

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}TECENTRIQ® SC

atezolizumab injection

Sterile solution, 125 mg/mL

1875 mg/15 mL single use vial

For subcutaneous injection

Professed Standard

ATC Code: L01FF05

Antineoplastic agent, monoclonal antibody

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TECENTRIQ SC (atezolizumab, solution for subcutaneous injection) is indicated for:

- First-Line Extensive-Stage Small Cell Lung Cancer (ES-SCLC)
 - TECENTRIQ SC in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).
- Non-Small Cell Lung Cancer (NSCLC)
 - TECENTRIQ SC as monotherapy, is indicated as adjuvant treatment following complete resection and no progression after platinum-based adjuvant chemotherapy for adult patients with Stage II to IIIA* NSCLC whose tumours have PD-L1 expression on $\geq 50\%$ of tumour cells (TCs) (see 14 CLINICAL TRIALS).
**According to American Joint Committee on Cancer [7th edition]*
 - TECENTRIQ SC as monotherapy, is indicated for the first-line treatment of patients with metastatic NSCLC whose tumours have high PD-L1 expression (PD-L1 stained $\geq 50\%$ of TCs or PD-L1 stained tumour-infiltrating immune cells [ICs] covering $\geq 10\%$ of the tumour area), as determined by a validated test and who do not have EGFR or ALK genomic tumour aberrations.
 - TECENTRIQ SC in combination with bevacizumab, paclitaxel and carboplatin is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumour aberrations, and no prior systemic non-squamous NSCLC, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic non-squamous NSCLC.
 - TECENTRIQ SC in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous, non-small cell lung cancer (NSCLC) who do not have EGFR or ALK genomic tumour aberrations.
 - TECENTRIQ SC is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving Tecentriq.
- First-Line Unresectable or Metastatic Hepatocellular Carcinoma (HCC)
 - TECENTRIQ SC in combination with bevacizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who require systemic therapy.
- Locally Advanced or Metastatic Triple-Negative Breast Cancer (TNBC)
 - TECENTRIQ SC in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression on tumour-infiltrating immune cells (IC) covering $\geq 1\%$ of the tumour area, and who have not received prior chemotherapy for metastatic disease.

Do not replace nab-paclitaxel with paclitaxel, in combination with Tecentriq SC, when treating patients with unresectable locally advanced or metastatic TNBC (see 7 WARNINGS AND PRECAUTIONS and 14 CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of TECENTRIQ SC in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.3 Pediatrics and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics– Special Populations and Conditions).

1.2 Geriatrics

Geriatrics (≥65 years of age): No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.

2 CONTRAINDICATIONS

Tecentriq SC is contraindicated in:

- Patients with a known hypersensitivity to atezolizumab or any of the excipients. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

For the use of Tecentriq SC in combination therapy, please also refer to the Product Monograph for the combination product. Tecentriq SC should be administered prior to IV combination therapy if given on the same day.

4.1 Dosing Considerations

- It is important to check the product labels to ensure that the correct formulation [Tecentriq (i.e., intravenous formulation - IV) or Tecentriq SC (i.e., subcutaneous formulation)] is being administered to the patient as prescribed. Patients currently receiving intravenous Tecentriq may transition to Tecentriq SC for injection.
- Tecentriq SC formulation is not intended for intravenous administration.

4.2 Recommended Dose and Dosage Adjustment

Tecentriq SC Combination Therapy

Extensive-Stage Small Cell Lung Cancer (ES-SCLC)

Tecentriq SC in combination with carboplatin and etoposide (First-Line)

During the induction phase, the recommended dose of Tecentriq SC is 1875 mg administered by subcutaneous injection 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 (see 14 CLINICAL TRIALS).

The induction phase is followed by a maintenance phase without chemotherapy in which 1875 mg Tecentriq SC is administered by subcutaneous injection every 3 weeks.

Non-Small Cell Lung Cancer (NSCLC)

Tecentriq SC in Combination with bevacizumab, Paclitaxel and Carboplatin (First-Line)

The recommended dosage of Tecentriq SC is 1875 mg administered by subcutaneous injection followed by bevacizumab, paclitaxel, and carboplatin, on Day 1 of each 21-day cycle for a maximum of 4 to 6 cycles of chemotherapy.

