NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Tecentriq® (atezolizumab), 840 mg/14 mL, concentrate for solution for intravenous infusion.

Tecentriq® (atezolizumab), 1200 mg/20 mL, concentrate for solution for intravenous infusion.

Tecentriq® SC (atezolizumab), 1875 mg/15 mL, solution for subcutaneous injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Atezolizumab 60 mg/mL supplied as:

- 14 mL vial containing 840 mg atezolizumab concentrate for solution for intravenous (IV) infusion
- 20 mL vial containing 1200 mg atezolizumab concentrate for solution for intravenous (IV) infusion

Atezolizumab 125 mg/mL supplied as:

- 15 mL vial containing 1875 mg atezolizumab solution for subcutaneous (SC) injection

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for intravenous (IV) infusion

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

Solution for subcutaneous (SC) injection

Tecentriq SC is supplied as a sterile, ready to use, single-dose vial containing 15 mL preservative-free, colourless to slightly yellow solution, at a concentration of 125 mg/mL.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Intravenous Tecentriq and Tecentriq SC

Early-stage non-small cell lung cancer

Tecentriq as monotherapy is indicated as adjuvant treatment following resection and platinum-based chemotherapy for patients with stage II to IIIA* non-small cell lung cancer (NSCLC) whose tumours have PD-L1 expression on ≥ 1% of tumour cells (TC).

* *According to American Joint Committee on Cancer [7th edition]*

Metastatic non-small cell lung cancer

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

Tecentriq, in combination with paclitaxel and carboplatin, is indicated for the first-line treatment of patients with metastatic non-squamous NSCLC who do not have tumour EGFR or ALK genomic aberrations and whose tumours have PD-L1 expression ≥ 1%.

Tecentriq, in combination with 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 first-line treatment of adults with metastatic NSCLC whose tumours have high PD-L1 expression (PD-L1 stained ≥ 50% of tumour cells [TC ≥ 50%] or PD-L1 stained tumour-infiltrating immune cells [IC] covering ≥ 10% of the tumour area [IC ≥ 10%]) as determined by a validated test, and who do not have EGFR or ALK genomic tumour aberrations.

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy.

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 adult patients with locally advanced or metastatic urothelial carcinoma (UC) who:

- are considered cisplatin ineligible and whose tumours have a PD-L1 expression ≥ 5%, or
- have disease progression during or following platinum-containing chemotherapy, or
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Triple-negative breast cancer

Tecentriq, in combination with nab-paclitaxel, is indicated for the treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1%, and who have not received prior chemotherapy for metastatic disease.

Hepatocellular carcinoma

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

4.2 DOSE AND METHOD OF ADMINISTRATION

General

Tecentriq must be administered under the supervision of a qualified healthcare professional.

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.

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

It is important to check the product labels to ensure that the correct formulation (intravenous Tecentriq or Tecentriq SC) is being administered to the patient as prescribed.

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

Intravenous Tecentriq
Tecentriq intravenous formulation is not intended for subcutaneous administration.

Tecentriq SC
Tecentriq SC formulation is not intended for intravenous administration.
Tecentriq SC must be administered as a subcutaneous injection only (see section 4.2 Instructions for Administration).

PD-L1 testing (1L cisplatin-ineligible metastatic urothelial carcinoma, TNBC and NSCLC PD-L1 selected indications):

Patients should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1 PD-L1 expression by IHC).

Dose

Tecentriq monotherapy

Table 1. Recommended Dosage of Tecentriq as Monotherapy by intravenous infusion or subcutaneous (SC) injection

Indication	**Recommended Dosage of Tecentriq**	**Duration of Therapy**
Urothelial carcinoma and Metastatic NSCLC	Intravenous Tecentriq • 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks or Tecentriq SC • 1875 mg every 3 weeks	Patients are treated with Tecentriq or Tecentriq SC until loss of clinical benefit (see section 5.1) or unmanageable toxicity.
Early stage NSCLC	Intravenous Tecentriq • 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks or Tecentriq SC 1875 mg every 3 weeks	Patients are treated with Tecentriq or Tecentriq SC for 1 year unless there is disease recurrence or unacceptable toxicity (see section 5.1).

Tecentriq combination therapy

Please also refer to the Data Sheets for the combination products.

Table 2. Recommended Dosage of Tecentriq in combination therapy by intravenous (IV) infusion or subcutaneous (SC) injection

Indication	Recommended Dosage of Tecentriq - Induction	Recommended Dosage of Tecentriq - Maintenance	Duration of Therapy
1L non-squamous metastatic NSCLC (in combination with bevacizumab, paclitaxel, and carboplatin)	During the induction phase, the recommended dose of Tecentriq is either: Intravenous Tecentriq 1200 mg, followed by bevacizumab then paclitaxel and carboplatin every 3 weeks for four or six cycles. or Tecentriq SC 1875 mg, followed by bevacizumab, then paclitaxel and carboplatin every 3 weeks for four or six cycles.	The induction phase is followed by a maintenance phase without chemotherapy in which the recommended dose is either: Intravenous Tecentriq 1200 mg, followed by bevacizumab administered every 3 weeks. or Tecentriq SC 1875 mg, followed by bevacizumab every 3 weeks. During the maintenance phase and if bevacizumab is discontinued, the recommended dosage of intravenous Tecentriq is either: • 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks or Tecentriq SC 1875 mg every 3 weeks.	Patients are treated with Tecentriq until loss of clinical benefit (see section 5.1) or unmanageable toxicity.

1L non-squamous metastatic NSCLC (in combination with paclitaxel and carboplatin)	During the induction phase, the recommended dose of Tecentriq is either: Intravenous Tecentriq 1200 mg, followed by paclitaxel and carboplatin every 3 weeks for four or six cycles or Tecentriq SC 1875 mg, followed by paclitaxel and carboplatin every 3 weeks for four or six cycles	The induction phase is followed by a maintenance phase without chemotherapy in which the recommended dosage of intravenous Tecentriq is either: • 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks or Tecentriq SC 1875 mg every 3 weeks.	Patients are treated with Tecentriq until loss of clinical benefit (see section 5.1) or unmanageable toxicity.
1L non-squamous metastatic NSCLC (in combination with nab-paclitaxel and carboplatin)	During the induction phase, the recommended dose of Tecentriq is either: Intravenous Tecentriq 1200 mg, followed by nab-paclitaxel and carboplatin every 3 weeks for four or six cycles. For each 21-day cycle, Tecentriq, nab-paclitaxel and carboplatin are administered on day 1. In addition, nab-paclitaxel is administered on days 8 and 15. or Tecentriq SC 1875 mg, followed by nab-paclitaxel and carboplatin every 3 weeks for four or six cycles. For each 21-day cycle, Tecentriq, nab-paclitaxel and carboplatin are administered on day 1. In addition, nab-paclitaxel is administered on days 8 and 15.	The induction phase is followed by a maintenance phase without chemotherapy in which the recommended dosage of Tecentriq is either: Intravenous Tecentriq • 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks or Tecentriq SC 1875 mg every 3 weeks.	Patients are treated with Tecentriq until loss of clinical benefit (see section 5.1) or unmanageable toxicity.

1L ES-SCLC (in combination with carboplatin and etoposide)	During the induction phase, the recommended dose of Tecentriq is either: Intravenous Tecentriq 1200 mg, followed by carboplatin, and then etoposide administered by IV infusion on day 1. Etoposide is also administered by IV infusion on days 2 and 3. This regimen is administered every 3 weeks for four cycles. or Tecentriq SC 1875 mg, followed by carboplatin, and then etoposide administered by IV infusion on day 1. Etoposide is also administered by IV infusion on days 2 and 3. This regimen is administered every 3 weeks for four cycles.	The induction phase is followed by a maintenance phase without chemotherapy in which the recommended dosage of Tecentriq is either: Intravenous Tecentriq • 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks or Tecentriq SC 1875 mg every 3 weeks.	Patients are treated with Tecentriq until loss of clinical benefit (see section 5.1) or unmanageable toxicity.
1L TNBC (in combination with nab-paclitaxel)	The recommended dose of Tecentriq is either: Intravenous Tecentriq 840 mg, followed by 100 mg/m^2 nab-paclitaxel (nanoparticle albumin-bound paclitaxel). For each 28-day cycle Tecentriq is administered on days 1 and 15, and nab-paclitaxel is administered on days 1, 8 and 15. or Tecentriq SC 1875 mg every 3 weeks. Nab-paclitaxel is administered over a 28 day cycle. For each cycle nab-paclitaxel 100 mg/m^2 is administered on days 1, 8 and 15.	N/A	Patients are treated with Tecentriq until disease progression or unacceptable toxicity (see section 5.1).

Hepatocellular carcinoma (in combination with bevacizumab)	The recommended dose of Tecentriq is either: Intravenous Tecentriq 1200 mg, followed by 15 mg/kg of bevacizumab administered by IV infusion every 3 weeks. or Tecentriq SC 1875 mg, followed by 15 mg/kg of bevacizumab administered by IV infusion every 3 weeks.	If bevacizumab is discontinued, the recommended dosage of Tecentriq is either: Intravenous Tecentriq • 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks or Tecentriq SC 1875 mg every 3 weeks.	Patients are treated with Tecentriq until loss of clinical benefit (see section 5.1) or unmanageable toxicity.

Delayed or Missed Doses

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

Dose Modifications

No dose reductions of Tecentriq or Tecentriq SC are recommended.

Dose modifications for immune-mediated adverse reactions

Recommendations for specific adverse drug reactions (see sections 4.4 and 4.8) are presented in Table 3.

Table 3. Recommended dose modification for specific adverse drug reactions

Adverse reaction	Severity	Treatment modification
Infusion-related reactions (see also section 4.4)	Grade 1 or 2	Reduce infusion/injection rate or withhold/pause treatment with Tecentriq. Premedication with antipyretic and antihistamines may be considered for subsequent doses.
	Grade 3 or 4	Permanently discontinue Tecentriq.
Rash/Severe cutaneous adverse reactions (see also section 4.8)	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[3]	Withhold Tecentriq[1].
	Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[3]	Permanently discontinue Tecentriq.
Immune-mediated pneumonitis (see also section 4.4)	Grade 2	Withhold Tecentriq[1].
	Grade 3 or 4	Permanently discontinue Tecentriq.
	Grade 2:	Withhold Tecentriq[1].

Adverse reaction	Severity	Treatment modification
Immune-mediated hepatitis in patients without HCC (see also section 4.4)	(ALT or AST > 3 x ULN or blood bilirubin > 1.5 x ULN for more than 5-7 days)	
	Grade 3 or 4: (ALT or AST > 5 x ULN or blood bilirubin > 3 x ULN)	Permanently discontinue Tecentriq.
Immune-mediated hepatitis in patients with HCC	If AST/ALT is within normal limits at baseline and increases to > 3 x to ≤ 10 x ULN *or* If AST/ALT is > 1 to ≤ 3 x ULN at baseline and increases to > 5 x to ≤10 x ULN *or* If AST/ALT is > 3 x to ≤ 5 x ULN at baseline and increases to > 8 x to ≤ 10 x ULN	Withhold Tecentriq[1].
	If AST/ALT increases to > 10 x ULN or total bilirubin increases to > 3 x ULN	Permanently discontinue Tecentriq.
Immune-mediated colitis (see also section 4.4)	Grade 2 diarrhoea or colitis	Withhold Tecentriq[1].
	Grade 3 diarrhoea or colitis	Withhold Tecentriq[1]. Initiate IV corticosteroids and convert to oral corticosteroids after improvement.
	Grade 4 diarrhoea or colitis	Permanently discontinue Tecentriq.
Immune-mediated hypothyroidism (see also section 4.4)	Symptomatic	Withhold Tecentriq[2]. Initiate thyroid hormone replacement therapy.
Immune-mediated hyperthyroidism (see also section 4.4)	Symptomatic	Withhold Tecentriq[2]. Initiate anti-thyroid therapy as needed.
Immune-mediated adrenal insufficiency (see also section 4.4)	Symptomatic	Withhold Tecentriq[1].
Immune-mediated hypophysitis (see also section 4.4)	Grade 2 or 3	Withhold Tecentriq[1].
	Grade 4	Permanently discontinue Tecentriq.
Immune-mediated type 1 diabetes mellitus (see also section 4.4)	≥ Grade 3 hyperglycaemia (fasting glucose greater than 13.9 mmol/L)	Withhold Tecentriq[2]. Initiate insulin.

Adverse reaction	Severity	Treatment modification
Immune-mediated meningitis, encephalitits, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome (see also section 4.4)	Any grade	Permanently discontinue Tecentriq.
Immune-mediated myelitis (see also section 4.4)	Grade 2, 3 or 4	Permanently discontinue Tecentriq.
Immune-mediated facial paresis (see also section 4.4)	Grade 1 or 2	Withhold Tecentriq[1].
	Grade 3 or 4	Permanently discontinue Tecentriq.
Immune-mediated pancreatitis (see also section 4.4)	Grade 2 or 3 pancreatitis *or* ≥ Grade 3 serum amylase or lipase levels increased (> 2 x ULN)	Withhold Tecentriq[1].
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue Tecentriq.
Immune-mediated myocarditis (see also section 4.4)	Grade 2 or above	Permanently discontinue Tecentriq.
Immune-mediated myositis (see also section 4.4)	Grade 2 or 3	Withhold Tecentriq[1].
	Grade 4 or grade 3 recurrent myositis	Permanently discontinue Tecentriq.
Immune-mediated nephritis (see also section 4.4)	Grade 2 (creatinine level >1.5 – 3 x baseline or >1.5 – 3 x ULN)	Withhold Tecentriq[1].
	Grade 3 (creatinine level > 3 x baseline or > 3-6 x ULN) or Grade 4 (creatinine level > 6 x ULN)	Permanently discontinue Tecentriq.
Immune-mediated pericardial disorders (see also section 4.4)	Grade 1 pericarditis	Withhold Tecentriq[4].
	Grade 2 or above	Permanently discontinue Tecentriq.
Haemophagocytic lymphohistiocytosis (see also section 4.4)	Suspected haemophagocytic lymphohistiocytosis[3]	Permanently discontinue Tecentriq.

[1] Treatment with corticosteroid therapy (1 - 2 mg/kg/day prednisone or equivalent) should be initiated. Treatment with Tecentriq may be resumed in patients with complete or partial resolution (Grade 0 to

1) within 12 weeks, and after corticosteroids have been reduced to ≤ 10 mg/day oral prednisone or equivalent.

[2] Treatment with Tecentriq may be resumed when symptoms are controlled and the patient is clinically stable.

[3] Regardless of severity

[4] Conduct a detailed cardiac evaluation to determine the aetiology and manage appropriately

For other immune-mediated reactions, based on the type and severity of the reaction, treatment with Tecentriq should be withheld for Grades 2 or 3 immune-mediated adverse reactions and corticosteroid therapy (1-2 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 oral prednisone or equivalent per day.

Treatment with Tecentriq should be permanently discontinued for Grade 4 immune-mediated adverse reactions, or when unable to reduce corticosteroid dose to the equivalent of ≤ 10 mg prednisone per day within 12 weeks after onset.

Special Dosage Instructions

Paediatric population

The safety and efficacy of Tecentriq in children and adolescents below 18 years of age have not been established .

Elderly population

Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq is required in patients ≥ 65 years of age (see sections 4.4 and 5.2).

Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with renal impairment (see sections 4.4 and 5.2).

Hepatic impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild or moderate hepatic impairment. There are no data in patients with severe hepatic impairment (see sections 4.4 and 5.2).

Instructions for dilution

Intravenous Tecentriq

Tecentriq does not contain any antimicrobial preservative and should be prepared by a healthcare professional using aseptic technique. Use sterile needles and syringes 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.

Tecentriq SC

Tecentriq SC is a ready-to-use solution for subcutaneous injection only and should not be diliuted or mixed with other drugs.

Instructions for administration

Intravenous Tecentriq

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.

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

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

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

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.

Tecentriq SC

Tecentriq SC should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.

Tecentriq solution for injection is for single use only and should be prepared by a healthcare professional.

Preparation of the Syringe

Tecentriq SC does not contain any antimicrobial preservative. If the dose is not administered immediately, refer to "Storage of the Syringe" below.

Prior to use, remove the vial from the refrigerator and allow the solution to come to room temperature.

Withdraw the entire contents of Tecentriq SC solution from the vial with a syringe and transfer needle (18G recommended).

Remove the transfer needle and attach a SC infusion set (e.g. winged / butterfly) containing a 23-25G stainless steel needle for injection. Use a SC infusion set with residual hold-up volume NOT exceeding 0.5 mL for administration.

Prime the SC infusion line with the drug product solution to eliminate the air in the infusion line and stop before the fluid reaches the needle.

Ensure the syringe contains exactly 15 mL of drug product solution after priming and expelling any excess volume from the syringe.

Administer immediately to avoid needle clogging. DO NOT store the prepared syringe that has been attached to the already-primed infusion set.

Administer Tecentriq SC solution subcutaneously in the thigh over approximately 7 minutes. DO NOT administer the remaining residual hold-up volume in the tubing to the patient.

