUC 6)[c]	Tecentriq (1200mg) [a]
B	Nab-paclitaxel (100 mg/m^2) [b] + Carboplatin (AUC 6) [c]	Best supportive care or pemetrexed

[a] Tecentriq 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 is administered until completion of 4 - 6 cycles, or progressive disease or unacceptable toxicity whichever occurs first

Patients were excluded if they had 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 medications within 2 weeks prior to randomisation, and active or untreated CNS metastases. Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, then every 9 weeks thereafter.

The demographics and baseline disease characteristics of the study population (n = 723) were well balanced between the treatment arms. The median age was 64 years (range 18 to 86). The majority of the patients were male (57%), white (90%). 14.8% of patients had liver metastases at baseline, and most patients were current or previous smokers (88%). The majority of patients had ECOG performance status of 0 or 1, with the latter group representing 58.6% of the patients.

The primary analysis was conducted in all patients, excluding those with EGFR or ALK genomic tumour aberrations (n = 679). Patients had a median survival follow up time of 18.6 months. Improvements in OS and PFS were demonstrated with Tecentriq + nab-paclitaxel + carboplatin compared to the control. The key results are summarised in Table 14 and Kaplan-Meier curves for OS and PFS are presented in Figures 6 and 8, respectively.

All PD-L1 subgroups, regardless of expression, derived benefit in terms of OS and PFS; the results are summarised in Figure 7 and 9. Consistent OS and PFS benefit was demonstrated in all other pre-specified subgroups, with the exception of patients with liver metastases who did not show improved OS with Tecentriq, nab-paclitaxel and carboplatin, compared to nab-paclitaxel and carboplatin (HR of 1.04, 95% CI: 0.63,1.72).

Approximately 66% of patients in the nab-paclitaxel and carboplatin arm received any anti-cancer therapy after disease progression compared to 39% in the Tecentriq, nab-paclitaxel and carboplatin arm. These included approximately 59% of patients in the nab-paclitaxel and carboplatin arm received any cancer immunotherapy after disease progression, which includes Tecentriq as crossover (41% of all patients), compared to 7.3% in the Tecentriq, nab-paclitaxel and carboplatin arm.

Table 14. Summary of efficacy from IMpower130 in the primary analysis population

Key efficacy endpoints	**Tecentriq + nab-paclitaxel + carboplatin**	**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	55
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 1.1)	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 tumour expression on TC and IC

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 6. Kaplan-Meier Plot for Overall Survival (IMpower130)

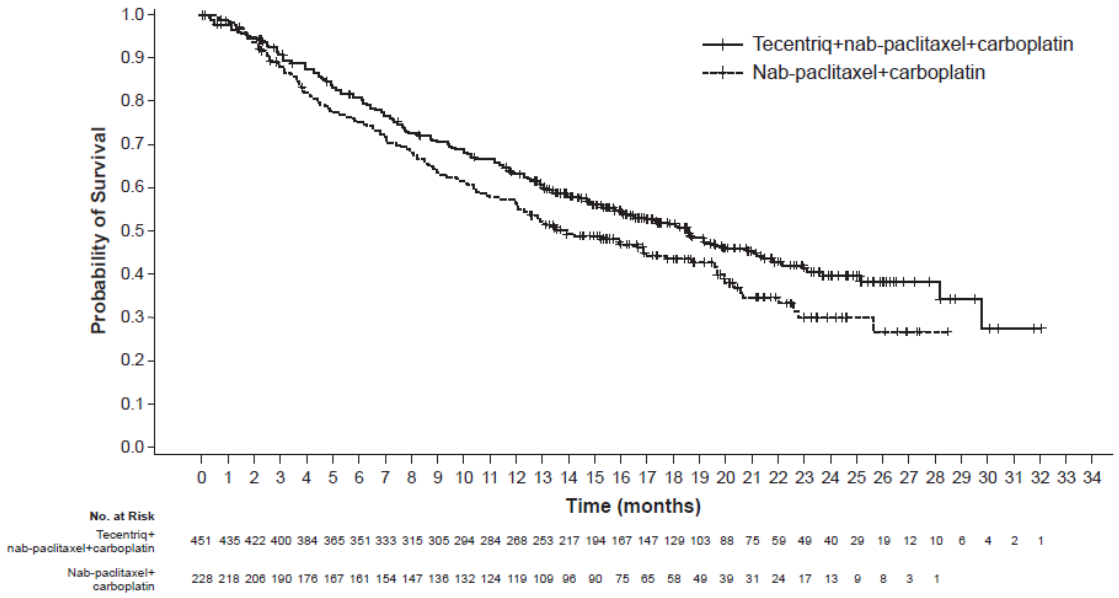


Figure 7. Forest Plot of Overall Survival by PD-L1 expression (IMpower130)

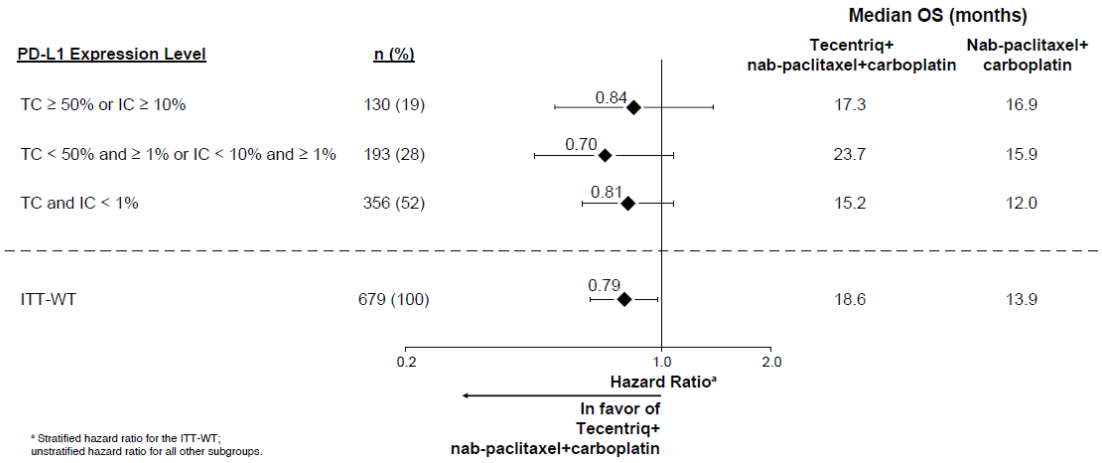


Figure 8. Kaplan-Meier Plot for Progression Free Survival (IMpower130)