After completion of chemotherapy, administer Tecentriq SC 1875 mg by subcutaneous injection, followed by bevacizumab on Day 1 of each 21-day cycle.

The paclitaxel starting dose for patients of Asian race/ethnicity was 175 mg/m² due to higher overall level of hematologic toxicities in patients from Asian countries compared with those from non-Asian countries.

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

Tecentriq SC in Combination with nab-Paclitaxel and Carboplatin (First-Line)

During the induction phase, the recommended dose of Tecentriq SC is 1875 mg administered by subcutaneous injection, followed by nab-paclitaxel and carboplatin every 3 weeks for four or six cycles. For each 21-day cycle, nab-paclitaxel and carboplatin is 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 1875 mg Tecentriq SC is administered by subcutaneous injection every 3 weeks.

Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

Tecentriq SC in Combination with Bevacizumab (First-Line)

The recommended dosage of Tecentriq SC is 1875 mg administered by subcutaneous injection, followed by 15 mg/kg of bevacizumab, every 3 weeks.

Refer to the Product Monograph for bevacizumab prior to initiation.

Triple-Negative Breast Cancer (TNBC)

Tecentriq SC in Combination with nab-Paclitaxel (First-Line)

The recommended dose of Tecentriq SC is 1875 mg administered by subcutaneous injection every 3 weeks, followed by 100 mg/m² nab-paclitaxel. Nab-paclitaxel is administered on days 1, 8 and 15 of each 28-day cycle.

Patients should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see 14 CLINICAL TRIALS).

Tecentriq SC Monotherapy

Adjuvant Treatment of Early-Stage NSCLC

The recommended dose of Tecentriq SC is 1875 mg administered by subcutaneous injection every 3 weeks.

Patients should be selected for treatment based on PD-L1 expression on $\geq 50\%$ of tumour cells (TCs), determined by an experienced laboratory using a validated test, which is equivalent to that used in the clinical trial (see 14 CLINICAL TRIALS).

Metastatic NSCLC (First Line)

The recommended dose of Tecentriq SC is 1875 mg administered by subcutaneous injection every 3 weeks.

Patients should be selected for treatment based on high PD-L1 expression (TCs $\geq 50\%$ or ICs $\geq 10\%$), determined by an experienced laboratory using a validated test (see 14 CLINICAL TRIALS).

Locally Advanced or Metastatic NSCLC (Second Line)

The recommended dose of Tecentriq SC is 1875 mg administered by subcutaneous injection every 3 weeks.

Duration of Treatment

Adjuvant Treatment of Early-Stage NSCLC

Patients are treated with Tecentriq SC for up to 1 year unless there is disease recurrence or unacceptable toxicity (see 14 CLINICAL TRIALS).

ES-SCLC (First-Line), Locally Advanced or Metastatic NSCLC (First Line and Second Line), and Unresectable or Metastatic Hepatocellular Carcinoma

It is recommended that patients are treated with Tecentriq SC until loss of clinical benefit or unmanageable toxicity.

For previously treated patients in pivotal studies, treatment with Tecentriq SC was permitted until loss of clinical benefit as defined by the following criteria:

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

TNBC

Patients are treated with Tecentriq SC until disease progression or unacceptable toxicity.

Dose Modifications for Immune-Mediated Adverse Reactions

No dose reductions of Tecentriq SC are recommended.

Tecentriq SC dose modifications for specific adverse drug reactions (see 7 WARNINGS AND PRECAUTIONS) are presented Table 1.