The injection site should be alternated between the left and right thigh only. New injections should be given at least 2.5 cm from the previous site on healthy skin and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with Tecentriq SC, other medications for subcutaneous administration should preferably be injected at different sites.

Storage of the syringe
If the dose is not used immediately, use aseptic technique to withdraw the entire contents of Tecentriq SC solution from the vial into the syringe to account for the dose volume (15mL) plus the priming volume for the SC infusion set. Replace the transfer needle with a syringe closing cap. DO NOT attach a SC infusion set for storage.

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

Immune-mediated pneumonitis

Cases of pneumonitis, including fatal cases, have been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis. Refer to section 4.2 for recommended dose modifications.

Immune-mediated hepatitis

Cases of hepatitis, some leading to fatal outcomes, have been observed in clinical trials with Tecentriq (see section 4.8). 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. Refer to section 4.2 for recommended dose modifications.

Immune-mediated colitis

Cases of diarrhoea or colitis have been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for signs and symptoms of colitis. Refer to section 4.2 for recommended dose modifications.

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). Patients should be monitored for clinical signs and symptoms of endocrinopathies. Monitor thyroid function prior to and periodically during treatment with Tecentriq. Appropriate management of patients with abnormal thyroid function tests at baseline should be considered. Patients with abnormal thyroid function tests who are asymptomatic may receive Tecentriq. Refer to section 4.2 for recommended dose modifications.

Immune-mediated meningoencephalitis

Meningoencephalitis has been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for clinical signs and symptoms of meningitis or encephalitis. Refer to section 4.2 for recommended dose modifications.

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). Patients should be monitored for symptoms of motor and sensory neuropathy. Refer to section 4.2 for recommended dose modifications.

Immune-mediated myelitis

Myelitis has been observed in clinical trials with Tecentriq (see section 4.8). Patients should be closely monitored for signs and symptoms that are suggestive of myelitis. Refer to section 4.2 for recommended dose modifications.

Immune-mediated pancreatitis

Pancreatitis, including increases in serum amylase and lipase levels, has been observed in clinical trials with Tecentriq (see section 4.8). Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis. Refer to section 4.2 for recommended dose modifications.

Haemophagocytic lymphohistiocytosis

Haemophagocytic lymphohistiocytosis (HLH), including fatal cases, has been reported in patients receiving Tecentriq (see section 4.8). HLH should be considered when the presentation of cytokine release syndrome is atypical or prolonged. Patients should be monitored for clinical signs and symptoms of HLH. Refer to section 4.2 for recommended dose modifications.

Immune-mediated myocarditis

Myocarditis, including fatal cases, has been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for signs and symptoms of myocarditis. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly. Refer to section 4.2 for recommended dose modifications.

Immune-mediated myositis

Cases of myositis, including fatal cases, have been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for signs and symptoms of myositis. Patients with possible myositis should be monitored for signs of myocarditis. Refer to section 4.2 for recommended dose modifications.

Immune-mediated nephritis

Nephritis has been observed in clinical trials with Tecentriq (see section 4.8). Patients should be monitored for changes in renal function. Refer to section 4.2 for recommended dose modifications.

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). Patients should be monitored for clinical signs and symptoms of pericardial disorders. Refer to section 4.2 for recommended dose modifications.

Infusion and injection related reactions

Infusion related reactions (IRRs) have been observed in clinical trials with intravenous Tecentriq, including anaphylaxis (see section 4.8). Injection related reactions have been

observed in clinical trials with Tecentriq SC. Refer to section 4.2 for recommended dose modifications.

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 until recovery to Grade ≤ 1 or permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered (see section 4.2).
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.

Patients with autoimmune disease

Patients with autoimmune disease were excluded from clinical trials with Tecentriq. In the absence of data, Tecentriq should be used with caution in patients with autoimmune disease, after assessment of the potential risk-benefit.

Use in renal impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with renal impairment (see sections 4.2 and 5.2).

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 and 5.2). There are no data in patients with severe hepatic impairment.

Paediatric use

Tecentriq is not approved for use in patients under the age of 18 years. The safety and efficacy of Tecentriq in this population has not been established. An early phase, multi-centre open-label study was conducted in paediatric (< 18, n=69) and young adult patients (18-30 years, n=18) with relapsed or progressive solid tumours as well as with Hodgkin's and non-Hodgkin's lymphoma, to evaluate the safety and pharmacokinetics of atezolizumab (see section 5.2). No new safety signals were observed and the safety profile in patients < 18 years was comparable to adults.

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 and 5.2).

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Contraception

Women of childbearing potential should use highly effective contraception and take active measures to avoid pregnancy during treatment with Tecentriq and for at least 5 months after the last dose.

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 fetus, including embryo lethality. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus 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.

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

Breastfeeding

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.

Fertility

Based on animal studies, Tecentriq may impair fertility in females of reproductive potential while receiving treatment (see *Preclinical safety data*).

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.

4.8 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 monotherapy is based on pooled data in 3075 patients with multiple tumour types, with supporting data from the estimated cumulative exposure in > 13,000 patients across all clinical trials in multiple tumour types.

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

Table 4. Summary of ADRs occurring in patients treated with intravenous Tecentriq or Tecentriq SC 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
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
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
Injection site reaction[gg]	29 (6.9%)	0 (0%)	0 (0%)	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
Infections and Infestations				

System Organ Class/ ADR (MedDRA Preferred Term)	Tecentriq (n = 3178)			
	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
Urinary tract infection[p]	368 (11.6%)	86 (2.7%)	0 (0%)	Very Common
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%)	Very Common
Myositis[t,u]	13 (0.4%)	5 (0.2%)	0 (0%)	Uncommon
Nervous System Disorders				
Headache	352 (11.1%)	10 (0.3%)	0 (0%)	Very Common
Peripheral neuropathy[ii]	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 (< 0.0%)	Very Common
Pruritus	400 (12.6%)	7 (0.2%)	0 (0%)	Very Common
Dry skin[hh]	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				
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, 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 pacreatitis, pancreatitis acute, lipase increased and 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, esophageal varices haemorrhage, varices esophageal

[j] Includes reports of Guillain-Barré syndrome and 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, 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 and 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 and Henoch-Schonlein Purpura nephritis

[t] Includes reports of myositis, rhabdomyolysis, polymyalgia rheumatica, dermatomyositis, bone 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] Reported instudies outside of the pooled dataset (subcutaneous administration related). The frequency is based on exposure to Tecentriq SC in IMscin001 (n=11/247; 4.5%) and in IMscin002 (n=18/175; 10.3%, patients received both Tecentriq SC and IV) and includes reports of injection site reaction, injection site pain, injection site erythema and injection site rash

[hh] Includes reports of dry skin, xerosis
[ii] 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

Tecentriq combination therapy

Additional ADRs identified in clinical trials (not reported in monotherapy trials) associated with the use of Tecentriq in combination therapy across multiple indications are summarised in Table 5. ADRs with a clinically relevant difference when compared to monotherapy (refer to Table 4) are also presented.

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

System Organ Class/ ADR (MedDRA Preferred Term)	Tecentriq + Combination Treatments (n = 4371)			Frequency
	All Grades (%)	Grade 3-4 (%)	Grade 5 (%)	(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 (0.2%)	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
Gastrointestinal Disorders				
Constipation[*]	1123 (25.7%)	24 (0.5%)	0 (0%)	Very Common
Stomatitis[*]	351 (8.0%)	23 (0.5%)	0 (0%)	Common
General Disorders and Administration Site Conditions				
Oedema Peripheral[*]	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

System Organ Class/ ADR (MedDRA Preferred Term)	Tecentriq + Combination Treatments (n = 4371)			Frequency
	All Grades (%)	Grade 3-4 (%)	Grade 5 (%)	(All Grades)
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[o]	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, neutrophil count decreased, febrile neutropenia, neutropenic sepsis and granulocytopenia

b. Includes reports of immune thrombocytopenia, thrombocytopenia and platelet count decreased

c. Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, blood thyroid stimulating hormone decreased, autoimmune thyroiditis, goitre, thyroiditis, thyroxine free decreased, tri−iodothyronine free decreased, thyroid disorder, thyroxine free increased, thyroxine increased, tri−iodothyronine decreased, tri-iodothyronine free increased, blood thyroid stimulating hormone abnormal, euthyroid sick syndrome, myxoedema coma, thyroid function test abnormal, thyroxine decreased, tri-iodothyronine abnormal, silent thyroiditis and thyroiditis chronic

d. Includes reports of adrenal insufficiency, cortisol decreased, adrenocortical insufficiency acute, secondary adrenocortical insufficiency, adrenocorticotropic hormone stimulation test abnormal, Addison's disease, adrenalitis and adrenocorticotropic hormone deficiency

e. Includes reports of hypophysitis, hypopituitarism and temperature regulation disorder

f. Includes reports of neuropathy peripheral, 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 and urine abnormality

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 white blood cell count decreased and leucopenia

j. Includes reports of hypomagnesaemia and blood magnesium decreased

k. Incluedes reports of lymphopenia and lymphocyte count decreased

l. Includes reports of nephritis, tubulointerstitial nephritis, autoimmune nephritis, nephritis allergic, glomerulonephritis, nephrotic syndrome and mesangioproliferative glomerulonephritis

m. Includes reports of hypertension, blood pressure increased, hypertensive crisis, blood pressure systolic increased, diastolic hypertension, blood pressure inadequately controlled and retinopathy hypertensive

n. Includes reports of alopecia, madarosis, alopecia areata, alopecia totalis and 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).

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 section 4.4 for management of the following:

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 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; where * 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; where * 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 monotherapy. 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*; where * 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; where * 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 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; where * 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; where * 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 months (range: 0.6 to 8.1 months). The median duration was 8.0 months (0.6 to 8.3* months; where * 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 months (range: 0.3 to 16.9 months). The median duration was 0.8 months (range 0.1 to 12.0* months; where * 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.

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; where * denotes a censored value). Myositis led to discontinuation of Tecentriq in 1 (<0.1%) patient. Myositis requiring the use of corticosteroids occurred in 0.2% (7/3178) of patients receiving Tecentriq.

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; where * denotes a censored value). Nephritis led to discontinuation of Tecentriq in 2 (<0.1%) o patients. One patient required the use of corticosteroids. (Note: Nephritis was reported in studies outside the pooled dataset. These reported frequencies are based on the program-wide exposure.)

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.

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.

Switching treatment from intravenous Tecentriq to Tecentriq SC (or vice versa)

Switching from intravenous Tecentriq to Tecentriq SC (or vice versa) was consistent with the safety profile observed in previous studies using intravenous Tecentriq administration (see section 5.1 Clinical trials).

Postmarketing experience

The following adverse reactions have been reported during postmarketing use of Tecentriq (see Table 6).

Table 6. 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
Nervous System Disorders	
Facial paresis[a]	Rare
Myelitis[a]	Rare

[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 authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

There is no information on overdose with Tecentriq.

For advice on the management of overdose contact the Poisons Information Centre on 0800 POISON (0800 764 766).

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 and tumour-infiltrating immune cells, and can contribute to the inhibition of the anti-tumour immune response in the tumour 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.

Tecentriq is a non-glycosylated IgG1 immunoglobulin that has a calculated molecular mass of 145 kDa.

Clinical trials

Non-small cell lung cancer

Intravenous Tecentriq

Early-stage NSCLC

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 7.

Table 7. 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 demographics and baseline disease characteristics were well balanced between the treatment arms. The median age was 62 years (range: 26 to 84), and 67% of patients were male. The majority of patients were White (73%), and 24% were Asian. Most patients were current or previous smokers (78%) and baseline ECOG performance status in patients was 0 (55%) or 1 (44%). Overall, 12% of patients had stage IB, 47% had stage II and 41% had stage IIIA disease. The percentage of patients who had tumours with PD-L1 expression ≥ 1% on TC as measured by the VENTANA PD-L1 (SP263) Assay was 55%.

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. A key secondary efficacy outcome measure was overall survival (OS).

At the time of the interim DFS analysis, the study met its primary endpoint and demonstrated a statistically significant and clinically meaningful 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. The OS data were immature at the time of the DFS interim analysis with approximately 18.9% of deaths reported in both arms in the PD-L1 ≥ 1% TC stage II - IIIA patient population. An exploratory analysis of OS suggested a trend in favor of Tecentriq over BSC (stratified HR=0.77 [95% CI: 0.51, 1.17]) in this patient population.

The study also demonstrated a statistically significant improvement in DFS for all randomised stage II - IIIA patients (stratified HR: 0.79 [95% CI 0.64, 0.96], p-value 0.0205).

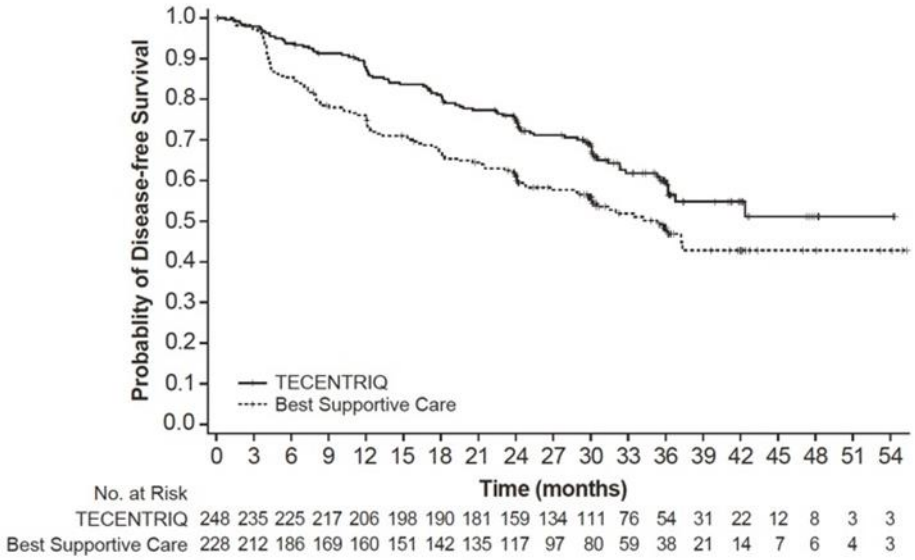
The key efficacy results are summarised in Table 8. The Kaplan-Meier curve for DFS is presented in Figure 1.

Table 8. Summary of efficacy from GO29527 (IMpower010) in PD-L1 expression ≥ 1% TC stage II - IIIA patient population

Efficacy endpoints	**Arm A** (Tecentriq)	**Arm B** (Best Supportive Care)
Investigator-assessed DFS	n = 248	n = 228
No. of events (%)	88 (35.5)	105 (46.1)
Median duration of DFS (months)	NE	35.3
95% CI	36.1, NE	29.0, NE
Stratified* hazard ratio (95% CI)	0.66 (0.50, 0.88)	
p-value	0.004	
3 year DFS rate (%)	60.0	48.2

DFS = Disease-free survival; CI = confidence interval; NE = not estimable
*Stratified by stage of disease, sex, and histology

Figure 1: Kaplan-Meier curve of Disease-Free Survival in the PD-L1 expression ≥ 1% TC stage II - IIIA patient population



The observed DFS improvement in the Tecentriq arm compared with the BSC arm was consistently shown across the majority of pre-specified subgroups in the PD-L1 ≥ 1% TC stage II - IIIA patient population including both non-squamous NSCLC patients (unstratified HR: 0.60 [95% CI: 0.42, 0.84], median DFS 42.3 vs. 30.1 months) and squamous NSCLC patients (unstratified HR: 0.78 [95% CI: 0.47, 1.29], median DFS (NE vs. NE months).

<u>1L metastatic non-squamous NSCLC</u>

GO29436

A phase III, open-label, multicentre, international randomised study, GO29436 (IMpower150), 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. A total of 1202 patients were enrolled and were randomised in a 1:1:1 ratio to receive one of the treatment regimens described in Table 9. Randomisation was stratified by sex, presence of liver metastases and PD-L1 tumour expression on tumour cells (TC) and tumour infiltrating cells (IC).

Table 9. Intravenous Treatment regimens in Study GO29436 (IMpower150)

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

CP = carboplatin + paclitaxel

[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 hematologic toxicities in patients from Asian countries compared with those from non-Asian countries.

[c] Carboplatin and paclitaxel 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

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.

The demographics and baseline disease characteristics of the study population were well balanced between the treatment arms. In this study, 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 mutations, 4% had known ALK rearrangements, 14% had liver metastases at baseline, and most patients were current or previous smokers (80%). 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. Baseline ECOG performance status was 0 (43%) or 1 (57%).

The intent-to-treat (ITT) population is defined as all randomised patients and the intent-to-treat wild-type (ITT-WT) population is defined as all randomised patients, excluding those with EGFR or ALK genomic tumour aberrations.

Results – Arm B (Tecentriq + bevacizumab + CP) versus Arm C (Bevacizumab + CP)

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 PFS improvement in Arm B as compared to Arm C (HR: 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 of the ITT population are summarised in Table 10. Kaplan-Meier curves for OS in the ITT population are presented in Figure 2. Figure 3 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% on tumour cells (TC) and tumour infiltrating cells (IC). Updated PFS results are also presented in Figures 4 and 5.