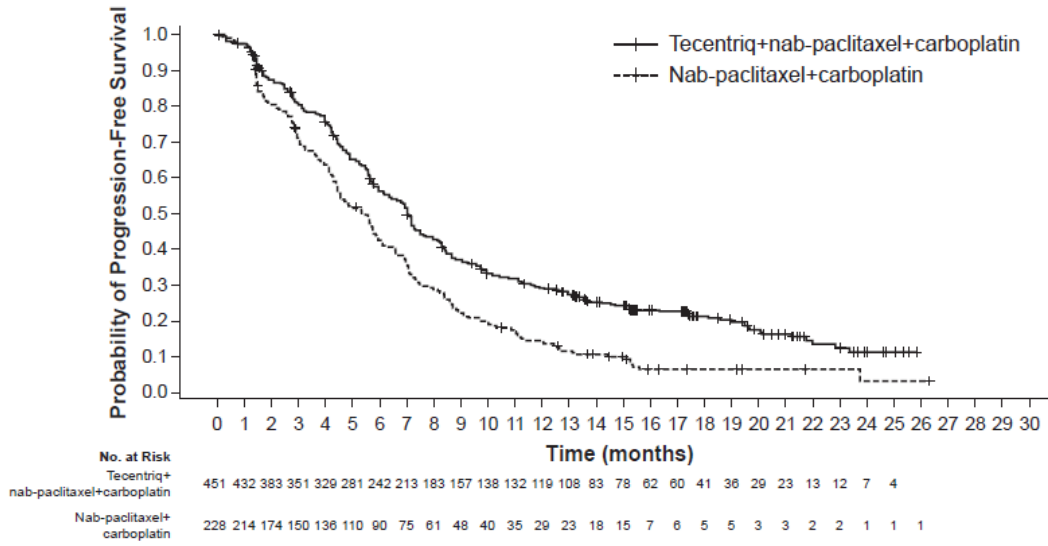
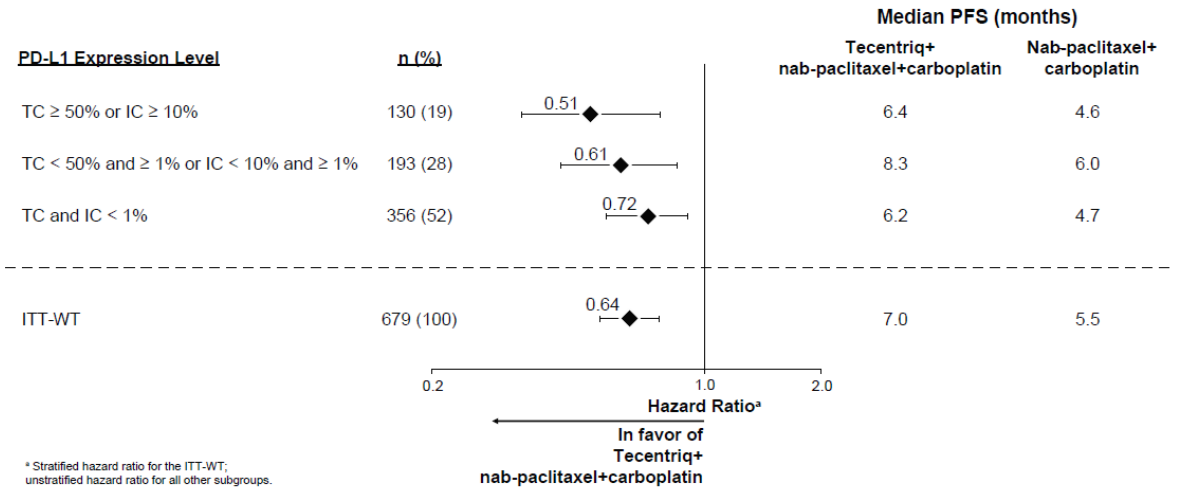


Figure 9. Forest Plot of Progression Free Survival by PD-L1 expression (IMpower130)



The study also evaluated Physical Function and Patient Reported Treatment-Related Symptoms using the EORTC QLQ-C30 and EORTC QLQ-LC13 measures. On average, patients who received Tecentriq with nab-paclitaxel and carboplatin reported high functioning and no clinically meaningful worsening in treatment-related symptoms. There was no difference in delay of lung-related symptoms (dypsnoea, cough and chest pain) however patients receiving Tecentriq, nab-paclitaxel and carboplatin reported less worsening of these symptoms over time.

2L NSCLC

OAK (GO28915)

A phase III, open-label, multicentre, international, randomised study, OAK (GO28915), was conducted to evaluate the efficacy and safety of Tecentriq compared with docetaxel in patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen. A total of 1225 patients were enrolled, with the primary analysis population consisting of the first 850 randomised patients. Eligible patients were stratified by PD-L1 expression status in tumour-infiltrating immune cells (IC), by the number of prior chemotherapy regimens, and by histology. Tumour specimens were evaluated prospectively for PD-L1 expression on TCs and ICs using the VENTANA PD-L1 (SP142) Assay. Patients were randomised (1:1) to receive either Tecentriq or docetaxel. 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 medications within 2 weeks prior to enrolment. Tumour assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter.

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 disease (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.

Tecentriq was administered as a fixed dose of 1200 mg by IV 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 at 75 mg/m^2 by IV infusion on day 1 of each 21 day

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 Tecentriq arm.