Table 1: Recommended Tecentriq SC Dose Modifications for Specific Adverse Drug Reactions

Adverse Reaction	Severity	Tecentriq SC dose modification
Immune-Mediated Pneumonitis	Grade 2	Withhold ¹
	Grade 3 or 4	Permanently discontinue
Immune-Mediated Hepatitis in patients without HCC	Grade 2 (ALT or AST >3x ULN or blood bilirubin >1.5x ULN for more than 5-7 days)	Withhold ¹
	Grade 3 or 4 (ALT or AST >5.0x ULN or blood bilirubin >3x ULN)	Permanently discontinue
Immune-Mediated Hepatitis in patients with HCC	If AST/ALT is within normal limits at baseline and increases to >3x to ≤10x ULN	Withhold ¹
	If AST/ALT is >1 to ≤3x ULN at baseline and increases to >5x to ≤10x ULN	Permanently discontinue for events lasting > 5 days of duration following withholding of Tecentriq
	If AST/ALT is >3x to ≤5x ULN at baseline and increases to >8x to ≤10x ULN	Permanently discontinue
	If AST/ALT increases to >10x ULN or total bilirubin increases to >3x ULN	Permanently discontinue
Immune-Mediated Colitis	Grade 2 diarrhea or colitis	Withhold ¹
	Grade 3 diarrhea or colitis	Withhold ¹ Initiate IV corticosteroids and convert to oral corticosteroids after improvement
	Grade 4 diarrhea or colitis	Permanently discontinue
Immune-Mediated Hypothyroidism	Symptomatic	Withhold ² Initiate thyroid hormone replacement therapy
Immune-Mediated Hyperthyroidism	Symptomatic	Withhold ² Initiate anti-thyroid therapy as needed
Immune-Mediated Adrenal Insufficiency	Symptomatic	Withhold ¹

Adverse Reaction	Severity	Tecentriq SC dose modification
Immune-Mediated Hypophysitis	Grade 2 or 3	Withhold ¹
	Grade 4	Permanently discontinue
Immune-Mediated Type 1 Diabetes	For \geq Grade 3 hyperglycemia (fasting glucose >13.9 mmol/L)	Withhold ² Initiate insulin
Immune-Mediated Meningitis, Encephalitis, Myasthenic Syndrome / Myasthenia Gravis, Guillain-Barré syndrome	All grades	Permanently discontinue
Immune-Mediated Myelitis	Grade 2, 3 or 4	Permanently discontinue
Immune-Mediated Facial Paresis	Grade 1 or 2	Withhold ¹
	Grade 3 or 4	Permanently discontinue
Immune-Mediated Pancreatitis	Grade 2 or 3 \geq Grade 3 serum amylase or lipase levels increased (> 2.0 ULN)	Withhold ¹
	Grade 4 or any grade recurrent pancreatitis	Permanently discontinue
Immune-Mediated Myocarditis	Grade 2 or above	Permanently discontinue
Immune-Mediated Myositis	Grade 2 or 3	Withhold ¹
	Grade 4 or grade 3 recurrent myositis	Permanently discontinue
Immune-Mediated Nephritis	Grade 2 (creatinine level $>1.5 - 3.0x$ baseline or $>1.5 - 3.0x$ ULN)	Withhold ¹
	Grade 3 (creatinine level $>3.0x$ baseline or $>3.0 - 6.0x$ ULN) or 4 (creatinine level $>6.0x$ ULN)	Permanently discontinue
Immune-Mediated Pericardial Disorders	Grade 1 pericarditis	Withhold ³
	Grade 2 or above	Permanently discontinue
Infusion-Related Reactions	Grade 1 or 2	Reduce rate of injection or withhold treatment/ pause the injection. Premedication with antipyretic and antihistamines may be considered for subsequent doses
	Grade 3 or 4	Permanently discontinue
Haemophagocytic Lymphohistiocytosis	Suspected haemophagocytic lymphohistiocytosis ³	Permanently discontinue

Adverse Reaction	Severity	Tecentriq SC dose modification
Immune-Mediated Skin Reactions	Grade 3 Or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) ⁴	Withhold ¹
	Grade 4 Or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) ⁴	Permanently discontinue
Persistent Grade 2 or 3 adverse reaction (excluding endocrinopathies)	Grade 2 or 3 adverse reaction that does not recover to Grade 0 or 1 within 12 weeks after last Tecentriq SC dose	Permanently discontinue
Inability to taper corticosteroid	Inability to reduce to less than or equal to prednisone 10 mg per day (or equivalent) within 12 weeks after last Tecentriq SC dose	Permanently discontinue
Recurrent Grade 3 or 4 adverse reaction	Recurrent Grade 3 or 4 (severe or life-threatening) adverse reaction	Permanently discontinue

¹ Treatment with corticosteroid therapy (1-2 mg/kg/day prednisone or equivalent) should be initiated. Treatment with TECENTRIQ SC 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 SC may be resumed when symptoms are controlled and the patient is clinically stable.