Table 10. Summary of updated efficacy in the ITT population (Study GO29436, IMpower150)

Efficacy endpoint	**Arm A (Tecentriq + paclitaxel + carboplatin**	**Arm B (Tecentriq + Bevacizumab + CP)**	**Arm C (Bevacizumab + CP)**
Co-Primary 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
Secondary Endpoints			
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)

CP = carboplatin + paclitaxel

1. Based on the stratified log-rank test
2. For informational purposes; in the ITT population, comparisons between Arm B 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
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 2. Kaplan-Meier curve for overall survival in the ITT population (Study GO29436, IMpower150)

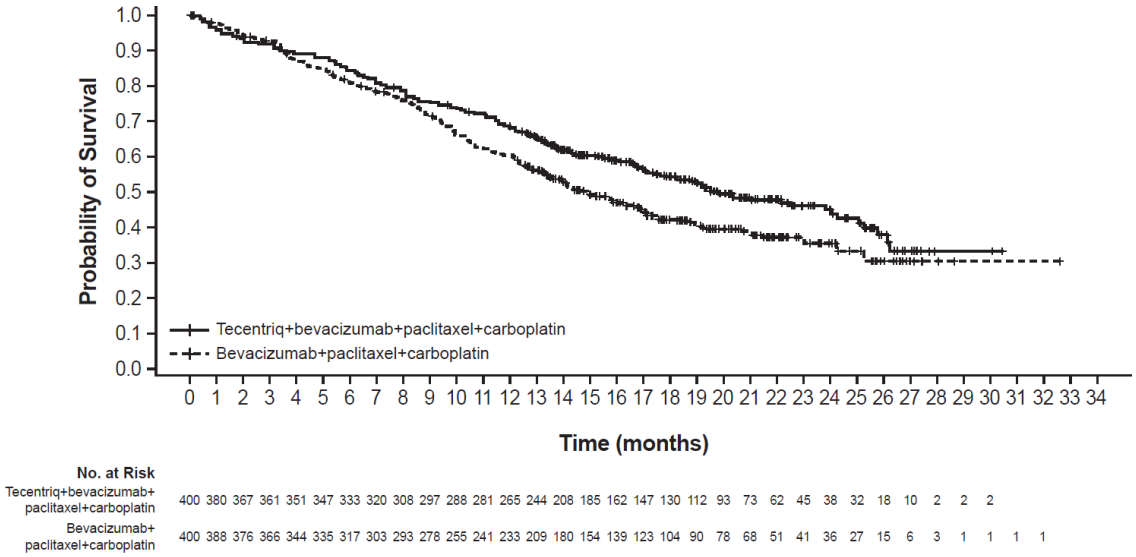


Figure 3: Forest plot of overall survival by PD-L1 expression in the ITT population, arm B vs C (Study GO29436, IMpower150)

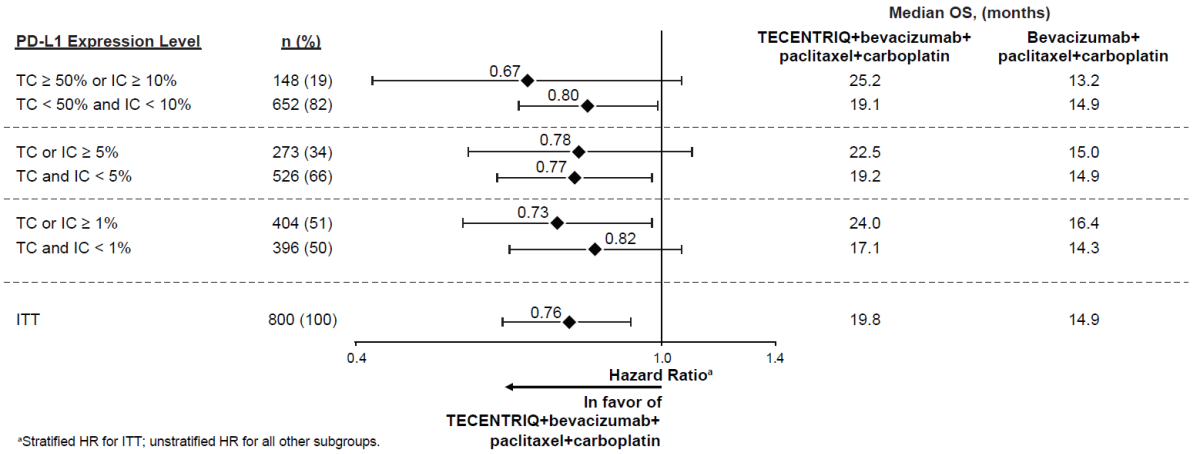


Figure 4: Kaplan-Meier curve for PFS in the ITT population (Study GO29436, IMpower150)

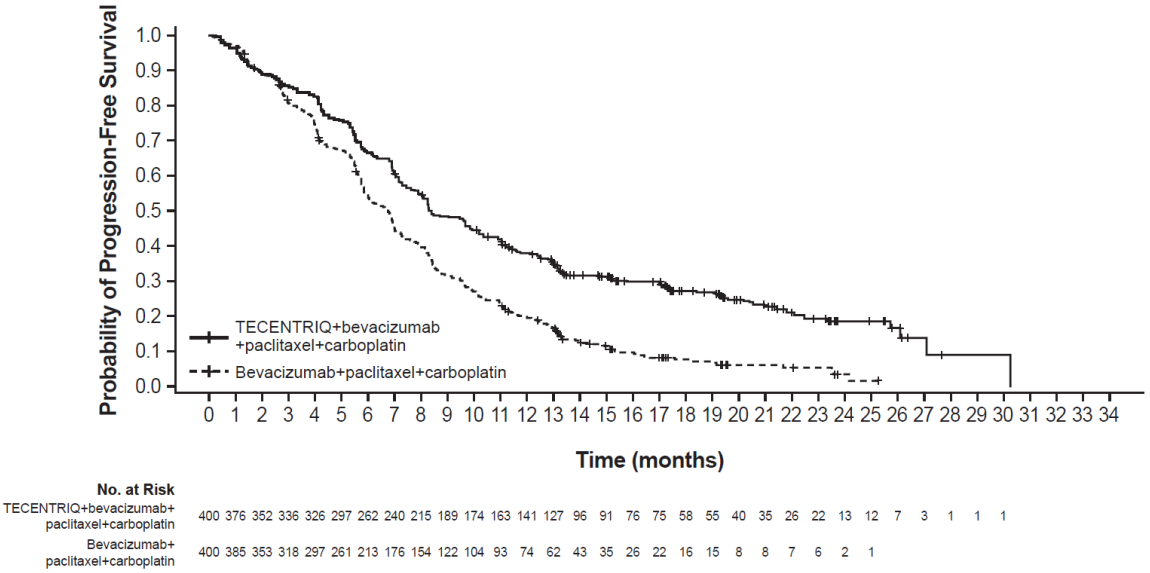
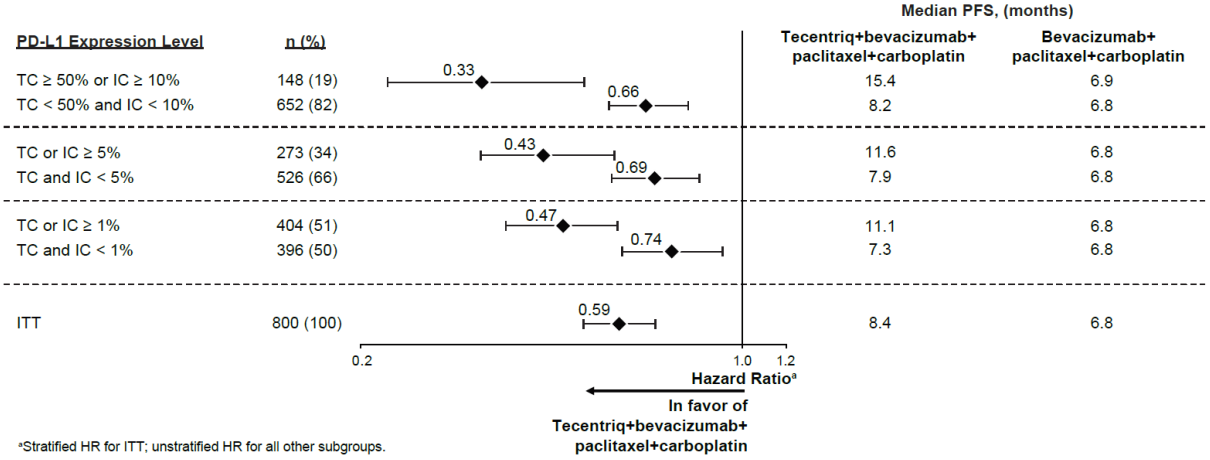


Figure 5: Forest plot of progression free survival by PD-L1 expression in the ITT population, Arm B vs C (Study GO29436, IMpower150)



In Arm B as compared to Arm C, pre-specified subgroup analyses from the interim OS analysis showed a numerical OS improvement for patients with EGFR mutations or ALK rearrangements (hazard ratio [HR] of 0.54, 95% CI: 0.29, 1.03; median OS NE vs. 17.5 months), and liver metastases (HR: 0.52 [95% CI 0.33, 0.82], median OS 13.3 vs 9.4 months). Numerical PFS improvements were also shown in patients with EGFR mutations or ALK rearrangements (HR: 0.55 [95% CI 0.35, 0.87], median PFS 10 vs. 6.1 months) and liver metastases (HR: 0.41 [95% CI 0.26, 0.62], median PFS 8.2 vs. 5.4 months).

This study also evaluated Physical Function and Patient-Reported Treatment-Related Symptoms using the EORTC QLQ-C30 and EORTC QLQ-LC13 measures at the time of the final PFS analysis. On average, patients who received Tecentriq with bevacizumab, paclitaxel and carboplatin reported minimal treatment burden as indicated by minimal deterioration in both Physical Function and Patient-Reported Treatment-Related Symptom Scores (i.e. fatigue, constipation, diarrhea, nausea/vomiting, hemoptysis, dysphagia, and sore mouth) while on treatment. Average patient-reported physical function and treatment-related symptom scores in both patients who received Tecentriq with bevacizumab, paclitaxel and carboplatin as well as

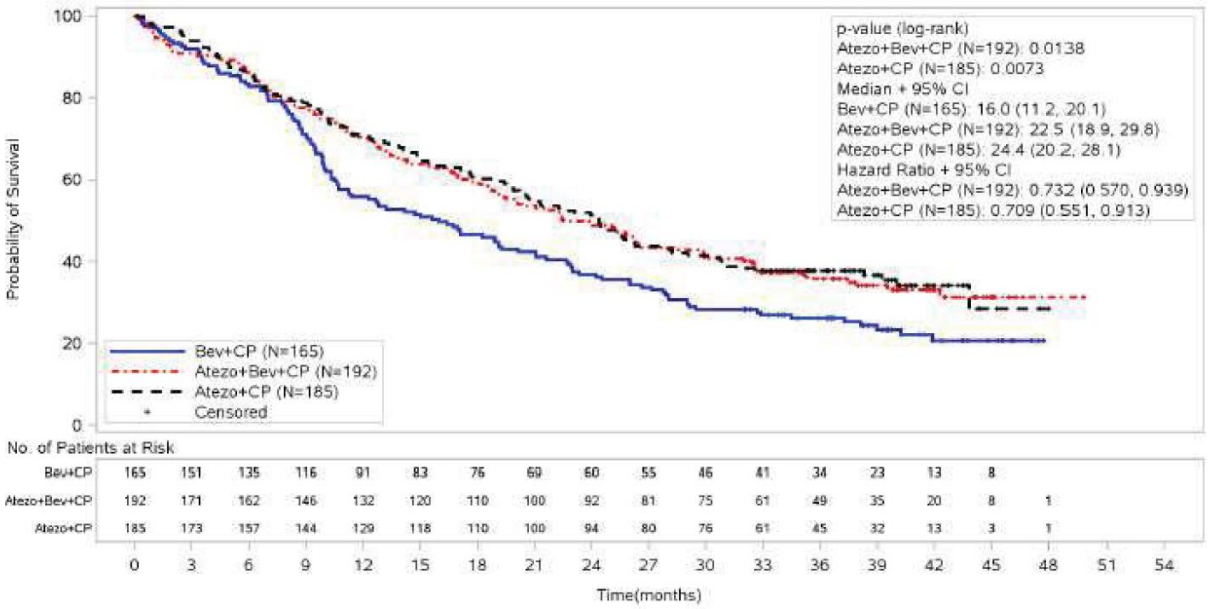
patients who received bevacizumab in combination with paclitaxel and carboplatin, were comparable while on treatment.

Results – Arm A (Tecentriq + CP) versus Arm C (Bevacizumab + CP)

At the time of the final analysis for PFS, patients had a median follow up time of 15.3 months. The unstratified PFS HR was 0.74 [95% CI: 0.58, 0.94] in patients treated with Tecentriq + carboplatin + paclitaxel (CP) compared with bevacizumab + CP (ITT-WT population with PD-L1 expression ≥ 1%).

At the time of the final OS analysis for Tecentriq + CP versus bevacizumab + CP, patients had a median follow up time of 39.3 months. The ITT-WT population with patients whose tumours are PD-L1 expression ≥ 1%, although not formally tested, demonstrated an OS improvement in Tecentriq + CP compared to bevacizumab + CP (unstratified HR of 0.71; [95% CI: 0.55, 0.91]) with a median duration of OS of 24.4 months, 8.4 months longer than that observed in the bevacizumab + CP arm with 16.0 months. This corresponds to a 29% relative reduction in the risk of death associated with Tecentriq + CP compared with bevacizumab + CP in the selected population. The Kaplan-Meier curves showed a separation from approximately 7.5 months, in favour of the Tecentriq + CP arm (Figure 6). Landmark OS event-free rates in the ITT-WT population with PD-L1-expression of ≥ 1 % for the Tecentriq + CP arm and the bevacizumab + CP arm were, respectively: 70.6% compared to 55.9% at one year and 51.5% and 36.9% at two years.

Figure 6: Kaplan-Meier curve for overall survival in the ITT-WT with PD-L1 expression ≥ 1% subgroup (Efficacy-Evaluable Population) (Study GO29436, IMpower150)



Atezo = atezolizumab; Bev = bevacizumab; CP = carboplatin + paclitaxel

GO29537

A Phase III, open-label, randomised study, GO29537 (IMpower130) 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 11. Randomisation was stratified by sex, presence of liver metastases and PD-L1 tumour expression on TC and IC. Patients in treatment regimen B were able to crossover and receive Tecentriq monotherapy following disease progression.

Table 11. Intravenous treatment regimens in study GO29537 (IMpower130)

Treatment Regimen	Induction (four or six 21-Day Cycles)	Maintenance (21-Day Cycles)
A	Tecentriq (1200 mg) [a] + nab-paclitaxel (100 mg/m^2) [b,c] + carboplatin (AUC 6)[c]	Tecentriq (1200 mg) [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 and 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 baseline ECOG performance status of 1 (58.7%).

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 12 and Kaplan-Meier curves for OS and PFS are presented in Figures 7 and 9, respectively.