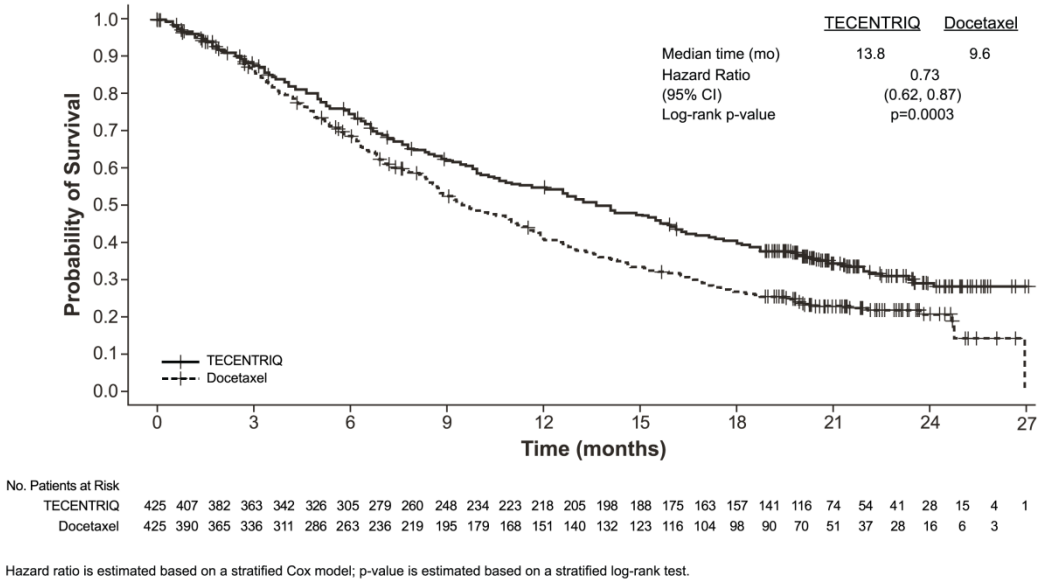
The primary efficacy endpoint was OS. The key results of this study with a median survival follow-up of 21 months are summarised in Table 15. Kaplan-Meier curves for OS in the ITT population are presented in Figure 10. Figure 11 summarises the results of OS in the ITT and PD-L1 subgroups, demonstrating OS benefit with Tecentriq in all subgroups, including those with PD-L1 expression < 1% in TC and IC.

Table 15. Summary of Efficacy in the Primary Analysis Population (OAK)

Efficacy endpoints	**Tecentriq**	**Docetaxel**
Primary Efficacy Endpoint		
OS		
All comers*	n = 425	n = 425
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%)
PD-L1 expression greater than or equal to 1% in TC or IC	n = 241	n = 222
No. of deaths (%)	151 (63%)	149 (67%)
Median time to events (months)	15.7	10.3
95% CI	(12.6, 18.0)	(8.8, 12.0)
Stratified[#] hazard ratio (95% CI)	0.74 (0.58, 0.93)	
p-value**	0.0102	
12-month OS (%)	58%	43%
18-month OS (%)	44%	29%
Secondary Endpoints		
Investigator-assessed PFS (RECIST v1.1)		
All comers*	n = 425	n = 425
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)		
All comers*	n = 425	n = 425
No. of responders (%)	58 (14%)	57 (13%)
95% CI	(10.5, 17.3)	(10.3, 17.0)
Investigator-assessed DOR (RECIST v1.1)		
All comers*	n = 58	n = 57
Median in months	16.3	6.2
95% CI	(10.0, NE)	(4.9, 7.6)

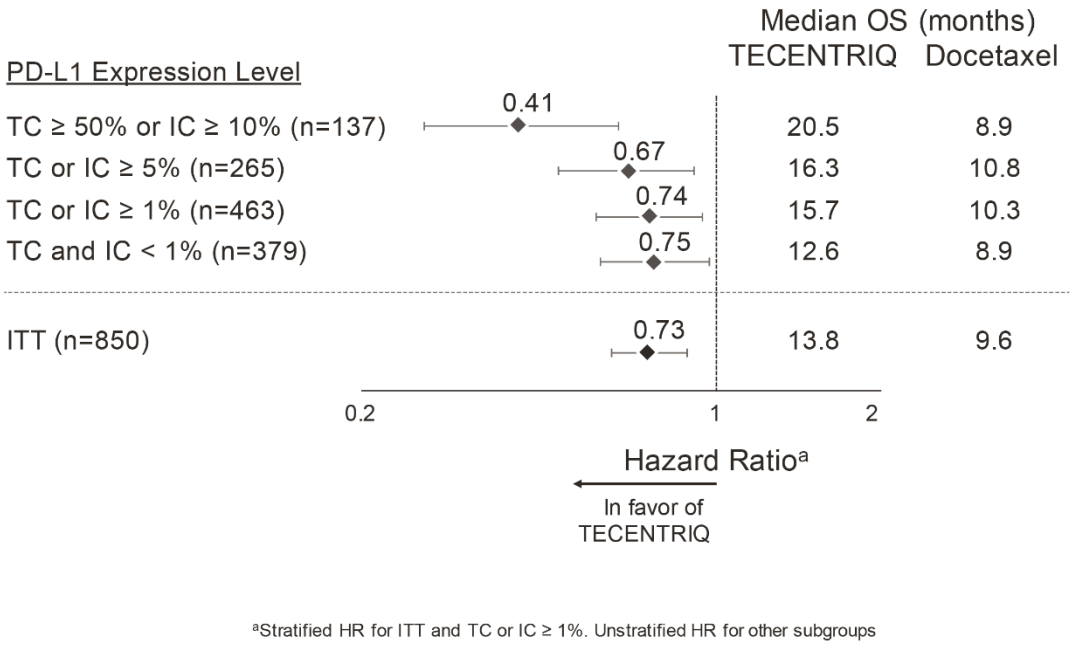
CI = confidence interval; DOR = duration of objective response; IC = tumour-infiltrating immune cells; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1; TC = tumour cells.
* All comers refers to the primary analysis population consisting of the first 850 randomised patients
# Stratified by PD-L1 expression in ICs, the number of prior chemotherapy regimens, and histology
** Based on the stratified log-rank test

Figure 10. Kaplan-Meier Plot for Overall Survival in the Primary Analysis Population (all comers) (OAK)



Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test.