³ Conduct a detailed cardiac evaluation to determine the etiology and manage appropriately.

⁴ Regardless of severity.

For other immune-mediated reactions, based on the type and severity of the reaction, treatment with Tecentriq SC 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 SC 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 SC 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.

See manufacturers' Product Monographs for toxicity management, dose adjustment guidelines for special populations and contraindications for coadministered products (bevacizumab, carboplatin, etoposide, nab-paclitaxel and paclitaxel). Withhold, dose reduce or discontinue these coadministered products in accordance with instructions in their respective Product Monographs.

Pediatrics:

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Tecentriq SC in pediatric patients (<18 years of age) has not been established; therefore Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special

Populations, 7.1.3 Pediatrics and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics-Special Populations and Conditions).

Geriatrics:

Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq SC is required in patients ≥ 65 years of age (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions).

Renal Impairment:

Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with mild or moderate renal impairment. There is insufficient data in patients with severe renal impairment (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions).

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 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions).

4.3 Reconstitution

Parenteral Products:

No reconstitution is required for Tecentriq SC.

4.4 Administration

Tecentriq SC must be administered under the supervision of a qualified healthcare professional. In order to improve the traceability of medicinal products, the trade name, Tecentriq SC, and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Tecentriq SC must be administered as a subcutaneous injection only.

Administer 15 mL of Tecentriq SC solution subcutaneously in the thigh in approximately 7 minutes. Use of a SC infusion set (*e.g.*, winged / butterfly) is recommended. 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.

Tecentriq SC is a ready-to-use solution for subcutaneous injection only and should not be diluted or mixed with other drugs. Tecentriq SC should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.

Tecentriq SC solution for injection is for single use only and should be prepared by a healthcare professional. Prior to administration, remove Tecentriq SC from refrigeration and allow the solution to reach room temperature.

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.

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.

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.

If the syringe was stored in a refrigerator, allow the syringe to reach room temperature prior to administration. See also 11 STORAGE, STABILITY AND DISPOSAL.

4.5 Missed Dose

Delayed or Missed Doses

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

5 OVERDOSAGE

There is no information on overdose with Tecentriq SC. Doses ranging from 0.01 to 20 mg/kg were tested in patients with Tecentriq (intravenous formulation) in various tumour types, and a maximum tolerated dose (MTD) was not determined.

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 2 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection	Solution for injection 1875 mg atezolizumab / 15 mL (125 mg/mL)	acetic acid, 30%, L-Histidine, L-Methionine, polysorbate 20, recombinant human hyaluronidase PH20 (rHuPH20), sucrose, water for injection

Tecentriq SC (solution for subcutaneous injection) is supplied as a sterile, ready-to-use, single-dose vial containing 1875 mg atezolizumab/15 mL preservative-free, colourless to slightly yellow solution, at an active ingredient concentration of 125 mg/mL. Each carton contains one vial of 1875 mg of atezolizumab.

Tecentriq SC contains recombinant human hyaluronidase (rHuPH20) at a concentration of 2,000 U/mL, an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously.

7 WARNINGS AND PRECAUTIONS

General

Therapy with Tecentriq SC should only be initiated under the supervision of physicians experienced in the treatment of cancer.

Other medications used in combination with Tecentriq SC

When Tecentriq SC is to be administered in combination with bevacizumab, etoposide, nab-paclitaxel, paclitaxel or carboplatin, refer to the respective product monographs for full prescribing information.

Discontinuation/Dose modification and dose interruption

Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving Tecentriq. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of Tecentriq, administration of corticosteroids and/or supportive care. Immune-mediated adverse reactions have also occurred after the last dose of Tecentriq. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. See 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS for additional information.