All PD-L1 subgroups, regardless of expression, derived benefit in terms of OS and PFS; the results are summarised in Figure 8 and 10. 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 who 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 12. Summary of efficacy from study GO29537 (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
Secondary 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 7. Kaplan-Meier curve for Overall Survival (Study GO29537, IMpower130)

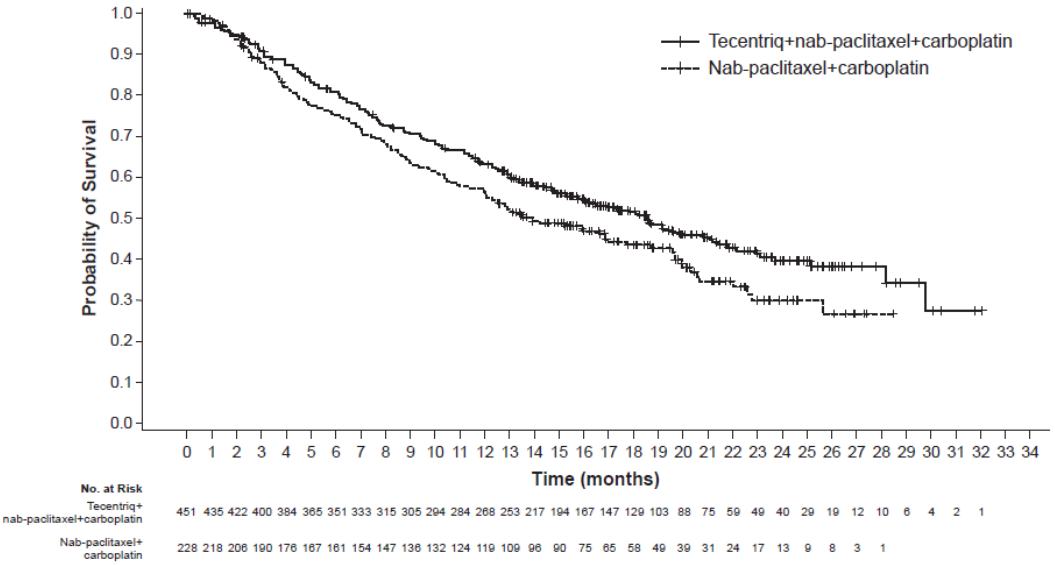


Figure 8. Forest Plot of Overall Survival by PD-L1 expression (Study GO29537, IMpower130)

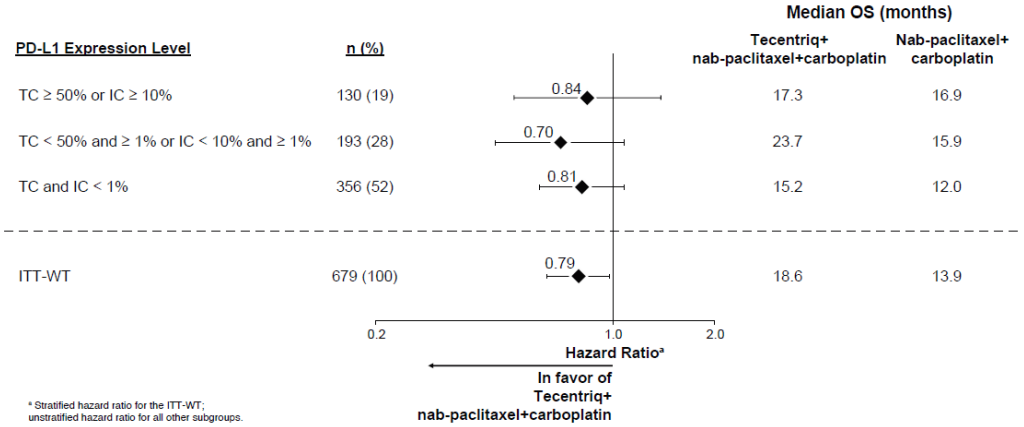


Figure 9. Kaplan-Meier curve for Progression Free Survival (Study GO29537, IMpower130)

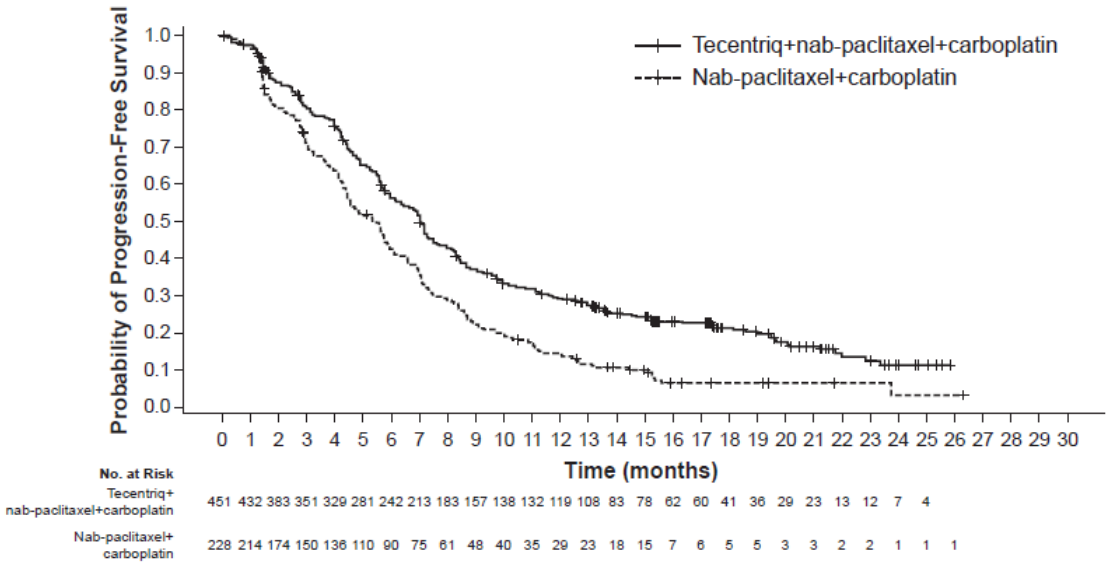
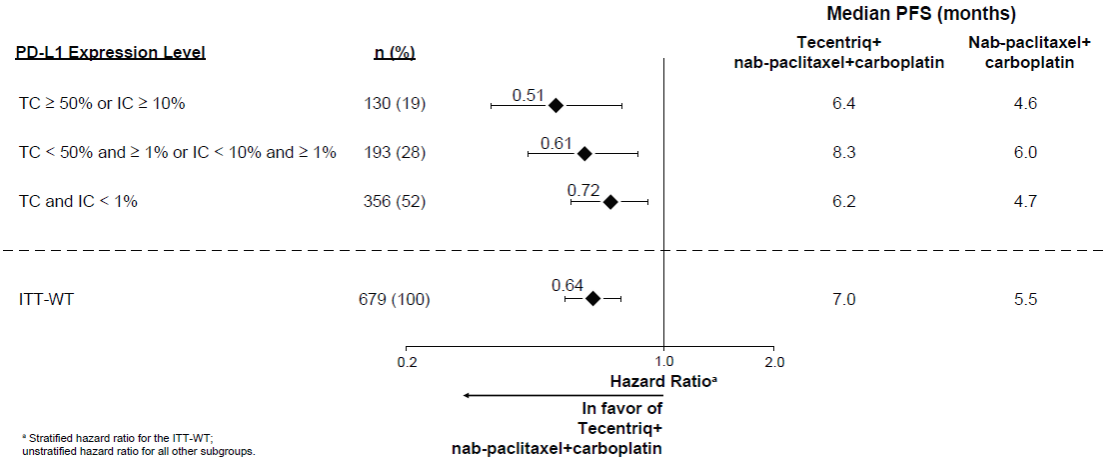


Figure 10. Forest Plot of Progression Free Survival by PD-L1 expression (Study GO29537, IMpower130)



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 (dyspnoea, cough and chest pain) however patients receiving Tecentriq, nab-paclitaxel and carboplatin reported less worsening of these symptoms over time.

1L non-squamous and squamous NSCLC

GO29431

A phase III, open label, multicentre, randomised study, GO29431 (IMpower110), was conducted to evaluate the efficacy and safety of Tecentriq in chemotherapy-naïve patients with metastatic NSCLC, with PD-L1 expression ≥ 1% on TC (PD-L1 stained ≥ 1% of tumour cells) (PD-L1 expression ≥ 1% TC) or ≥ 1% IC (PD-L1 stained tumour-infiltrating immune cells covering ≥ 1% of the tumour area) (PD-L1 expression ≥ 1% IC). A total of 572 patients were randomised in a 1:1 ratio to receive Tecentriq (Arm A) or chemotherapy (Arm B). Tecentriq was administered as a fixed dose of 1200 mg by IV infusion every 3 weeks until loss of clinical

benefit as assessed by the investigator or unacceptable toxicity. The chemotherapy regimens are described in Table 13. Randomisation was stratified by sex, ECOG performance status, histology, and PD- L1 tumour expression on TC and IC.

Table 13. Chemotherapy Intravenous Treatment Regimens in Study GO29431 (IMpower110)

Treatment regimen	Induction (Four or Six 21-day cycles)	Maintenance (21-day cycles)
B (Non-squamous)	Cisplatin[a] (75 mg/m²) + pemetrexed[a] (500 mg/m²) OR carboplatin[a] (AUC 6) + pemetrexed[a] (500 mg/m²)	Pemetrexed[b,d] (500 mg/m²)
B (Squamous)	Cisplatin[a] (75 mg/m²) + gemcitabine[a,c] (1250 mg/m^2) OR carboplatin[a] (AUC 5) + gemcitabine[a,c] (1000 mg/m^2)	Best supportive care[d]

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

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. Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter.

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

The primary endpoint was OS. At the time of the interim OS analysis, patients with high PD-L1 expression excluding those with EGFR or ALK genomic tumour aberrations (n=205) demonstrated statistically significant improvement in OS for the patients randomised to Tecentriq (Arm A) as compared with chemotherapy (Arm B). The median survival follow-up time in patients with high PD-L1 expression was 15.7 months. The key results are summarised in Table 14. The Kaplan-Meier curves for OS and PFS in patients with high PD-L1 expression are presented in Figure 11 and Figure 12.

Table 14. Summary of efficacy from Study GO29431 (IMpower110) in patients with high PD-L1 expression (≥ 50% TC or ≥ 10% IC)

Key efficacy endpoints	Arm A (Tecentriq)	Arm B (Chemotherapy)
Primary endpoint		
OS analysis	n=107	n=98

Key efficacy endpoints	**Arm A** (Tecentriq)	**Arm B** (Chemotherapy)
No. of deaths (%)	44 (41.1%)	57 (58.2%)
Median time to events (months)	20.2	13.1
95% CI	(16.5, NE)	(7.4, 16.5)
Stratified hazard ratio‡ (95% CI)	0.59 (0.40, 0.89)	
p-value‡	0.0106	
12-month OS (%)	64.9	50.6
Secondary endpoints		
Investigator-assessed PFS (RECIST v1.1)	n=107	n=98
No. of events (%)	67 (62.6%)	79 (80.6%)
Median duration of PFS (months)	8.1	5.0
95% CI	(6.8, 11.0)	(4.2, 5.7)
Stratified hazard ratio‡ (95% CI)	0.63 (0.45, 0.88)	
12-month PFS (%)	36.9	21.6
Investigator-assessed ORR (RECIST 1.1)	n = 107	n = 98
No. of responders (%)	41 (38.3%)	28 (28.6%)
95% CI	(29.1, 48.2)	(19.9, 38.6)
No. of complete response (%)	1 (0.9%)	1 (1.0%)
No. of partial response (%)	40 (37.4%)	27 (27.6%)
Investigator-assessed DOR (RECIST 1.1)	n = 41	n = 28
Median in months	NE	6.7
95% CI	(11.8, NE)	(5.5, 17.3)

‡ Stratified by sex and ECOG performance status (0 vs 1)
PFS = progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1; CI = confidence interval; ORR = objective response rate; DOR = duration of response; OS = overall survival; NE = not estimable.

Figure 11. Kaplan-Meier curve in Study GO29431 (IMpower110) of Overall Survival in Patients with high PD-L1 Expression (≥ 50% TC or ≥ 10% IC)

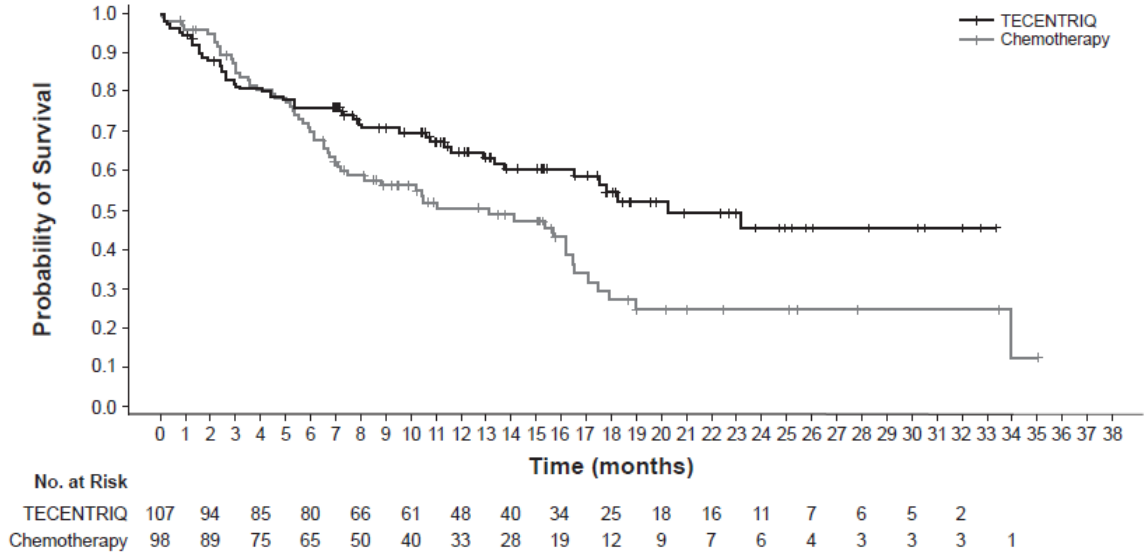
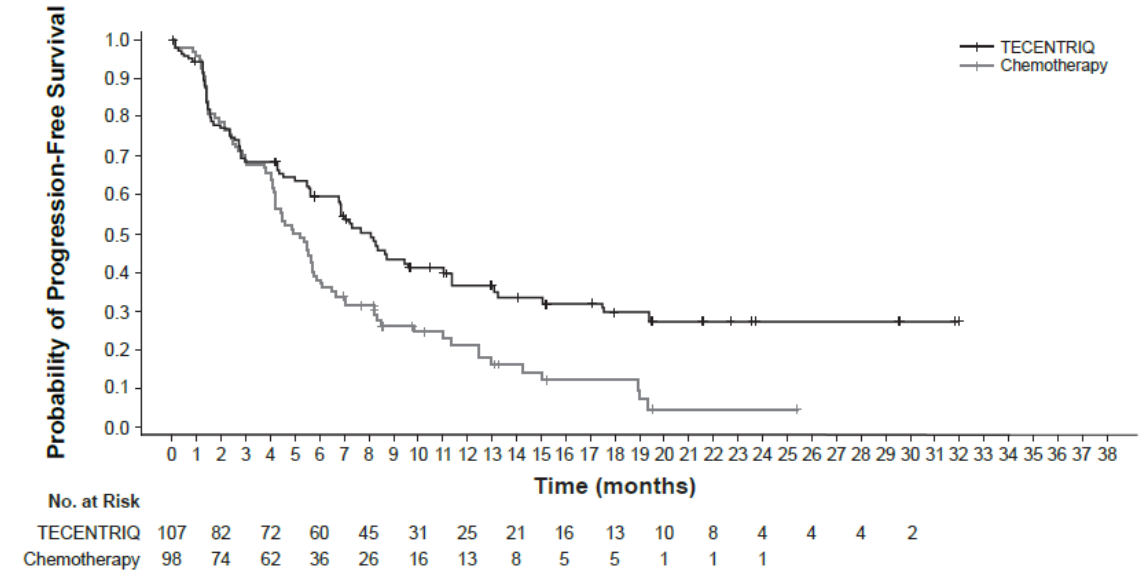


Figure 12. Kaplan-Meier curve in Study GO29431 (IMpower110) of Progression Free Survival in Patients with high PD-L1 Expression (≥ 50% TC or ≥ 10% IC)



The observed OS improvement in the Tecentriq arm compared with the chemotherapy arm was consistently demonstrated across subgroups in patients with high PD-L1 expression including both non-squamous NSCLC patients (HR: 0.62 [95% CI: 0.40, 0.96], median OS 20.2 vs. 10.5 months) and squamous NSCLC patients (HR: 0.56 [95% CI: 0.23, 1.37], median OS NE vs 15.3 months). The data for patients ≥75 years old and patients who were never smokers are too limited to draw conclusions in these subgroups.

Additional pre-specified analyses were conducted to evaluate efficacy by PD-L1 status assessed by the VENTANA PD-L1 (SP263) Assay and by the PD-L1 IHC 22C3 pharmDxTM kit. These analyses were conducted in all randomised patients with PD-L1 expression ≥ 1% TC or ≥ 1% IC by the VENTANA PD-L1 (SP142) Assay who do not have EGFR or ALK genomic tumour abberations (n=554). An OS improvement was observed with atezolizumab compared to chemotherapy in patients with high PD-L1 expression (PD-L1 ≥ 50% TC) using the

VENTANA PD-L1 (SP263) Assay (n=293; HR: 0.71 [95% CI: 0.50, 1.00], median OS 19.5 vs. 16.1 months) and in patients with high PD-L1 expression (Tumour Proportion Score (TPS) ≥ 50%) using the PD-L1 IHC 22C3 pharmDxTM Kit (n=260; HR: 0.60 [95% CI: 0.42, 0.86], median OS 20.2 vs 11.0 months).

The study also evaluated Patient Reported Physical Function, Global Health Status/Health Related Quality of Life and Lung Related Symptoms using the EORTC QLQ-C30, EORTC QLQ-LC13, and Symptoms in Lung Cancer (SILC) measures at the time of interim OS analysis. Patients who were randomised to Tecentriq (Arm A) on average reported sustained moderate improvement in physical functioning and no worsening in lung cancer-related symptoms (dyspnoea, cough, and chest pain) compared to patients randomised to chemotherapy (Arm B). Time to deterioration of these lung-related symptoms as measured by the SILC and EORTC QLQ-LC13 was similar in both treatment groups indicating that patients maintained low disease burden for a comparable duration of time.

2L NSCLC

GO28915

A phase III, open-label, multi-centre, international, randomised study, GO28915 (OAK), 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. 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 enrollment, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Tumour assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter. Tumour specimens were evaluated prospectively for PD-L1 expression on tumour cells (TC) and IC and the results were used to define the PD-L1 expression subgroups for the analyses described below. Scoring for tumour cells was defined as TC0 (< 1%), TC1 (≥ 1% and < 5%), TC2 (≥ 5% and < 50%), and TC3 (≥ 50%). Scoring for tumour-infiltrating immune cells was defined as IC0 (< 1%), IC1 (≥ 1% and < 5%), IC2 (≥ 5% and < 10%) and IC3 (≥ 10%).