Figure 11. 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 subgroups

An improvement in OS was observed with Tecentriq 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 Tecentriq 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 Tecentriq 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 Tecentriq 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 Tecentriq and docetaxel, respectively). However, patients with EGFR mutations did not show improved OS with Tecentriq compared to docetaxel (HR of 1.24, 95% CI: 0.71, 2.18; median OS of 10.5 vs. 16.2 months for Tecentriq and docetaxel respectively).

Based on patient responses to the EORTC QLQ-LC13 questionnaire in the OAK study, the hazard ratio (Tecentriq versus docetaxel) for time to deterioration of patient-reported pain in chest was 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) was similar between arms. A delay in the time to deterioration (TTD) in physical function (HR, 0.75; 95% CI, 0.58-0.98) was observed with Tecentriq. These results should be interpreted with caution due to the open-label design of the study and lack of multiplicity control for these study endpoints.

POPLAR (GO28753)

A phase II, multicentre, international, randomised, open-label, controlled study, POPLAR (GO28753) 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 Tecentriq (1200 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 (according to the VENTANA PD-L1 (SP142) Assay), 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 Tecentriq, 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 Tecentriq vs. docetaxel, respectively.

Small cell lung cancer

IMpower133 (GO30081)

A Phase I/III, randomised, multicentre, double-blind, placebo controlled study, IMpower133 (GO30081), was conducted to evaluate the efficacy and safety of Tecentriq in combination with carboplatin and etoposide in patients with chemotherapy-naïve ES-SCLC. A total of 403 patients were 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.

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

Table 16. Intravenous treatment regimen in IMpower133

Treatment regimen	Induction (four 21-day cycles)	Maintenance (21-day cycles)

A	Tecentriq (1200 mg)[a] + carboplatin (AUC 5)[b] + etoposide (100 mg/m^2)[b,c]	Tecentriq (1200 mg) [a]
B	placebo + carboplatin (AUC 5)[b] + etoposide (100 mg/m^2)[b,c]	placebo

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

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: 26 to 90 years). The majority of patients were male (65%), white (80%), and 9% had brain metastases and most patients were current or previous smokers (97%). Baseline ECOG performance status was 0 (35%) or 1 (65%).

At the time of the primary analysis, patients had a median survival follow up time of 13.9 months. The key results are summarised in Table 17. Kaplan-Meier curves for OS and PFS are presented in Figure 12 and 13.

Table 17. Summary of efficacy from IMpower133

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

Key efficacy endpoints	Arm A (Tecentriq + carboplatin + etoposide)	Arm B (placebo + carboplatin + etoposide)
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

Figure 12. Kaplan-Meier plot of overall survival (IMpower133)

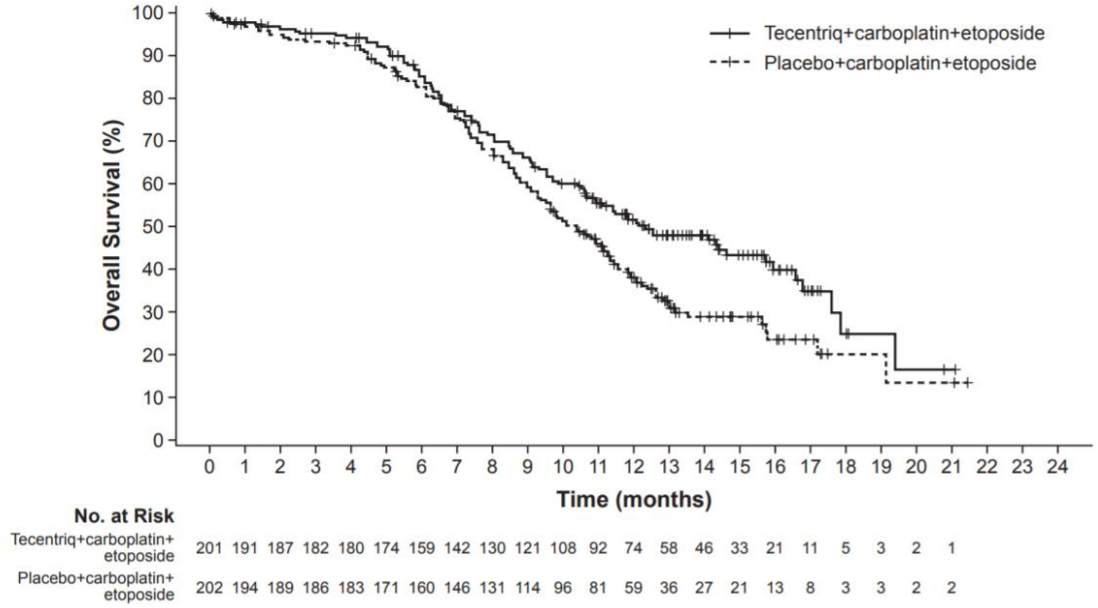
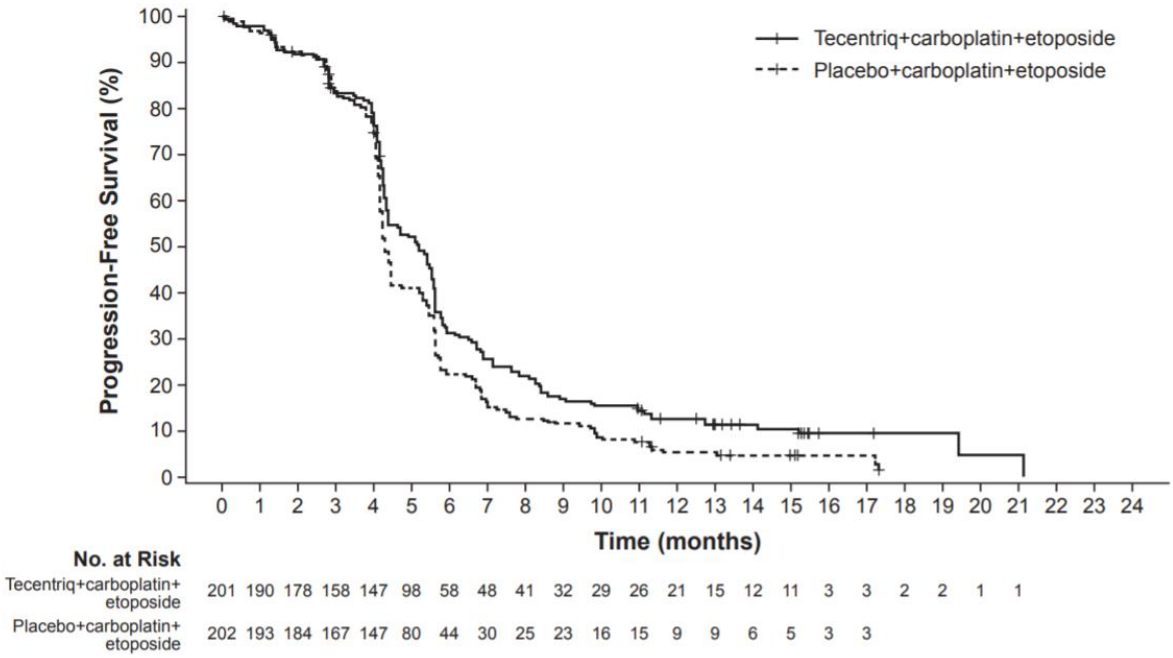