Numeric increase in the risk of death in patients with metastatic TNBC when Tecentriq is used in combination with paclitaxel

In a randomized clinical trial in patients with locally advanced or metastatic TNBC, Study MO39196 (IMpassion131), an increase in the risk of death was observed in patients treated with Tecentriq (intravenous formulation) plus paclitaxel compared with placebo and paclitaxel in the PD-L1-positive population (Overall Survival stratified HR: 1.11, 95% CI [0.76, 1.64]). Do not replace nab-paclitaxel with paclitaxel in combination with Tecentriq SC in clinical practice for unresectable locally advanced or metastatic TNBC outside of controlled clinical trials. See 1 INDICATIONS and 14 CLINICAL TRIALS for additional information.

Use in lung and hepatocellular cancer patients treated with the combination of Tecentriq and bevacizumab

Bleeding (including fatal events) is a known adverse reaction with bevacizumab. Serious bleeding events, including fatalities, have occurred in lung and hepatocellular cancer patients treated with the combination of Tecentriq (intravenous formulation) and bevacizumab. Lung cancer patients, who had clear tumour infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging, were excluded from the pivotal clinical study GO29436 (IMpower150) after several cases of fatal pulmonary hemorrhage occurred following initiation of treatment with Tecentriq (intravenous formulation) in combination with bevacizumab, paclitaxel and carboplatin.

There is lack of clinical data to support the combination of Tecentriq SC and bevacizumab in hepatocellular cancer patients with bleeding varices (including recent bleeds), untreated varices or varices at high risk of bleeding because these patients were excluded from treatment with Tecentriq (intravenous formulation) and bevacizumab in the YO40245 (IMbrave150) pivotal study (see 14 CLINICAL TRIALS).

Carefully consider the risks of Tecentriq SC plus bevacizumab in patients with HCC or the four-drug regimen of Tecentriq SC in combination with bevacizumab, paclitaxel, and carboplatin in lung cancer patients before initiating treatment. Patients with HCC should be evaluated for the presence of varices and have varices treated as indicated within 6 months prior to initiating therapy with the combination of Tecentriq SC and bevacizumab.

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

Driving and Operating Machinery

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

Immune

Autoimmune Hemolytic Anemia

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

Haemophagocytic Lymphohistiocytosis

Tecentriq can cause haemophagocytic lymphohistiocytosis (HLH), including fatal cases, which were observed in patients receiving Tecentriq (see section 8 ADVERSE REACTIONS). 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 DOSAGE AND ADMINISTRATION for recommended dose modifications.

Immune-Mediated Colitis

Tecentriq can cause diarrhea or colitis. Patients should be monitored for signs and symptoms of colitis. Refer to section 4 DOSAGE AND ADMINISTRATION for recommended dose modifications.

Treatment with Tecentriq SC should be withheld for Grade 2 or Grade 3 diarrhea (increase of ≥ 4 stools/day over baseline) or colitis (symptomatic). For Grade 2 diarrhea or colitis, if symptoms persist > 5 days or recur, start 1–2 mg/kg prednisone or equivalent per day. Treat Grade 3 diarrhea or colitis with IV corticosteroids (1–2 mg/kg/day methylprednisolone or equivalent) and convert to oral

corticosteroids (prednisone 1–2 mg/kg or equivalent per day) after improvement. If symptoms improve to \leq Grade 1, taper corticosteroids over \geq 1 month. Treatment with Tecentriq SC may be resumed if the event improves to \leq Grade 1 within 12 weeks and corticosteroids have been reduced to \leq 10 mg oral prednisone or equivalent per day. Treatment with Tecentriq SC should be permanently discontinued for Grade 4 (life threatening; urgent intervention indicated) diarrhea or colitis.

Immune-Mediated Endocrinopathies

Tecentriq can cause hypothyroidism, hyperthyroidism, adrenal insufficiency and type 1 diabetes mellitus, including diabetic ketoacidosis across tumour types. Patients should be monitored for clinical signs and symptoms of endocrinopathies.