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 13. Figure 14 summarises the results of OS in the ITT and PD-L1 subgroups, demonstrating OS benefit with Tecentriq in all subgroups, including the TC0/IC0 subgroup (PD-L1 expression < 1% in TC and IC).

Table 15. Summary of Efficacy in the Primary Analysis Population (Study GO28915, 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%)
TC1/2/3 or IC1/2/3	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)

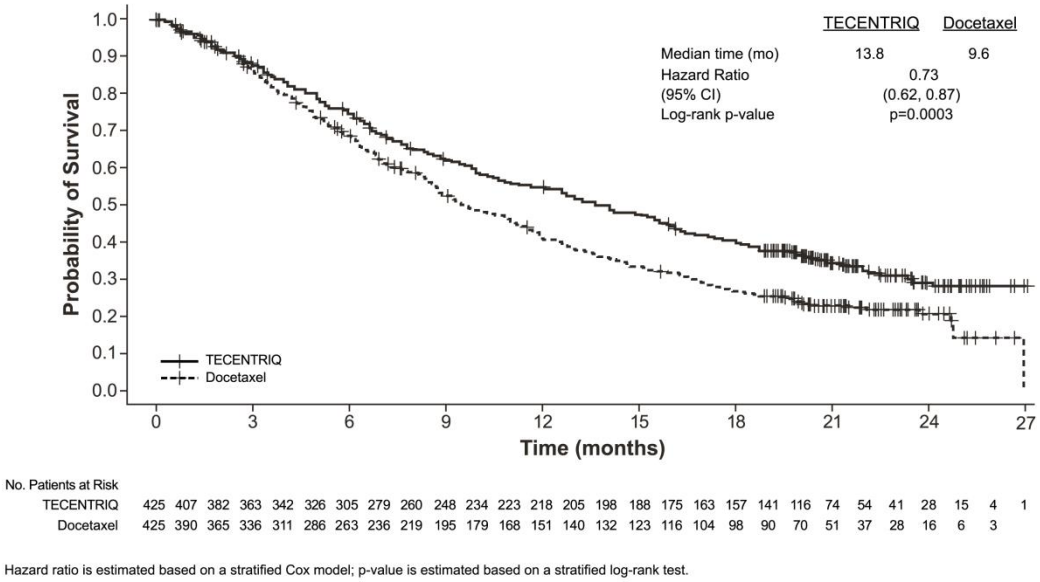
* All comers refers to the primary analysis population consisting of the first 850 randomised patients

[#] Stratified by PD-L1 expression in ICs, the number of prior chemotherapy regimens, and histology

** Based on the stratified log-rank test

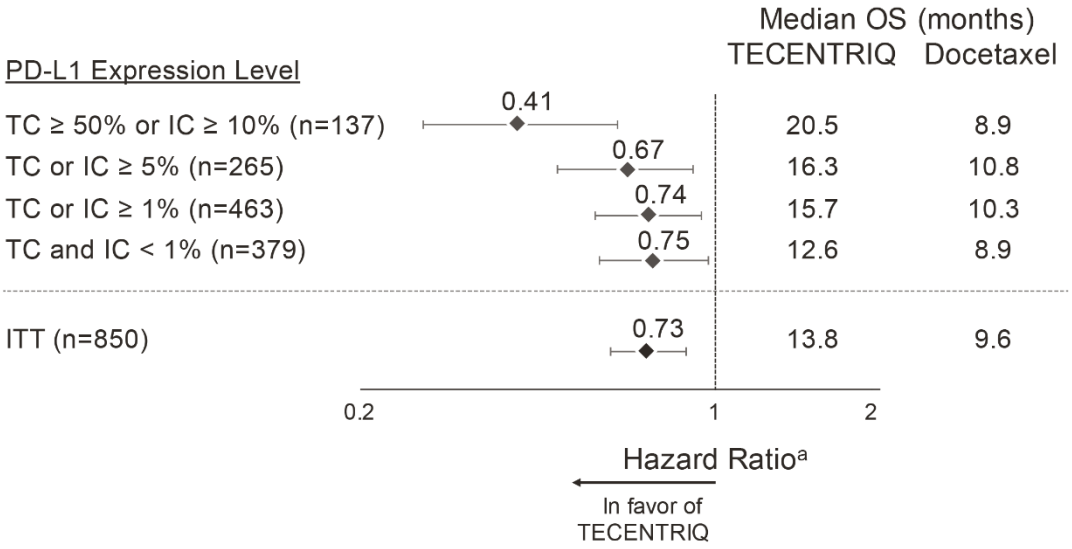
CI = confidence interval; DOR = duration of response; IC = tumour-infiltrating immune cells; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1; TC = tumour cells.

Figure 13. Kaplan-Meier curve for Overall Survival in the Primary Analysis Population (all comers) (Study GO28915, OAK)



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

Figure 14. Forest Plot of Overall Survival by PD-L1 Expression in the Primary Analysis Population (Study GO28915, 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).

Prolonged time to deterioration of patient-reported pain in chest as measured by the EORTC QLQ-LC13 was observed with Tecentriq compared with docetaxel (HR 0.71, 95% CI: 0.49, 1.05; median not reached in either arm). The time to deterioration in other lung cancer symptoms (i.e. cough, dyspnoea, and arm/shoulder pain) as measured by the EORTC QLQ-LC13 was similar between Tecentriq and docetaxel. The average global health status and functioning scores (i.e. physical, role, social, emotional, and cognitive) as measured by the EORTC QLQ-C30 did not show clinically meaningful deterioration over time for both treatment groups, suggesting maintained health-related quality of life and patient-reported functioning for patients remaining on treatment.

GO28753
A phase II, multi-centre, international, randomised, open-label, controlled study, GO28753 (POPLAR), was conducted in patients with locally advanced or metastatic NSCLC. A total of 287 patients were randomised 1:1 to receive either Tecentriq or docetaxel. Randomisation was stratified by PD-L1 expression status in IC, by the number of prior chemotherapy regimens and by histology. An updated analysis with a total of 200 deaths observed and a median survival follow-up of 22 months showed a median OS of 12.6 months in patients treated with 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.

Tecentriq SC
IMscin001
A phase Ib/III, open-label, multi-centre, international, randomised study, BP40657 (IMscin001), was conducted to evaluate the pharmacokinetics, efficacy and safety of Tecentriq SC compared with intravenous Tecentriq in patients with locally advanced or metastatic NSCLC who have not been exposed to cancer immunotherapy (CIT) and for whom prior platinum-based therapy has failed. IMscin001 was designed to demonstrate non-inferiority of the atezolizumab Cycle 1 (pre-dose Cycle 2) serum C_{trough} and model-predicted AUC from 0 to 21 days at Cycle 1 of atezolizumab SC compared with atezolizumab IV (co-primary endpoint). Secondary endpoints included efficacy [progression free survival (PFS), objective response rate (ORR), overall survival (OS), duration of response (DOR)] and patient reported outcomes.

In Part 2 (Phase III), a total of 371 patients were enrolled and randomised to receive either 1875 mg of Tecentriq SC every 3 weeks or 1200 mg of intravenous Tecentriq every 3 weeks. No dose reduction was allowed.

Patients were excluded if they had a history of autoimmune disease; active or corticosteroid-dependent brain metastases, 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.

The demographics and baseline disease characteristics were generally balanced between the treatment arms. The median age was 64 years (range: 27 to 85), and 69% of patients were male. The majority of patients were White (67%). Approximately two-thirds of patients (65%) had non-squamous disease, 5% had known EGFR mutation, 2% had known ALK rearrangements, 40% were PD-L1 positive (TC≥1% and/or IC≥1%), 16% had non-active CNS metastases at

baseline, 26% had an ECOG PS of 0, 74% had an ECOG PS of 1, and most patients were current or previous smokers (70%). 80% received one prior therapeutic regimen.

Non-inferiority of the exposure from atezolizumab in Tecentriq SC compared to intravenous atezolizumab was demonstrated (see section 5.2 Pharmacokinetic properties). Other key results are summarised below (see Table 16). At the time of primary analysis, the median survival follow-up was 4.7 months and OS and DOR results were immature. There were 86 (35%) deaths in the Tecentriq SC arm and 37 (30%) deaths in the intravenous atezolizumab arm.

Table 16. Summary of Efficacy from IMscin001

Efficacy endpoint	**Tecentriq SC**	**Intravenous Tecentriq**
Investigator-assessed PFS (RECIST v1.1)*	n = 247	n = 124
No. of PFS events (%)	168 (68%)	84 (68%)
Median duration of PFS (months)	2.8	2.9
95% CI**	(2.1, 3.1)	(1.7, 4.2)
Investigator-assessed confirmed ORR (RECIST v1.1)*	n = 245	n = 124
No. of responders (%)	21 (8.6%)	10 (8.1%)
95% CI***	(5.4, 13)	(3.9, 14)

CI=confidence interval; ORR=objective response rate; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1
*descriptive analyses
**95% CI was calculated using the standard error derived from Greenwood's formula.
***95% CI for rate was constructed using the Clopper–Pearson method.

No clinically meaningful deterioration in the average health-related quality of life, role functioning, or physical functioning scores as measured by EORTC IL 57 was observed in the Tecentriq SC or the intravenous Tecentriq arm, suggesting health-related quality of life and patient-reported functioning was maintained for patients remaining on treatment.

A post hoc updated analysis was performed 9 months after the primary analysis with a median survival follow-up of 9.5 months and mature OS results. The updated efficacy analysis results are summarised in Table 17.

Table 17. Summary of efficacy at updated analysis (IMscin001)

Efficacy endpoint	**Tecentriq SC**	**Intravenous Tecentriq**
Investigator-assessed PFS (RECIST v1.1)*	n = 247	n = 124
No. of events (%)	219 (89%)	107 (86%)
Median (months) (95% CI)***	2.8 (2.7, 4.1)	2.9 (1.8, 4.2)
Investigator-assessed confirmed ORR (RECIST v1.1)*	n = 245	n = 124
No. of responders (%)	27 (11%)	13 (11%)
95% CI**	(7.4, 15.6)	(5.7, 17.3)
OS*	n = 247	n = 124
No. of events (%)	144 (58%)	79 (64%)
Median (months) (95% CI)****	10.7 (8.5, 14)	10.1 (7.5, 12)

CI = confidence interval; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors v1.1
* descriptive analyses
**95% CI was calculated using the standard error derived from Greenwood's formula.
***95% CI for rate was constructed using the Clopper–Pearson method.
**** 95% CI for rate was constructed using the Brookmeyer and Crowley method.

IMScin002
The IMscin002 study was a randomised, multi-centre, open-label cross-over trial conducted in patients with non-small cell lung cancer (NSCLC) with the primary objective to evaluate patient preference for Tecentriq SC compared with intravenous Tecentriq. The 179 patients randomised in the study had either PD-L1-positive early-stage NSCLC and completed adjuvant treatment or were chemotherapy-naïve with high PD-L1 stage IV NSCLC. Following randomisation, patients received 3 cycles of Tecentriq SC followed by 3 cycles of intravenous Tecentriq (Arm A) or 3 cycles of intravenous Tecentriq followed by 3 cycles of Tecentriq SC (Arm B).

Out of the 126 eligible patients, 123 (98%) completed the patient preference questionnaire (PPQ). At primary analysis, 87 out of 123 patients (71%) reported preferring subcutaneous administration of Tecentriq SC over intravenous Tecentriq and the main reason cited was that administration required less time in the clinic. Twenty-six out of 123 patients (21%) reported preferring intravenous Tecentriq over Tecentriq SC and the main reason cited was that it felt more comfortable during administration. Ten out of 123 patients (8%) had no preference for the route of administration.

Following the crossover periods, patients in both arms could continue treatment for up to 16 cycles (patients with early-stage NSCLC) or until disease progression or unacceptable toxicity (patients with stage IV NSCLC). Out of the 107 patients who entered the treatment continuation period, 85 (79%) patients (42 from IV/SC and 43 from SC/IV) chose to continue treatment with the SC route of administration.

The overall safety profile for all patients during the combined periods of intravenous Tecentriq and Tecentriq SC of the study was consistent with the established atezolizumab safety profile of IV and SC. No new or unexpected safety findings were observed and results were consistent with intravenous Tecentriq. Switching between Tecentriq SC and IV (and vice versa) was generally well tolerated and well-managed.

Overall, 77% of patients experienced at least one AE. During the crossover period, the proportion of patients who experienced AEs leading to treatment discontinuation/interruption were comparable between IV and SC administration.

Intravenous Tecentriq

Small cell lung cancer

GO30081
A Phase I/III, randomised, multi-centre, double-blind, placebo controlled study, GO30081 (IMpower133), 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 18. 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 18. Intravenous treatment regimen in study GO30081 (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 19. Kaplan-Meier curves for OS and PFS are presented in Figure 15 and Figure 16.

Table 19. Summary of efficacy from GO30081 (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

Key efficacy endpoints	Arm A (Tecentriq + carboplatin + etoposide)	Arm B (placebo + carboplatin + etoposide)
Secondary endpoints		
Investigator-assessed ORR (RECIST 1.1)	n = 201	n = 202
No. of responders (%)	121 (60.2%)	130 (64.4%)
95% CI	(53.1, 67.0)	(57.3, 71.0.)
No. of complete response (%)	5 (2.5%)	2 (1.0%)
No. of partial response (%)	116 (57.7%)	128 (63.4%)
Investigator-assessed DOR (RECIST 1.1)	n = 121	n = 130
Median in months	4.2	3.9
95% CI	(4.1, 4.5)	(3.1, 4.2)

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

Figure 15. Kaplan-Meier curve of overall survival (Study GO30081, IMpower133)

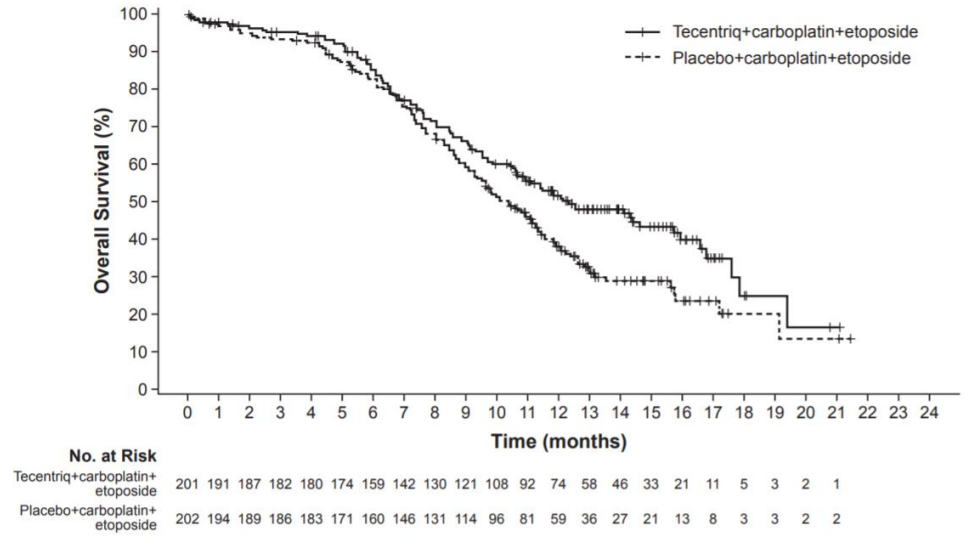
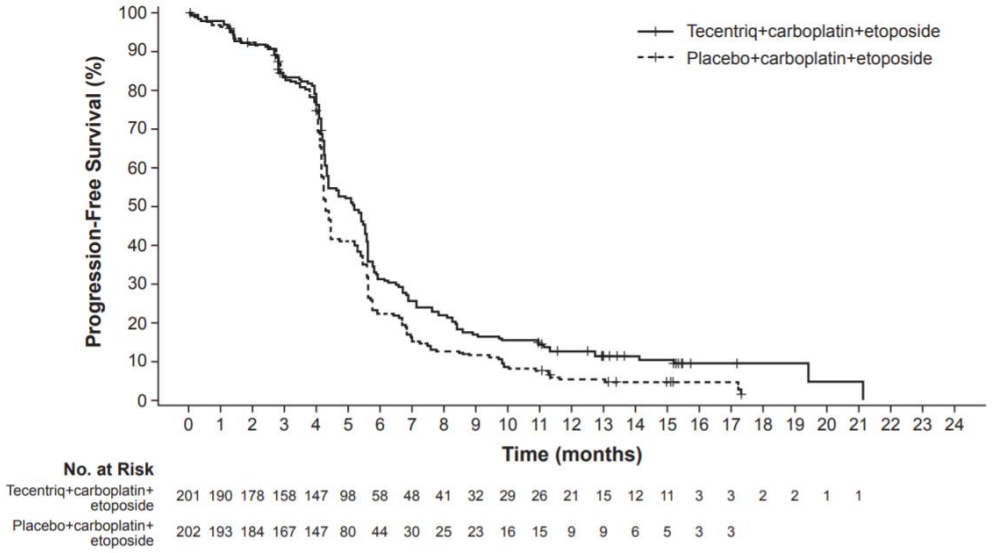


Figure 16. Kaplan-Meier curve of progression-free survival (Study GO30081, IMpower133)



This study also included an exploratory analysis of average score changes from baseline in patient-reported symptoms, physical function, and health-related quality of life (measured using the EORTC QLC-C30 and QLC-LC13). On average, patients who received Tecentriq with carboplatin and etoposide reported early and notable improvements in lung cancer-related symptoms (e.g., coughing, chest pain, dyspnea) and physical function. Changes in treatment-related symptoms (e.g., diarrhoea, nausea and vomiting, sore mouth, peripheral neuropathy) were comparable between arms throughout induction and most visits through week 54. Overall, patients treated with Tecentriq, carboplatin and etoposide achieved more pronounced and enduring improvements in health-related quality of life (≥ 10-point score increases at most visits through Week 48) compared to patients treated with placebo, carboplatin and etoposide, who reported nominal improvements (< 10-point score increases) at most study treatment visits.