Figure 13. Kaplan-Meier plot of progression-free survival (IMpower133)



Urothelial carcinoma

IMvigor210 (GO29293)

The efficacy of Tecentriq was investigated in IMvigor210 (Cohort 1) (GO29293), a multicentre, open-label, single-arm trial that included 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy and were either previously untreated or had disease progression at least 12 months after neoadjuvant or adjuvant chemotherapy. Patients were considered cisplatin-ineligible if they met any one of the following criteria at study entry: impaired renal function [creatinine clearance (CLcr) of 30 to 59 mL/min], ECOG performance status (PS) of 2, hearing loss of ≥ 25 decibels (dB) at two contiguous frequencies, or Grades 2 to 4 peripheral neuropathy. 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; or administration of systemic immunostimulatory agents within 6 weeks or systemic immunosuppressive medications within 2 weeks prior to enrolment.

Patients received Tecentriq 1200 mg as an intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Tumour response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed overall response rate (ORR) as assessed by independent review facility (IRF) using Response Evaluation Criteria in Solid Tumours (RECIST v1.1), duration of response (DoR) and overall survival (OS).

In this study, the median age was 73 years, 81% were male, and 91% were White. Thirty-five percent of patients had non-bladder urothelial carcinoma and 66% had visceral metastases. Eighty percent of patients had an ECOG PS of 0 or 1. Reasons for ineligibility for cisplatin containing chemotherapy were: 70% had impaired renal function, 20% had an ECOG PS of 2, 14% had a hearing loss of ≥ 25dB, and 6% had Grades 2 to 4 peripheral neuropathy at baseline. Twenty percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy.

Tumour specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory, and the results were used to define subgroups for pre-specified analyses. Of the 119 patients, 27% were classified as having PD-L1 expression of ≥ 5% (defined as PD-L1 stained tumour-infiltrating immune cells [IC] covering ≥ 5% of the tumour area). The remaining 73% of patients were classified as having PD-L1 expression of < 5% (PD-L1 stained tumour infiltrating IC covering < 5% of the tumour area).

Among the 32 patients with PD-L1 expression of ≥ 5%, median age was 67 years, 81% were male, 19% female, and 88% were White. Twenty-eight percent of patients had non-bladder urothelial carcinoma and 56% had visceral metastases. Seventy-two percent of patients had an ECOG PS of 0 or 1. Reasons for ineligibility for cisplatin-containing chemotherapy were: 66% had impaired renal function, 28% had an ECOG PS of 2, 16% had a hearing loss ≥ 25 dB, and 9% had Grades 2 - 4 peripheral neuropathy at baseline. Thirty-one percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy.

Confirmed ORR in all patients and the two PD-L1 subgroups are summarised in Table 18. The median follow-up time for this study was 14.4 months. In 24 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 33% (95% CI: 16%, 55%).

Table 18. Efficacy results from IMvigor210 Cohort 1

	All patients	PD-L1 expression subgroups	
		PD-L1 expression of < 5% in ICs[1]	PD-L1 expression of ≥ 5% in ICs[1]
	n = 119	n = 87	n = 32
Number of IRF-assessed confirmed responders	28	19	9
ORR% (95% CI)	23.5% (16.2, 32.2)	21.8% (13.7, 32)	28.1% (13.8, 46.8)
Complete response (CR) (%)	6.7%	6.9%	6.3%
Partial response (PR) (%)	16.8%	14.9%	21.9%
Median DoR, months (range)	NR (3.7, 16.6+)	NR (3.7, 16.6+)	NR (8.1, 15.6+)

NR = not reached
+ Denotes a censored value
[1] PD-L1 expression in tumour-infiltrating immune cells (ICs)

IMvigor130 (WO30070)

The phase III, multicentre, randomised study IMvigor130 (WO30070) enrolled patients with locally advanced or metastatic urothelial carcinoma who had not received prior systemic therapy in the metastatic setting and were eligible for platinum-containing chemotherapy. Cisplatin eligibility was by investigator judgement, guided by Galsky criteria. Tumour specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory. A total of 1213 patients were enrolled and were randomised 1:1:1 to receive Tecentriq, chemotherapy or both, as summarised in Table 19. Changes to study design over time resulted in uneven arm sizes and a population enriched for patients who were cisplatin ineligible. Randomisation was stratified by PD-L1 tumour expression on tumour-infiltrating immune cells (IC), Bajorin model risk factor score / liver metastasis and whether the pre-randomisation investigator's choice of chemotherapy was cisplatin or carboplatin.