Intravenous Tecentriq

Urothelial Carcinoma

GO29294
A phase III, open label, multi-centre, international, randomised study, GO29294 (IMvigor211), was conducted to evaluate the efficacy and safety of Tecentriq compared with chemotherapy (investigator's choice of vinflunine, docetaxel, or paclitaxel) in patients with locally advanced or metastatic urothelial carcinoma who progressed during or following a platinum containing regimen. This study excluded patients who had a history of autoimmune disease; active or corticosteroid dependent brain metastases; administration of a live, attenuated vaccine within 28 days prior to enrolment; and administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal product within 2 weeks prior to enrolment. Tumour assessments were conducted every 9 weeks for the first 54 weeks, and every 12 weeks thereafter. Tumour specimens were evaluated prospectively for PD-L1 expression on tumour infiltrating immune cells (IC) and the results were used to define the PD-L1 expression subgroups for the analyses described below.

A total of 931 patients were enrolled. Patients were randomised (1:1) to receive either Tecentriq or chemotherapy. Randomisation was stratified by chemotherapy (vinflunine vs. taxane), PD-L1 expression status on IC (IC0/1 vs IC2/3), number of prognostic risk factors (0 vs. 1 - 3), and liver metastases (yes vs. no). Prognostic risk factors included time from prior chemotherapy of < 3 months, ECOG performance status > 0 and haemoglobin < 100 g/L.

Tecentriq was administered as a fixed dose of 1200 mg by intravenous infusion every 3 weeks. No dose reduction of Tecentriq was allowed. Patients were treated until loss of clinical benefit as assessed by the investigator or unacceptable toxicity. Vinflunine was administered 320 mg/m^2 by intravenous infusion on day 1 of each 3 week cycle until disease progression or unacceptable toxicity. Paclitaxel was administered 175 mg/m^2 by intravenous infusion over 3 hours on day 1 of each 3 week cycle until disease progression or unacceptable toxicity. Docetaxel was administered 75 mg/m^2 by intravenous infusion on day 1 of each 3 week cycle until disease progression or unacceptable toxicity. For all treated patients, the median duration of treatment was 2.8 months for the Tecentriq arm, 2.1 months for the vinflunine and paclitaxel arms and 1.6 months for the docetaxel arm.

The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 67 years (range: 31 to 88), and 77.1% of patients were male. The majority of patients were white (72.1%), 53.9% of patients within the chemotherapy arm received vinflunine, 71.4% of patients had at least one poor

prognostic risk factor and 28.8% had liver metastases at baseline. Baseline ECOG performance status was 0 (45.6%) or 1 (54.4%). Bladder was the primary tumour site for 71.1% of patients and 25.4% of patients had upper tract urothelial carcinoma. There were 24.2% of patients who received only prior platinum-containing adjuvant or neoadjuvant therapy and progressed within 12 months.

The primary efficacy endpoint for IMvigor211 was overall survival (OS). Secondary efficacy endpoints were objective response rate (ORR), progression free survival (PFS), and duration of response (DOR). OS comparisons between the treatment arm and control arm were tested using a hierarchical fixed sequence procedure based on a stratified log rank test at two-sided level of 5% as follows: step 1) PD-L1 expression IC2/3 subgroup, step 2) PD-L1 expression IC1/2/3 subgroup, step 3) all comers. OS results for each of steps 2 and 3 could only be formally tested if the result in the preceding step was statistically significant.

The median survival follow up was 17 months. Study IMvigor211 did not meet its primary endpoint. In the subset of patients with tumours having IC2/3 expression, Tecentriq did not demonstrate a statistically significant survival benefit compared to chemotherapy with an OS HR of 0.87 (95% CI: 0.63, 1.21; median OS of 11.1 vs. 10.6 months for Tecentriq and chemotherapy respectively). The stratified log rank p value was 0.41. As a consequence, no formal statistical testing was performed for OS in the PD-L1 expression IC1/2/3 subgroup or in all comers, and results of those analyses are considered exploratory. The key results in the all comer population are summarised in Table 20. The Kaplan Meier curve for OS in the all comer population is presented in Figure 17.

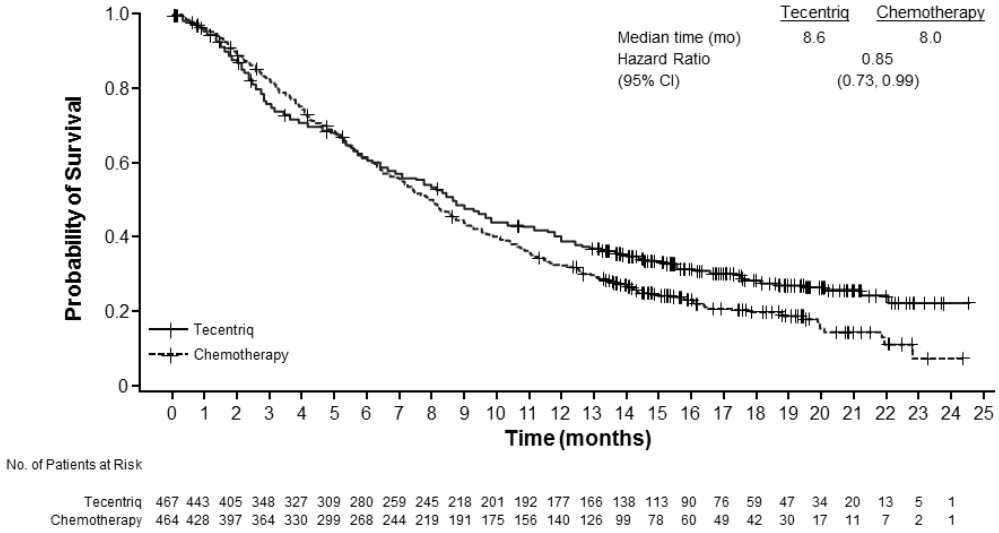
Table 20. Summary of efficacy in all comers (Study GO29294, IMvigor211)

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

* Based on Kaplan Meier estimate

ǂ Stratified by chemotherapy (vinflunine vs taxane), PD-L1 status on IC (IC0/1 vs. IC2/3), number of prognostic risk factors (0 vs. 1 - 3), and liver metastases (yes vs. no).
** Responses were ongoing in 63% of responders in the Tecentriq arm and in 21% of responders in the chemotherapy arm.
CI = confidence interval; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

Figure 17. Kaplan Meier curve for overall survival in all-comers (Study GO29294, IMvigor211)



GO29293
A phase II, multi-centre, international, two-cohort, single-arm clinical trial, GO29293 (IMvigor210), was conducted in patients with locally advanced or metastatic urothelial carcinoma (also known as urothelial bladder cancer). The study enrolled a total of 438 patients and had two patient cohorts. Cohort 1 included previously untreated patients with locally advanced or metastatic urothelial carcinoma who were ineligible or unfit for cisplatin-based chemotherapy or had disease progression at least 12 months after treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. Cohort 2 included patients who received at least one platinum-based chemotherapy regimen for locally advanced or metastatic urothelial carcinoma or had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. Tumour specimens were evaluated prospectively for PD-L1 expression in IC and the results were used to define the PD-L1 expression subgroups for the analyses described below.

In Cohort 1, 119 patients were treated with Tecentriq 1200 mg by intravenous infusion every 3 weeks until disease progression. The median age was 73 years. Most patients were male (81%), and the majority of patients were white (91%). Cohort 1 included 45 patients (38%) with ECOG performance status of 0, 50 patients (42%) with ECOG performance status of 1 and 24 patients (20%) with ECOG performance status of 2, 35 patients (29%) with no Bajorin risk factors (ECOG performance status ≥ 2 and visceral metastasis), 66 patients (56%) with one Bajorin risk factor and 18 patients (15%) with two Bajorin risk factors, 84 patients (71%) with impaired renal function (GFR < 60 mL/min), and 25 patients (21%) with liver metastasis.

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

performed when all patients had at least 24 weeks of follow-up. Median duration of treatment was 15.0 weeks and median duration of survival follow up was 8.5 months in all comers.

Clinically relevant IRF-assessed ORRs per RECIST v1.1 were shown; however, when compared to a pre-specified historical control response rate of 10%, statistical significance was not reached for the primary endpoint. The confirmed ORRs per IRF-RECIST v1.1 were 21.9% (95% CI: 9.3, 40.0) in patients with PD-L1 expression IC2/3, 18.8% (95% CI: 10.9, 29.0) in patients with PD-L1 expression IC1/2/3, and 19.3% (95% CI: 12.7, 27.6) in all comers. The median duration of response (DOR) was not reached in any PD-L1 expression subgroup or in all comers. OS was not mature with an event ratio of approximately 40%. Median OS for all patient subgroups (PD-L1 expression IC2/3 and IC1/2/3) and in all comers was 10.6 months.

An updated analysis was performed with a median duration of survival follow up of 17.2 months for Cohort 1 and is summarised in Table 21. The median DOR was not reached in any PD-L1 expression subgroup or in all comers.

Table 21. Summary of updated efficacy from (IMvigor210) GO29293 Cohort 1

Efficacy Endpoints	All Comers	IC2/3	IC1/2/3
ORR (IRF-Assessed; RECIST v1.1)	n = 119	n = 32	n = 80
No. of Responders (%)	27 (22.7%)	9 (28.1%)	19 (23.8%)
95% CI	15.5, 31.3	13.8, 46.8	15.0, 34.6
No. of complete response (%)	11 (9.2%)	4 (12.5%)	8 (10.0%)
95% CI	(4.7, 15.9)	(3.5, 29.0)	(4.4, 18.8)
No. of partial response (%)	16 (13.4%)	5 (15.6%)	11 (13.8%)
95% CI	(7.9, 20.9)	(5.3, 32.8)	(7.1, 23.3)
DOR (IRF-Assessed; RECIST v1.1)	n = 27	n = 9	n = 19
Patients with event (%)	8 (29.6%)	3 (33.3%)	5 (26.3%)
Median (months) (95% CI)	NE (14.1, NE)	NE (11.1, NE)	NE (NE, NE)
PFS (IRF-Assessed; RECIST v1.1)	n = 119	n = 32	n = 80
Patients with event (%)	88 (73.9%)	24 (75.0%)	59 (73.8%)
Median (months) (95% CI)	2.7 (2.1, 4.2)	4.1 (2.3, 11.8)	2.9 (2.1, 5.4)
OS	n = 119	n = 32	n = 80
Patients with event (%)	59 (49.6%)	18 (56.3%)	42 (52.5%)
Median (months) (95% CI)	15.9 (10.4, NE)	12.3 (6.0, NE)	14.1 (9.2, NE)
1-year OS rate (%)	57.2%	52.4%	54.8%

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

In Cohort 2, the co primary efficacy endpoints were confirmed ORR as assessed by an IRF using RECIST v1.1 and investigator assessed ORR according to Modified RECIST (mRECIST) criteria. There were 310 patients treated with Tecentriq 1200 mg by intravenous infusion every 3 weeks until loss of clinical benefit. The primary analysis of Cohort 2 was performed when all patients had at least 24 weeks of follow-up. The study met its co-primary endpoints in Cohort 2, demonstrating statistically significant ORRs per IRF-assessed RECIST v1.1 and

investigator-assessed mRECIST compared to a pre-specified historical control response rate of 10%.

An analysis was also performed with a median duration of survival follow up 21.1 months for Cohort 2. The confirmed ORRs per IRF-RECIST v1.1 were 28.0% (95% CI: 19.5, 37.9) in patients with PD-L1 expression IC2/3, 19.3% (95% CI: 14.2, 25.4) in patients with PD-L1 expression IC1/2/3, and 15.8% (95% CI: 11.9, 20.4) in all comers. The confirmed ORR per investigator assessed mRECIST was 29.0% (95% CI: 20.4, 38.9) in patients with PD-L1 expression IC2/3, 23.7% (95% CI: 18.1, 30.1) in patients with PD-L1 expression IC1/2/3, and 19.7% (95% CI: 15.4, 24.6) in all comers. The rate of complete response per IRF RECIST v1.1 in the all comer population was 6.1% (95% CI: 3.7, 9.4). Median DOR was not reached in any PD-L1 expression subgroup or in all comers, however was reached in patients with PD-L1 expression IC0 (13.3 months; 95% CI 4.2, NE). The OS rate at 12 months was 37% in all comers.

WO30070
An phase III, multi-centre, randomised, placebo-controlled study (IMvigor130) was conducted to evaluate Tecentriq as monotherapy (Arm B) and in combination with platinum-based chemotherapy (either cisplatin or carboplatin with gemcitabine) (Arm A) compared to chemotherapy plus placebo (Arm C) in patients with untreated locally advanced or metastatic urothelial carcinoma.

Based on an independent Data Monitoring Committee (iDMC) recommendation, accrual of patients on the Tecentriq monotherapy treatment arm whose tumours have a low PD-L1 expression (PD-L1 expression IC0/1) was stopped after observing decreased overall survival for this subgroup at an unplanned early analysis. The iDMC did not recommend any change of therapy for patients who had already been randomised to and were receiving treatment in the monotherapy arm. No changes were recommended to the chemotherapy plus Tecentriq monotherapy or chemotherapy plus placebo arms. No safety issues were identified in this recommendation.

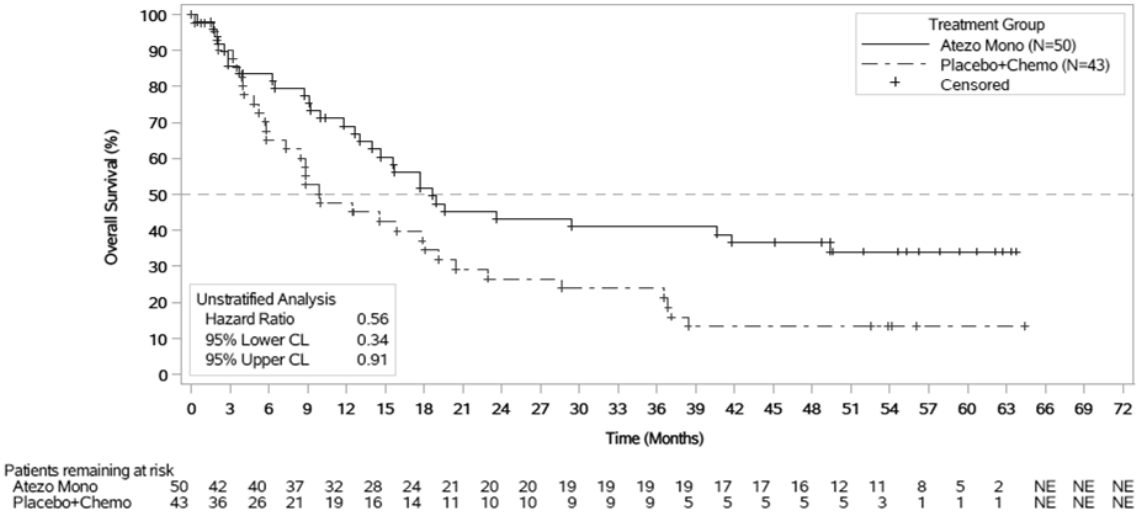
The co-primary efficacy endpoints for IMvigor130 were investigator-assessed progression-free survival (PFS) and overall survival (OS). Secondary efficacy endpoints were objective response rate (ORR) and duration of response (DOR). The median survival follow up was 13.4 months (range: 0.0 – 71.7 months). The study did not meet its co-primary endpoint of OS. In the all comer population, Tecentriq in combination with chemotherapy did not demonstrate a statistically significant survival benefit compared to chemotherapy alone with an OS HR of 0.85 (95% CI:0.73, 1.00; median OS of 16.1 vs. 13.4 months for Tecentriq in combination with chemotherapy and chemotherapy alone respectively).
In an exploratory analysis of OS in the intent-to-treat population comparing Tecentriq monotherapy vs. chemotherapy alone, the OS HR was 0.98 (95% CI: 0.82, 1.16). The median OS was 15.2 months (95% CI: 13.1, 17.7) in the Tecentriq monotherapy arm vs. 13.3 months (95% CI: 11.9, 15.6) in chemotherapy alone. In a subgroup of patients whose tumours were considered PD-L1 high (PD-L1 stained tumour-infiltrating immune cells [IC] covering >5% of the tumour area), the OS HR was 0.70 (95% CI: 0.48, 1.03). The median OS was 27.5 months (95% CI: 17.7, 49.4) in the Tecentriq monotherapy arm vs. 16.7 months (95% CI: 10.0, 26.1) in chemotherapy alone.
Key exploratory results for the co-primary and secondary endpoints in patients who were cisplatin-ineligible by Galsky criteria and whose tumours are PD-L1 high are provided in Table 22. Kaplan-Meier curve for OS is presented in Figure 18.