At an unplanned early analysis, based on an independent Data Monitoring Committee (iDMC) recommendation, accrual of patients on the Tecentriq monotherapy treatment arm whose tumours had a low PD-L1 expression (PD-L1 stained tumour-infiltrating immune cells [IC] covering <5% of the tumour area) was stopped. This was recommended due to an observation of decreased overall survival (OS) for this subgroup at an unplanned early analysis, which occurred after the vast majority of patients had already been enrolled. No other changes were recommended for the study, including any change of therapy for patients who had already been randomised to and were receiving treatment in the monotherapy arm.

Table 19. Intravenous treatment regimens in the IMvigor130 study

Treatment arm	Treatment regimen	Blinding
A	Tecentriq [a] + chemotherapy [b]	Blinded (Tecentriq vs placebo)
B	Tecentriq [a]	Open-label
C	Placebo + chemotherapy [b]	Blinded (Tecentriq vs placebo)

[a] Tecentriq (1200 mg) was administered every 3 weeks until progressive disease or unacceptable toxicity as assessed by the investigator
[b] Chemotherapy (gemcitabine [1000 mg/m^2] plus either carboplatin [AUC 4.5] or cisplatin [70 mg/m^2]) was administered until progressive disease or unacceptable toxicity. For each 21-day cycle, gemcitabine was administered on days 1 and 8; cisplatin or carboplatin was administered on day 1.

The co-primary efficacy endpoints for IMvigor130 were investigator-assessed progression-free survival (PFS) and overall survival (OS). Secondary efficacy endpoints were objective response

rate (ORR) and duration of response (DOR). The median survival follow up was 13.4 months (range: 0.0 – 71.7 months).

The study did not meet the co-primary endpoint of OS and did not demonstrate a comparative clinical benefit of atezolizumab over platinum-based chemotherapy, whether given as monotherapy or in combination with chemotherapy, in the intention-to-treat (ITT) population. A description of selected exploratory findings from IMvigor130 are provided in Table 20, including amongst the stratum of patients for whom the investigator's pre-randomisation choice of platinum agent was carboplatin, and in subgroups based on whether PD-L1 stained tumour-infiltrating immune cells [IC] covered <5% (PD-L1 low) or at least 5% higher (PD-L1 high) of the tumour area.

Table 20. Description of exploratory, investigator-assessed outcomes in Arms B and C of IMvigor130 in the ITT and in selected subgroups

	ITT		**Carboplatin [a]**		**PD-L1 low [b]**		**PD-L1 high [c]**	
	B	**C**	**B**	**C**	**B**	**C**	**B**	**C**
	n=360	**n=359**	**n=225**	**n=223**	**n=272**	**n=274**	**n=88**	**n=85**
ORR								
ORR, %	24	44	25	41	19	44	41	45
ORR 95% CI	20, 29	39, 59	20, 32	34, 48	14, 24	38, 50	31, 52	34, 57
CR rate (%)	8	8	9	6	7	6	13	13
DOR								
Median, months	29.6	8.1	20.8	6.5	22.3	7.6	48.5	8.6
95% CI	15.9, NE	6.3, 8.5	13.1, 40.9	6.1, 8.5	13.9, 38.4	6.3, 8.5	13.9, NE	5.8, 14.4
PFS								
Median, months	2.7	6.3	2.8	6.2	2.2	6.3	7.0	6.3
95% CI	2.2, 4.0	6.2, 6.7	2.2, 4.2	6.1, 6.7	2.1, 2.4	6.2, 6.7	4.7, 12.5	6.0, 8.3
OS								
Median, months	15.2	13.3	14.6	13.0	13.5	12.9	27.5	16.7
95% CI	13.1, 17.7	11.9, 15.6	11.8, 17.7	10.6, 15.6	11.1, 16.3	11.6, 15.0	17.7, 49.4	10.0, 26.1
HR (95% CI)	0.98 (0.82, 1.16)		0.92 (0.75, 1.14)		1.03 (0.85, 1.24)		0.70 (0.48, 1.03)	

B = Tecentriq monotherapy; C = platinum-based chemotherapy; CI = confidence interval; CR = complete response; DOR = duration of response; HR = hazard ratio; ITT = intent-to-treat; n = number of patients; NE = not estimable; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; ORR = objective response rate amongst those with measurable disease; OS=overall survival.

[a] Patients for whom the investigator's pre-randomisation choice of platinum agent was carboplatin.

[b] PD-L1 positive tumour-infiltrating immune cells (IC) covered <5% of the tumour area

[c] PD-L1 positive IC covered at least 5% of the tumour area

<u>Hepatocellular carcinoma</u>

IMbrave150 (YO40245)

A global phase III, randomised, multicentre, open-label study, IMbrave150 (YO40245) was conducted to evaluate the efficacy and safety of Tecentriq 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 randomised (2:1) to receive either

Tecentriq 1200 mg and 15 mg/kg of bevacizumab every 3 weeks administered via IV infusion, or sorafenib 400 mg orally twice per day. Randomisation was stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), baseline AFP (< 400 vs. ≥ 400 ng/mL) and ECOG performance status (0 vs. 1). Patients in both arms received treatment until loss of clinical benefit or unacceptable toxicity. Patients could discontinue either Tecentriq 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 who were ECOG 0/1. 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. Patients were also excluded if they had Child-Pugh B or C cirrhosis; moderate or severe ascites; history of hepatic encephalopathy; a history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomisation; administration of systemic immunostimulatory agents within 4 weeks, or systemic immunosuppressive medications within 2 weeks, prior to randomisation; untreated or corticosteroid-dependent brain metastases. Tumour assessments were performed every 6 weeks for the first 54 weeks and every 9 weeks thereafter.

The demographic and baseline disease characteristics of the study population were 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). 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%). HCC risk factors 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 categorised 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 overall survival (OS) and independent review facility (IRF)-assessed progression free survival (PFS) according to RECIST v1.1. Additional efficacy outcome measures were IRF-assessed objective response rate (ORR) per RECIST v1.1 and HCC modified RECIST (mRECIST). Efficacy results are summarised in Table 21. Kaplan-Meier curves for OS and PFS are presented in Figures 14 and 15.

Table 21. Summary of efficacy from IMbrave150

Key efficacy endpoints	Tecentriq + 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[1] (95% CI)	0.58 (0.42, 0.79)	
p-value[2]	0.0006[2]	
IRF-assessed PFS[3]	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[1] (95% CI)	0.59 (0.47, 0.76)	
p-value[1]	<0.0001	

Key efficacy endpoints	Tecentriq + bevacizumab		Sorafenib	
	RECIST v1.1		HCC mRECIST	
	Tecentriq + bevacizumab	Sorafenib	Tecentriq + bevacizumab	Sorafenib
IRF-assessed ORR[3,5]	n = 336	n = 165	n = 336	n = 165
No. of confirmed responders (%)	93 (27.7%)	19 (11.5%)	112 (33.3%)	21 (12.7%)
95% CI	(23.0, 32.8)	(7.1, 17.4)	(28.3, 38.7)	(8.1, 18.8)
p-value[4]	<0.0001		<0.0001	
No. of complete responses (%)	22 (6.5%)	0	37(11.0%)	3 (1.8%)
No. of partial responses (%)	71 (21.1%)	19 (11.5%)	75 (22.3%)	18 (10.9%)
IRF-assessed DOR[3,5]	n = 93	n = 19	n = 112	n = 21
Median in months	NE	6.3	NE	6.3
95% CI	(NE, NE)	(4.7, NE)	(NE, NE)	(4.9, NE)
Range (months)	(1.3+, 13.4+)	(1.4+, 9.1+)	(1.3+, 13.4+)	(1.4+, 9.1+)

[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)
[2] Based on stratified log-rank test; as compared to significance level 0.004 (2-sided) based on 161/312=52% information using the OBF method
[3] Per independent radiology review
[4] Based on stratified Cochran-Mantel-Haenszel test
[5] Confirmed responses
[+] Denotes a censored value
PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours 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; N/A = not applicable

Figure 14. Kaplan-Meier Plot for Overall Survival (IMbrave150)

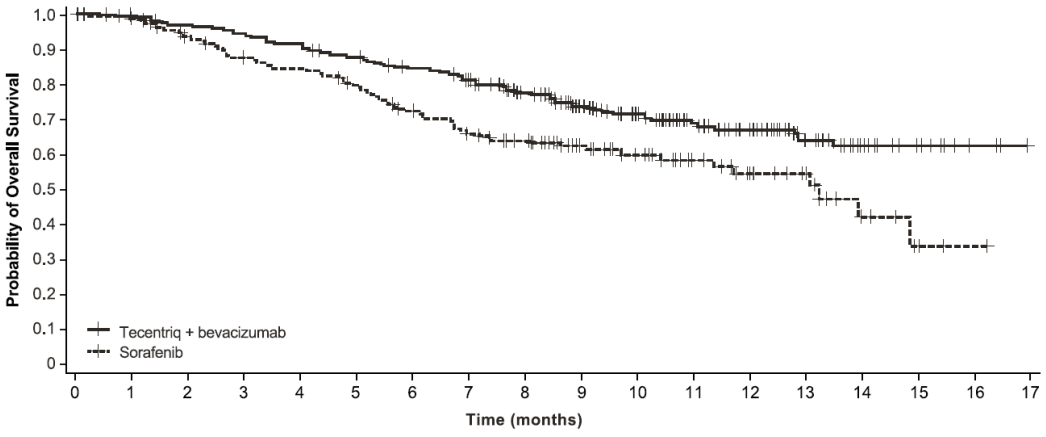
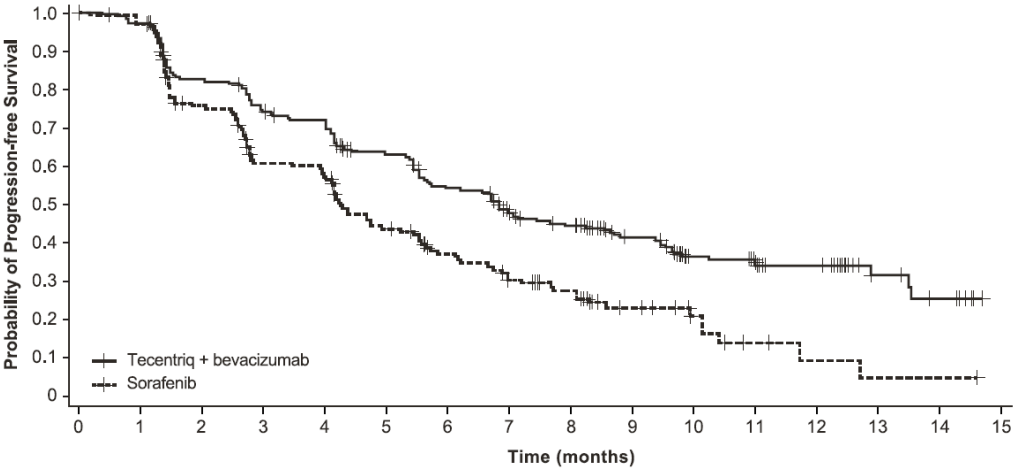


Figure 15. Kaplan-Meier Plot for Progression-Free Survival per RECIST v1.1 (IMbrave150)



No. of Patients at Risk																
Tecentriq + bevacizumab	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

The study also evaluated patient-reported outcomes using the EORTC QLQ-C30 and EORTC QLQ-HCC18 questionnaires. Treatment with Tecentriq and bevacizumab delayed clinically meaningful deterioration of patient-reported physical functioning, role functioning, global health status/quality of life and key symptoms (i.e. appetite loss, diarrhoea, fatigue and pain) versus sorafenib.

Immunogenicity

GO29436 (IMpower150)

Exploratory analyses adjusting for imbalances in baseline health and disease characteristics showed that the subset of patients in the four drug regimen arm who were ADA positive by week 4 (32%) appeared to have similar efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 (68%). The OS hazard ratio comparing the ADA-positive subgroup of the four drug regimen to the three drug regimen (control) was 0.77 (95% CI: 0.57, 1.02). The OS hazard ratio comparing the ADA-negative subgroup to control was 0.73 (95% CI: 0.58, 0.93).