Table 22. Summary of Efficacy from IMvigor130 in Cisplatin-ineligible Patients Whose Tumours are PD-L1 High (Arm B vs. Arm C)

Efficacy Endpoint	Tecentriq Monotherapy (Arm B)	Chemotherapy Alone (Arm C)
Co-Primary Endpoint		
Overall Survival	n=50	n=43
No. of deaths (%)	31 (62.0%)	34 (79.1%)
Median time to events (months)	18.6	10.0
95% CI	14.0, 49.4	7.4, 18.1
Unstratified Hazard Ratio (95% CI)	0.56 (0.34, 0.91)	
Secondary Endpoints		
Investigator-assessed ORR (Measurable Disease Population)	n=50	n=43
No. of confirmed responders (%)	20 (40.0%)	14 (32.6%)
95% CI	26.4, 54.8	19.1, 48.5
No. of complete response (%)	6 (12.0%)	4 (9.3%)
Investigator-assessed DOR (DOR-Evaluable Population)	n= 20	n=14
Median in months	NE	6.2
95% CI	7.2, NE	4.2, 10.9

PFS=progression-free survival; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival; ITT=intent-to-treat; NE=not estimable; PD L1=programmed death-ligand 1.

Figure 18. Kaplan-Meier curve of Overall Survival in Cisplatin-ineligible Patients Whose Tumours are PD-L1 High (Arm B vs. Arm C)



Intravenous Tecentriq

1L triple-negative breast cancer

WO29522

A phase III, double-blind, two-arm, randomised, placebo-controlled study, WO29522 (IMpassion130), was conducted to evaluate the efficacy and safety of Tecentriq in combination with nab-paclitaxel, in patients with unresectable locally advanced or metastatic TNBC who had not received prior chemotherapy for metastatic disease. A total of 902 patients were enrolled and stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumour-infiltrating immune cells (IC) (PD-L1 stained tumour-infiltrating immune cells [IC] in <1% of the tumour area vs. ≥1% of the tumour area).

Patients were randomised to receive Tecentriq (840 mg) or placebo IV infusions on Days 1 and 15 of every 28-day cycle, plus nab-paclitaxel (100 mg/m^2) administered via IV infusion on Days 1, 8 and 15 of every 28-day cycle. Patients received treatment until radiographic disease progression per RECIST v1.1, or unacceptable toxicity. Treatment with Tecentriq could be continued when nab-paclitaxel was stopped due to unacceptable toxicity.

Patients were excluded if they had 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 8 weeks (± 1 week) for the first 12 months after Cycle 1, day 1 and every 12 weeks (± 1 week) thereafter.

The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. Most patients were women (99.6%). Sixty-seven percent of patients were white (67.5%), 17.8% were Asian, 6.5% were Black or African American, and 4.4% were American Indian or Alaskan Native. The median age was 55 years (range: 20-86). Baseline ECOG performance status was 0 (58.4%) or 1 (41.3%). Overall, 41% of enrolled patients had PD-L1 expression ≥ 1%, 27% had liver metastases and 7% brain metastases at baseline. Approximately half the patients had received a taxane (51%) or anthracycline (54%) in the (neo)adjuvant setting. Patient demographics and baseline tumour disease in the PD-L1 expression ≥ 1% population were generally representative of the broader study population.

PFS, ORR and DOR results for patients with PD-L1 expression ≥ 1% with a median survival follow up of 13 months are summarised in Table 23 and Figure 19. In addition, PFS benefit was observed in subgroups.

A final OS analysis was performed in patients with PD-L1 expression ≥1% with a median follow-up of 19.12 months. OS results are presented in Table 23 and Figure 20.

Table 23. Summary of efficacy in patients with PD-L1 expression ≥ 1% IC from Study WO29522 (IMpassion130)

Key efficacy endpoints	Tecentriq + nab-paclitaxel	Placebo + nab-paclitaxel
Co-primary endpoints		
Investigator-assessed PFS (RECIST v1.1)	n=185	n=184
No. of events (%)	138 (74.6%)	157 (85.3%)
Median duration of PFS (months)	7.5	5.0

Key efficacy endpoints	Tecentriq + nab-paclitaxel	Placebo + nab-paclitaxel
95% CI	(6.7, 9.2)	(3.8, 5.6)
Stratified hazard ratio‡ (95% CI)	0.62 (0.49, 0.78)	
p-value[1]	<0.0001	
12-month PFS (%)	29.1	16.4
OS	n=185	n=184
No. of deaths (%)	120 (64.9%)	139 (75.5%)
Median time to events (months)	25.4	17.9
95% CI	(19.6, 30.7)	(13.6, 20.3)
Stratified hazard ratio‡ (95% CI)	0.67 (0.53, 0.86)	
p-value[1,2]	0.0016	
Secondary endpoints		
Investigator-assessed ORR (RECIST 1.1)	n=185	n=183
No. of responders (%)	109 (58.9%)	78 (42.6%)
95% CI	(51.5, 66.1)	(35.4, 50.1)
No. of complete response (%)	19 (10.3%)	2 (1.1%)
No. of partial response (%)	90 (48.6%)	76 (41.5%)
No. of stable disease	38 (20.5%)	49 (26.8%)
Investigator-assessed DOR	n=109	n=78
Median in months	8.5	5.5
95% CI	(7.3, 9.7)	(3.7, 7.1)
Unstratified hazard ratio (95% CI)	0.60 (0.43, 0.86)	

1. Based on the stratified log-rank test
2. OS comparisons between treatment arms in patients with PD-L1 expression ≥ 1% were not formally tested, as per the pre-specified analysis hierarchy.

‡ Stratified by presence of liver metastases, and by prior taxane treatment

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 19. Kaplan-Meier curve for Progression Free Survival in patients with PD-L1 expression ≥ 1% IC (Study WO29522, Impassion130)

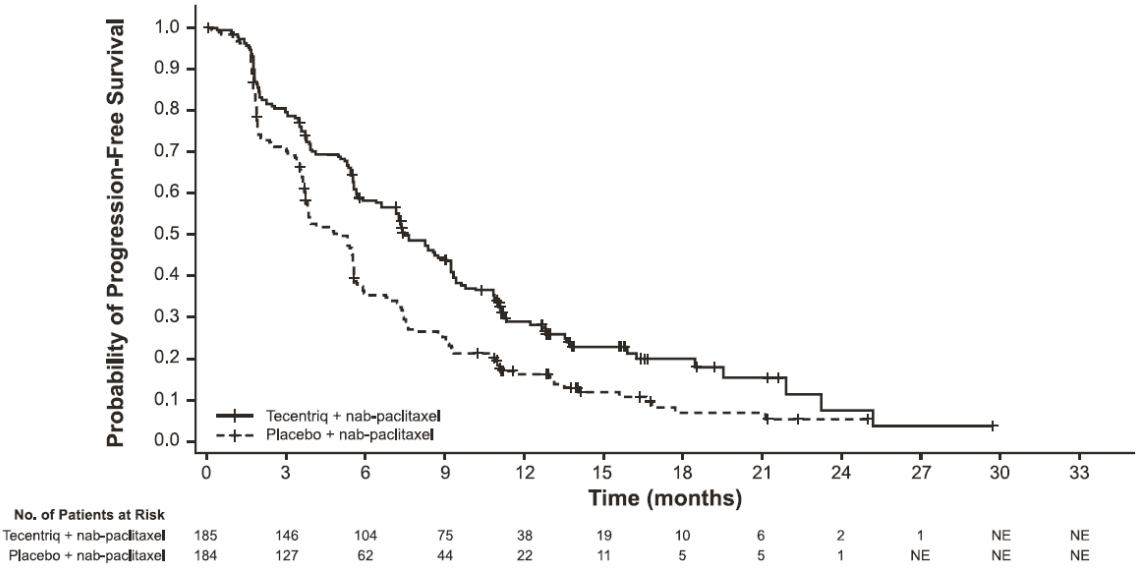
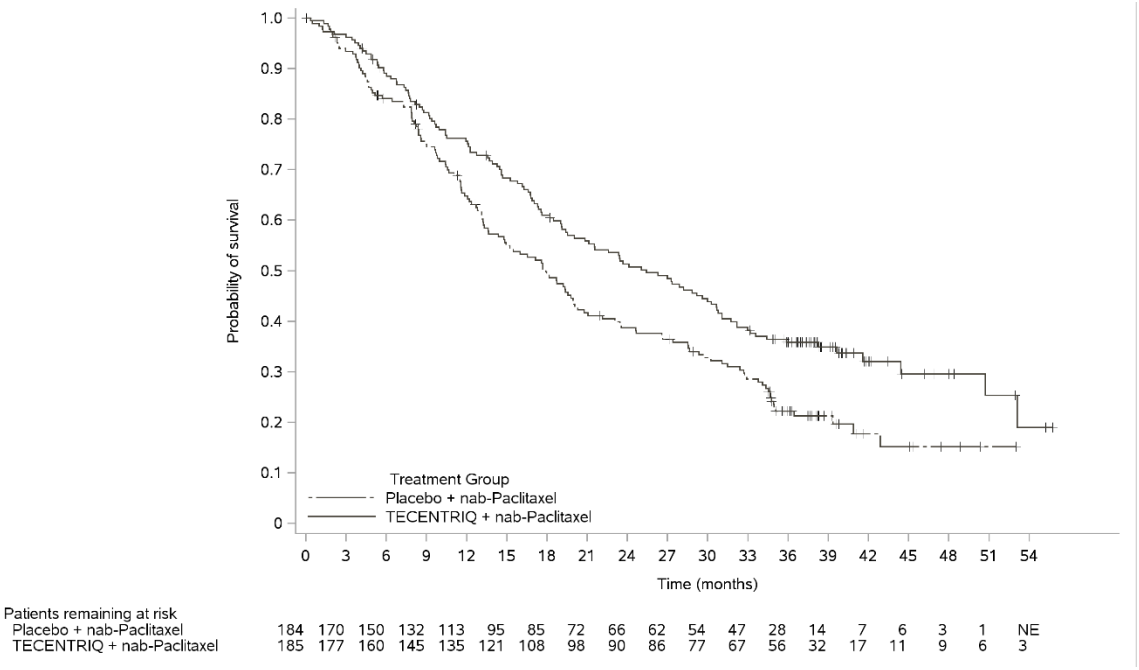


Figure 20. Kaplan-Meier curve for Overall Survival in patients with PD-L1 expression ≥1% (Study WO29522, Impassion130)



Patient-reported endpoints measured by the EORTC QLQ-C30 suggest that patients maintained their global health status/health-related quality of life (HRQoL), physical functioning, and role functioning while on treatment. No differences in the time to a ≥ 10-point deterioration in HRQoL (HR: 0.94; 95% CI: 0.69, 1.28), physical function (HR: 1.02; 95% CI: 0.76, 1.37), or role function (HR: 0.77; 95% CI: 0.57, 1.04) were observed between the two arms. Mean scores at baseline for HRQoL (67.5 Tecentriq + nab-paclitaxel vs. 65.0 placebo + nab-paclitaxel), physical function (82.7 vs. 79.4), and role function (73.6 vs. 71.7) were comparable between arms; as well as throughout the course of treatment. In both arms, HRQoL, physical function and role function remained stable during treatment, with no clinically meaningful changes (a ≥ 10-point difference from baseline mean score) observed.

Lack of Efficacy in Combination with Paclitaxel in Locally Advanced or Metastatic TNBC

The efficacy of Tecentriq in combination with paclitaxel in patients with unresectable locally advanced or metastatic triple-negative breast cancer has not been demonstrated. IMpassion131 was a multicentre, international, double-blinded, placebo-controlled, randomised (2:1) trial that included 651 patients with unresectable locally advanced or metastatic triple-negative breast cancer that had not received prior chemotherapy for metastatic disease. Patients were randomised to receive Tecentriq 840 mg or placebo intravenously on Days 1 and 15 of every 28-day cycle with paclitaxel 90 mg/m^2 intravenously on Days 1, 8 and 15 of every 28-day cycle. Patients received treatment until radiographic disease progression or unacceptable toxicity. Randomisation was stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumour infiltrating immune cells (IC) (PD-L1 stained tumour-infiltrating immune cells [IC] <1% of tumour area vs. ≥ 1% of the tumour area) determined by the VENTANA PD-L1 (SP142) Assay.

The major efficacy endpoint of investigator assessed progression free survival (PFS) in the PD-L1 expressing population after 61% of patients experienced a PFS event showed a HR of 0.82

(95% CI: 0.60, 1.12). Overall Survival (OS), an additional efficacy outcome with 42% deaths in the same population, showed a HR of 1.11 (95% CI:0.76, 1.64).

Intravenous Tecentriq

Hepatocellular carcinoma

YO40245
A global phase III, randomised, multi-centre, open-label study, YO40245 (IMbrave150), 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 Child-Pugh A, ECOG 0/1 and who had not received prior systemic treatment. Bleeding (including fatal events) is a known adverse reaction with bevacizumab and upper gastrointestinal bleeding is a common and life threatening complication in patients with HCC. Hence, patients were required to be evaluated for the presence of varices within 6 months prior to treatment, and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding or high risk of bleeding. Patients were also excluded if they had 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 following Cycle 1, Day 1, then every 9 weeks thereafter.

The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. The median age was 65 years (range: 26 to 88 years) and 83% were male. The majority of patients were Asian (57%) and white (35%). 40% were from Asia (excluding Japan), while 60% were from rest of world. Approximately 75% of patients presented with macrovascular invasion and/or extrahepatic spread and 37% had a baseline AFP ≥400 ng/mL. Baseline ECOG performance status was 0 (62%) or 1 (38%). The primary risk factors for the development of HCC were Hepatitis B virus infection in 48% of patients, Hepatitis C virus infection in 22% of patients, and non-viral disease in 31% of patients. HCC was 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 OS and IRF-assessed PFS according to RECIST v1.1. At the time of the primary analysis, patients had a median survival follow up time of 8.6 months. The data demonstrated a statistically significant improvement in OS and PFS as assessed by IRF per RECIST v1.1 with Tecentriq + bevacizumab compared to sorafenib. A statistically significant improvement was also observed in confirmed objective response rate (ORR) by IRF

per RECIST v1.1 and HCC modified RECIST (mRECIST). The key efficacy results from the primary analysis are summarised in Table 24.
A descriptive updated efficacy analysis was performed with a median survival follow up time of 15.6 months. The key results from the updated analysis are summarised in Table 24. Kaplan-Meier curves for OS (updated analysis) and PFS (primary analysis) are presented in Figures 21 and 22, respectively

Table 24. Summary of efficacy from Study YO40245 (IMbrave150 Primary Analysis)

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‡ (95% CI)	0.58 (0.42, 0.79)			
p-value[1]	0.0006			
6-month OS (%)	84.8%		72.3%	
	RECIST v1.1		**HCC mRECIST**	
	Tecentriq + Bevacizumab	Sorafenib	Tecentriq + Bevacizumab	Sorafenib
IRF-assessed PFS	n = 336	n = 165	n = 336	n = 165
No. of events (%)	197 (58.6%)	109 (66.1%)	199 (59.2%)	111 (67.3%)
Median duration of PFS (months)	6.8	4.3	6.8	4.2
95% CI	(5.8, 8.3)	(4.0, 5.6)	(5.7, 7.7)	(4.0, 5.5)
Stratified hazard ratio‡ (95% CI)	0.59 (0.47, 0.76)		0.59 (0.46, 0.74)	
p-value[1]	<0.0001		N/A	
6-month PFS	54.5%	37.2%	54.3%	36.4%
IRF-assessed ORR	n = 326	n = 159	n = 325	n = 158
No. of confirmed responders (%)	89 (27.3%)	19 (11.9%)	108 (33.2%)	21 (13.3%)
95% CI	(22.5, 32.5)	(7.4, 18.0)	(28.1, 38.6)	(8.4, 19.6)
p-value[2]	<0.0001		<0.0001	
No. of complete responses (%)	18 (5.5%)	0	33 (10.2%)	3 (1.9%)
No. of partial responses (%)	71 (21.8%)	19 (11.9%)	75 (23.1%)	18 (11.4%)
No. of stable disease (%)	151 (46.3%)	69 (43.4%)	127 (39.1%)	66 (41.8%)
IRF-assessed DOR	n = 89	n = 19	n = 108	n = 21
Median in months	NE	6.3	NE	6.3
95% CI	(NE, NE)	(4.7, NE)	(NE, NE)	(4.9, NE)
6-month DOR (%)	87.6%	59.1%	82.3%	62.5%

‡ Stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥400 ng/mL)
[1] Based on stratified log-rank test
[2] Based on stratified Cochran-Mantel-Haenszel test

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

Table 25. Summary of efficacy from Study YO40245 (IMbrave150 Updated Analysis)

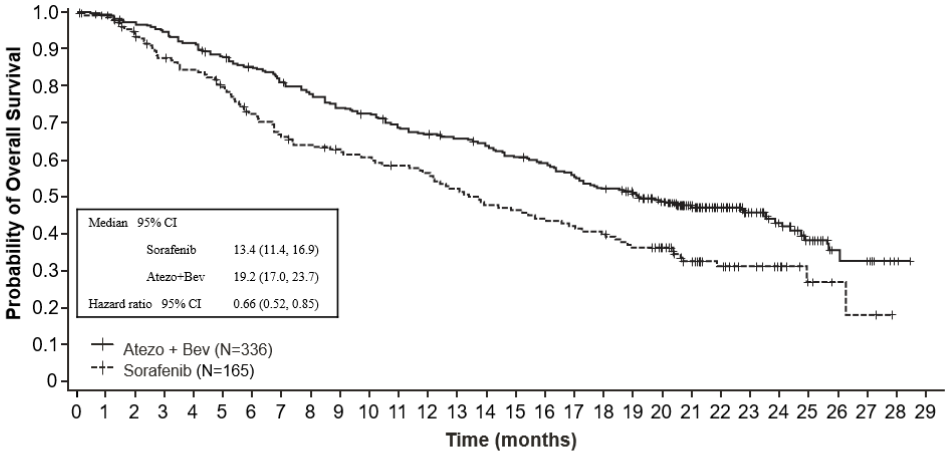
Key efficacy endpoints	Tecentriq + bevacizumab	sorafenib
OS	n=336	n=165
No. of deaths (%)	180 (53.6%)	100 (60.6%)
Median time to event (months)	19.2	13.4
95% CI	(17.0, 23.7)	(11.4, 16.9)
Stratified hazard ratio‡ (95% CI)	0.66 (0.52, 0.85)	
IRF-assessed ORR, RECIST 1.1	n=326	n=159
No. of confirmed responders (%)*	97 (29.8%)	18 (11.3%)
95% CI	(24.8, 35.0)	(6.9, 17.3)
IRF-assessed DOR, RECIST 1.1	n=97	n=18
Median in months	18.1	14.9
95% CI	(14.6, NE)	(4.9, 17.0)

‡ 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)

* No. of complete responses (%): 25 (7.7%) in the Tecentriq + bevacizumab arm and 1 (0.6%) in the sorafenib arm

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

Figure 21. Kaplan-Meier curve for Overall Survival from Study YO40245 (IMbrave150 Updated Analysis)

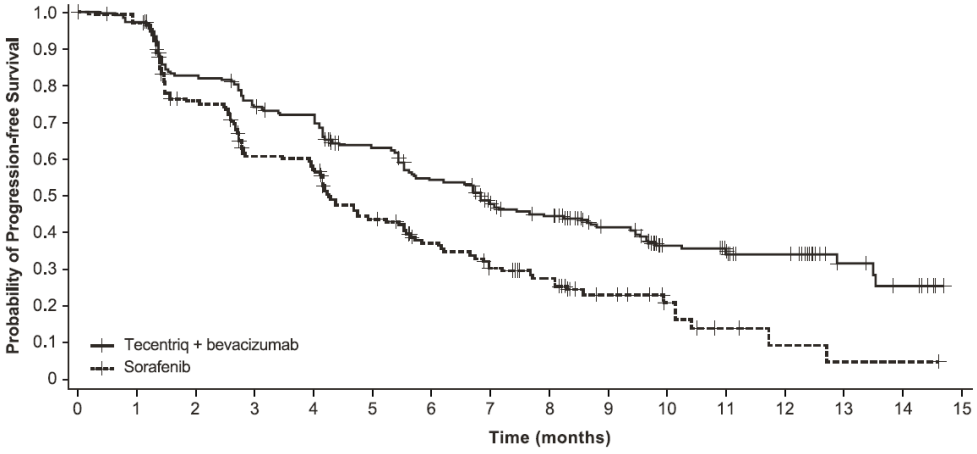


No. of Patients at Risk

Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

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

Figure 22. Kaplan-Meier curve for Progression-Free Survival per RECIST v1.1 from Study YO40245 (IMbrave150 Primary Analysis)



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 evaluated patient-reported outcomes using the EORTC QLQ-C30 and EORTC QLQ-HCC18 questionnaires. Time to deterioration (TTD) of patient-reported physical functioning, role functioning, and global health status/quality of life (GHS/QoL) on the EORTC QLQ-C30 were pre-specified secondary endpoints. TTD was defined as the time from randomisation to the first deterioration (decrease from baseline of ≥10 points) maintained for two consecutive assessments, or one assessment followed by death from any cause within 3 weeks. Compared with sorafenib, treatment with Tecentriq and bevacizumab delayed deterioration of patient-reported physical functioning (median TTD: 13.1 vs. 4.9 months; HR 0.53, 95% CI 0.39, 0.73), role functioning (median TTD: 9.1 vs. 3.6 months; HR 0.62, 95% CI 0.46, 0.84), and GHS/QoL (median TTD: 11.2 vs. 3.6 months; HR 0.63, 95% CI 0.46, 0.85). In pre-specified exploratory analyses, compared with sorafenib, treatment with Tecentriq and bevacizumab also delayed deterioration of patient-reported symptoms (i.e. appetite loss, diarrhoea, fatigue, pain, and jaundice) on the EORTC QLQ-C30 and EORTC QLQ-HCC18.

GO30140

A global, open-label, multi-centre, multi-arm Phase Ib study (GO30140) was also conducted in patients with solid tumours. Arm F of the study used a randomised design to evaluate the safety and efficacy of Tecentriq administered in combination with bevacizumab versus Tecentriq monotherapy in patients with advanced or metastatic and/or unresectable HCC who had not received prior systemic treatment. The primary efficacy endpoint was PFS assessed by IRF according to RECIST v1.1. A total of 119 patients were randomised 1:1 to receive either Tecentriq (1200 mg) and bevacizumab (15 mg/kg) by IV infusion every 3 weeks or Tecentriq (1200 mg) every 3 weeks. At the time of the primary analysis, the median survival follow up was 6.6 months. The combination of Tecentriq with bevacizumab showed a statistically significant PFS benefit compared to Tecentriq monotherapy (HR of 0.55, 80% CI: 0.40, 0.74, p-value=0.0108) with a median PFS of 5.6 months in patients treated with Tecentriq and bevacizumab, vs 3.4 months in patients treated with Tecentriq monotherapy.

PD-L1 expression by IHC

PD-L1 status is determined by the percentage of tumour cells (TC) with any membrane staining above background or by the percentage of tumour-associated immune cells with staining (IC+) at any intensity above background.

Study GO29527 (IMpower010)

Patients were considered to have tumour expression of PD-L1 ≥ 1% if PD-L1 stained TC covered ≥ 1% of the tumour area using VENTANA PD-L1 (SP263) Assay.

Study GO29431 (IMpower110)

Patients were initially deemed to be PD-L1 high if PD-L1 expression ≥ 50% TC or ≥ 10% IC using VENTANA PD-L1 (SP142) Assay. Additional PD-L1 analysis was performed using the Dako PD-L1 (22C3) IHC and VENTANA PD-L1 (SP263) IHC assays. Results from these pre-specified analyses show that the OS benefit with Tecentriq monotherapy over chemotherapy in PD-L1-high NSCLC is maintained when PD-L1 expression is measured using either the PD-L1 22C3 or SP263 IHC assays. Patients were considered to have high levels of PD-L1 expression if:

- PD-L1 expression ≥ 50% TC or ≥ 10% IC using VENTANA PD-L1 (SP142) Assay
- PD-L1 expression ≥ 50% TC using VENTANA PD-L1 (SP263) Assay
- PD-L1 expression (Tumour Proportion Score (TPS)* ≥ 50%) using the Dako PD-L1 (22C3) IHC pharmDxTM Kit

* TPS is the percentage of viable tumour cells showing partial or complete membrane staining at any intensity.

Study GO29436 (IMpower150)

Patients were considered to have tumour expression of PD-L1 ≥ 1% if PD-L1 stained TC covered ≥ 1% of the tumour area or if PD-L1 stained IC covered ≥ 1% of the tumour area using VENTANA PD-L1 (SP142) Assay.

Study WO30070 (IMvigor130)

Patients were considered to have tumour expression of PD-L1 ≥ 5% if PD-L1 stained IC covered ≥ 5% of the tumour area using VENTANA PD-L1 (SP142) Assay .

Study WO29522 (IMpassion130)

Patients were considered to have tumour expression of PD-L1 ≥ 1% if PD-L1 stained IC covered ≥ 1% of the tumour area using VENTANA PD-L1 (SP142) Assay.

Immunogenicity

As with all therapeutic proteins, there is the potential for immune response to atezolizumab. Across multiple phase III studies with intravenous atezolizumab, 13.1% to 36.4% of patients developed treatment-emergent anti-drug antibodies (ADAs) and 4.3% to 19.7% of patients developed neutralising antibodies (NAbs). Overall, ADA and NAb status appeared to have no clinically relevant impact on atezolizumab pharmacokinetics, efficacy or safety.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to Tecentriq with the incidence of antibodies to other products may be misleading.

In IMscin001, the incidence of treatment-emergent anti-atezolizumab antibodies in patients treated with Tecentriq SC and intravenous Tecentriq was comparable (19.5% [43/221] and 13.9% [15/108], respectively). Anti-atezolizumab antibody status did not appear to have a clinically relevant impact on atezolizumab PK, efficacy or safety. The incidence of treatment-emergent anti-rHuPH20 (vorhyaluronidase alfa) antibodies in patients treated with Tecentriq SC was 5.4% (12/224). The clinical relevance of the development of anti-rHuPH20 antibodies after treatment with Tecentriq SC is unknown.

5.2 PHARMACOKINETIC PROPERTIES

Intravenous Tecentriq

The pharmacokinetics of atezolizumab have been characterised in patients in multiple clinical trials at doses 0.01 mg/kg to 20 mg/kg and 1200 mg every 3 weeks, as well as 840 mg every 2 weeks. 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. Based on pharmacokinetic modeling, the overall exposure of atezolizumab administered at doses of 840 mg administered every 2 weeks, 1200 mg every 3 weeks and 1680 mg every 4 weeks are comparable. A population pharmacokinetic analysis suggests that steady-state is obtained after 6 to 9 weeks after multiple doses. The maximum systemic accumulation ratio across dosing regimens is 3.3.

Based on an analysis of exposure, safety and efficacy data, the following factors have no clinically relevant effect: age (2 - 89 years), body weight, gender, positive ADA status, albumin levels, tumour burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or Eastern Cooperative Oncology Group (ECOG) status.

Tecentriq SC

Atezolizumab model-predicted exposure metrics following Tecentriq SC (1875 mg SC administered every 3 weeks) and intravenous atezolizumab (1200 mg IV administered every 3 weeks) administration in the IMscin001 study are shown in Table 26. Atezolizumab Cycle 1 observed serum C_{trough} (i.e. pre-dose cycle 2) showed non-inferiority of atezolizumab within Tecentriq SC to intravenous atezolizumab, with a geometric mean ratio (GMR) of 1.05 (90% CI: 0.88–1.24).

The GMR for Cycle 1 model-predicted for AUC from 0 to 21 days (AUC0-21d) was 0.87 (90% CI: 0.83–0.92). The maximum systemic accumulation ratio following 1875 mg of Tecentriq SC administered every 3 weeks is 2.2. The model-predicted C_{trough} and AUC at steady state were comparable for Tecentriq SC and intravenous atezolizumab (see Table 26).

Table 26. Atezolizumab steady state exposure (geometric mean with 5th-95th Percentiles) following subcutaneous or intravenous administration of atezolizumab

Parameter	Atezolizumab within Tecentriq SC	Intravenous Atezolizumab
C_{trough} at steady state[a] (mcg/mL)	205 (70.3-427)	179 (98.4-313)
AUC at steady state[a] (mcg/mL day)	6163 (2561-11340)	6107 (3890-9334)

a) Model predicted exposure based on population pharmacokinetics analysis

Absorption

Intravenous Tecentriq is administered as an intravenous (IV) infusion.

Tecentriq SC

Based on population PK analysis, the absolute bioavailability was 72% and the first-order absorption rate (Ka) is 0.3 (1/day). The atezolizumab geometric mean maximum serum concentration (Cmax) was 189 mcg/mL and median time to maximum serum concentration (Tmax) was 4.5 days (median; 2.2-9.0 days min-max).

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

Paediatric population

The pharmacokinetic results from one early-phase, multi-centre open-label study that was conducted in paediatric (<18 years, n=69) and young adult patients (18-30 years, n = 18), show that the clearance and volume of distribution of atezolizumab were comparable between paediatric patients receiving 15 mg/kg and young adult patients receiving 1200 mg of atezolizumab every 3 weeks when normalised by body weight, with exposure trending lower in paediatric patients as body weight decreased. These differences were not associated with a decrease in atezolizumab concentrations below the therapeutic target exposure. Data for children < 2 years is limited thus no definitive conclusions can be made.

No dedicated studies of Tecentriq SC have been conducted in paediatric patients.

Elderly population

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 intravenous 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 intravenous atezolizumab among patients < 65 years (n = 274), patients between 65 - 75 years (n = 152) and patients > 75 years (n = 46) (see section 4.2).

No clinically relevant difference was observed in the pharmacokinetics of subcutaneous atezolizumab among patients <65 years (n = 138), patients between 65 - 75 years (n = 89), and patents > 75 years of age (n = 19).

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 intravenous 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 m2; 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).

No clinically relevant differences in the clearance of subcutaneous atezolizumab were found in patients with mild (eGFR 60 to 89 mL/min/1.73 m2; n = 111) or moderate (eGFR 30 to 59 mL/min/1.73 m2; n = 32) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m2; n = 103) renal function.

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 intravenous or subcutaneously administered 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 3 x ULN and any AST). No data are available in patients with severe (bilirubin > 3.0 x ULN and any AST) hepatic impairment. Hepatic impairment was defined by the National Cancer Institute (NCI) criteria of hepatic dysfunction (see section 4.2).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No mutagenicity studies have been conducted with atezolizumab.

Carcinogenicity

No carcinogenicity studies have been conducted with atezolizumab.

Fertility

No fertility studies have been conducted with Tecentriq; however assessment of the cynomolgus monkey male and female reproductive organs was included in the chronic toxicity study. Tecentriq 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. There was no effect on the male reproductive organs.

Subcutaneous formulation

Tecentriq SC contains vorhyaluronidase alfa (see section 6.1 List of excipients). No carcinogenicity, genotoxicity, or fertility studies were conducted for vorhyaluronidase alfa.

Reproductive toxicology studies with vorhyaluronidase alfa revealed embryofetal toxicity in mice at high systemic exposure, but did not show teratogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

Tecentriq SC
Vorhyaluronidase alfa (an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously), histidine, acetic acid, methionine, sucrose, polysorbate 20 and water for injections.

6.2 INCOMPATIBILITIES

Intravenous Tecentriq
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.

Tecentriq SC
No incompatibilities have been observed between Tecentriq SC and polypropylene (PP), polycarbondate (PC), stainless steel (ss), polyvinyl chloride (PVC), and polyurethanes (PU).

6.3 SHELF-LIFE

Intravenous Tecentriq
3 years.

The diluted solution for infusion should be used immediately. If the solution is not used immediately, it can be stored for up to 30 days at 2 °C to 8 °C, or 24 hours at ambient temperature (≤ 25°C) if prepared under aseptic conditions.

Tecentriq SC
2 years.

From a microbiological point of view, the product should be used immediately once transferred from the vial to the syringe since the medicine does not contain any antimicrobial-preservative. If not used immediately, in-use storage times and conditions prior to use are the responsiblity of the user and normally not longer than 24 hours at 2°C to 8°C, unless preparation has taken place under controlled and validated aseptic conditions.

The closed syringe can be stored at ≤ 30°C for up to 8 hours in diffuse daylight; or in the refrigerator (2°C to 8°C) for up to 24 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Intravenous Tecentriq and Tecentriq SC
Store the vials at 2°C to 8°C. Do not freeze.

Tecentriq and Tecentriq SC vials should be kept in the outer caton in order to protect 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

Intravenous Tecentriq
Tecentriq is available in a single-use glass vial containing 14 mL (840 mg) or 20 mL (1200 mg) solution in a pack size of 1 vial.

Tecentriq SC
Tecentriq SC is available in a single-use glass vial containing 15 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.

7. MEDICINE SCHEDULE

Prescription

8. SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113, Newmarket, Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 276 243

9. DATE OF FIRST APPROVAL

06 April 2017

10. DATE OF REVISION OF THE TEXT

24 April 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of anaphylaxis under ‘Infusion and Injection related reactions’
4.8	Change in number of Infusion related reaction ADRs; additional PTs (anaphylaxis) added to Table 4 footnote for exisiting concepts.