GO28915 (OAK)

Exploratory analyses adjusting for imbalances in baseline health and disease characteristics showed that the subset of patients who were ADA positive by week 4 (22%) appeared to have similar efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 (78%). The OS hazard ratio comparing the ADA-positive subgroup of the Tecentriq arm to docetaxel was 0.75 (95% CI: (0.57, 0.98). The OS hazard ratio comparing the ADA-negative subgroup to docetaxel was 0.69 (95% CI: (0.56, 0.84).

YO40245 (IMbrave150)

Exploratory analyses adjusting for imbalances in baseline health and disease characteristics showed that the subset of patients (20%) who were ADA-positive by week 6 appeared to have reduced efficacy (effect on OS) as compared to patients (80%) who tested negative for treatment-emergent ADA by week 6. ADA-positive patients by week 6 appeared to have similar overall survival compared to sorafenib-treated patients. The OS hazard ratio comparing the ADA-positive subgroup of the Tecentriq and bevacizumab arm to sorafenib was 0.95 (95% CI: 0.57, 1.59). The OS hazard ratio comparing the ADA-negative subgroup to sorafenib was 0.41 (95% CI: 0.27, 0.62).

5.2 Pharmacokinetic properties

The pharmacokinetics of atezolizumab have been characterised in patients in multiple clinical trials at doses 0.01 mg/kg to 20 mg/kg every 3 weeks including the fixed dose of 1200 mg. Exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg. A population analysis that included 472 patients described atezolizumab pharmacokinetics for the dose range 1 - 20 mg/kg with a linear two-compartment disposition model with first-order elimination. The pharmacokinetic properties of atezolizumab 840 mg administered every 2 weeks and 1200 mg administered every 3 weeks, are comparable. A population pharmacokinetic analysis suggests that steady-state is obtained after multiple doses. The maximum systemic accumulation in area under the curve (AUC), maximum concentration (C_{max}) and trough concentration (C_{min}) are 2.54, 1.84 and 3.05-fold, respectively.

Based on analyses of population pharmacokinetics and exposure-safety and -efficacy relationships, the following factors have no clinically relevant effect: age (21 - 89 years), body weight, gender, albumin levels, tumour burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or Eastern Cooperative Oncology Group (ECOG) status. No dose adjustments are recommended.

Absorption

Tecentriq is administered as an intravenous (IV) infusion. There have been no studies performed with other routes of administration.

Distribution

A population pharmacokinetic analysis indicates that central compartment volume of distribution (V_1) is 3.28 L and volume at steady-state (V_{ss}) is 6.91 L in the typical patient.

Metabolism

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

Excretion

A population pharmacokinetic analysis indicates that the clearance of atezolizumab is 0.200 L/day and the typical terminal elimination half-life ($t_{1/2}$) is 27 days.

Pharmacokinetics in Special Populations

Hepatic impairment

No dedicated studies of Tecentriq have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of atezolizumab between patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 X ULN and any AST) or moderate hepatic impairment (bilirubin >1.5 to 3x ULN and any AST). No data are available in patients with severe (bilirubin > 3.0 × ULN and any AST) hepatic impairment. Hepatic impairment was defined by the National Cancer Institute (NCI) criteria of hepatic dysfunction (see section *4.2 Dose and method of administration*). The effect of moderate or severe hepatic impairment (bilirubin > 1.5 × to 3 × ULN and any AST or bilirubin > 3 × ULN and any AST) on the pharmacokinetics of atezolizumab is unknown.

Renal impairment

No dedicated studies of Tecentriq 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 (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 Dose and method of a administration*). The effect of severe renal impairment on the pharmacokinetics of atezolizumab is unknown.

Elderly

No dedicated studies of Tecentriq 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 Dose and method of administration*).

5.3 Preclinical safety data

Genotoxicity

No genotoxicity studies have been conducted with atezolizumab.

Carcinogenicity

No carcinogenicity studies have been conducted with atezolizumab.

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. Atezolizumab had an effect on menstrual cycles in all female monkeys in the 50 mg/kg dose group characterised by an irregular cycle pattern during the dosing phase and correlated with the lack of fresh corpora lutea in the ovaries at the terminal necropsy; this effect was reversible during the dose-free recovery period. The AUC at the no effect level was approximately 5 times that anticipated in patients. There was no effect on the male reproductive organs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine, glacial acetic acid, sucrose, polysorbate 20 and water for injections.

6.2 Incompatibilities

No incompatibilities have been observed between Tecentriq and IV bags with product-contacting surfaces of polyvinyl chloride (PVC), polyethylene (PE), polyolefin or polypropylene (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.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

The diluted solution for infusion should be used immediately. If the solution is not used immediately, it can be stored for up to 24 hours at 2 °C to 8 °C, or 8 hours at ambient temperature (≤ 25 °C).

6.4 Special precautions for storage

Store the vials at 2 °C to 8 °C. Do not freeze.

Tecentriq should be protected from light. Do not shake.

This medicine should not be used after the expiry date (EXP) shown on the pack.

6.5 Nature and contents of container

Tecentriq is available in a single-use glass vial containing 14 mL or 20 mL solution in a pack size of 1 vial.

6.6 Special precautions for disposal

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 Physicochemical properties

Chemical structure

Tecentriq is an engineered, humanised, monoclonal antibody that directly binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors. Tecentriq is a non-glycosylated IgG1 immunoglobulin that has a calculated molecular mass of 145 kDa.

CAS number

1380723-44-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9 DATE OF FIRST APPROVAL

27 July 2017

10 DATE OF REVISION

29 January 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Information added regarding switching patients from intravenous Tecentriq to Tecentriq SC (and vice versa) based on IMscin002 data
4.4	Addition of uveitis; CMV infection/reactivation in some patients with immune-mediated colitis
4.8	Addition of ADRs: Neutropenia, Uveitis, Sarcoidosis, Cytomegalovirus infection, Arthritis, Tenosynovitis
5.1	Addition of ATC code