Adrenal Insufficiency

For symptomatic adrenal insufficiency, Tecentriq SC should be withheld and treatment of 1–2 mg/kg per day of IV methylprednisolone or equivalent should be started. Once symptoms improve, follow with 1–2 mg/kg per day of oral prednisone or equivalent. If symptoms improve to \leq Grade 1, taper corticosteroids over \geq 1 month. Treatment may be resumed if the event improves to \leq Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of \leq 10 mg oral prednisone or equivalent per day and patient is stable on replacement therapy (if required). Refer to section 4 DOSAGE AND ADMINISTRATION for recommended dose modifications.

Diabetes Mellitus

Treatment with insulin should be initiated for type 1 diabetes mellitus. For \geq Grade 3 hyperglycemia (fasting glucose >13.9 mmol/L), Tecentriq SC should be withheld. Treatment with Tecentriq SC may be resumed if metabolic control is achieved on insulin replacement therapy. Refer to section 4 DOSAGE AND ADMINISTRATION for recommended dose modifications. ***Hypophysitis***

Tecentriq can cause hypophysitis across tumour types. Monitor for signs and symptoms of hypophysitis. Administer corticosteroids and hormone replacement as clinically indicated. Withhold Tecentriq SC for Grade 2 or Grade 3 and permanently discontinue for Grade 4 hypophysitis. Refer to section 4 DOSAGE AND ADMINISTRATION for recommended dose modifications.

Thyroid Disorders

Monitor thyroid function prior to and periodically during treatment with Tecentriq SC. Consider appropriate management of patients with abnormal thyroid function tests at baseline. Patients with abnormal thyroid function tests who are asymptomatic may receive Tecentriq SC. Refer to section 4 DOSAGE AND ADMINISTRATION for recommended dose modifications.

Asymptomatic patients with abnormal thyroid function tests can receive Tecentriq SC. For symptomatic hypothyroidism, Tecentriq SC should be withheld and thyroid hormone replacement should be initiated as needed. Isolated hypothyroidism may be managed with replacement therapy and without corticosteroids. For symptomatic hyperthyroidism, Tecentriq SC should be withheld and an anti-thyroid drug such as methimazole or carbimazole should be initiated as needed. Treatment with Tecentriq SC may be resumed when symptoms are controlled and thyroid function is improving.

Refer to section 8 ADVERSE REACTIONS for additional information.

Immune-Mediated Hepatitis

Tecentriq can cause hepatitis, some leading to fatal outcomes across tumour types. 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 SC. Consider appropriate management of patients with abnormal liver function tests (LFTs) at baseline. Refer to section 4 DOSAGE AND ADMINISTRATION for recommended dose modifications.

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

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

Immune-Mediated Meningoencephalitis

Tecentriq can cause meningoencephalitis across tumour types. Patients should be monitored for clinical signs and symptoms of meningitis or encephalitis. Refer to section 4 DOSAGE AND ADMINISTRATION for recommended dose modifications.

Treatment with Tecentriq SC should be permanently discontinued for any grade of meningitis or encephalitis. Treat with 1–2 mg/kg IV methylprednisolone or equivalent per day. Convert to 1–2 mg/kg oral prednisone or equivalent per day once the patient has improved. If symptoms improve to ≤ Grade 1, taper corticosteroids over ≥ 1 month.

Immune-Mediated Myelitis

Tecentriq can cause myelitis, including fatal cases. Patients should be closely monitored for signs and symptoms that are suggestive of myelitis. Refer to section 4 DOSAGE AND ADMINISTRATION for recommended dose modifications.

Immune-Mediated Myocarditis

Tecentriq can cause myocarditis, including fatal cases, observed in clinical trials. 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 DOSAGE AND ADMINISTRATION for recommended dose modifications.

Treatment with Tecentriq SC should be permanently discontinued for myocarditis Grade 2 or above. Corticosteroids and/or additional immunosuppressive agents should be administered as clinically indicated.

Immune-Mediated Myositis

Tecentriq can cause myositis, including fatal cases. Cases of rhabdomyolysis were also observed. 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 DOSAGE AND ADMINISTRATION for recommended dose modifications.

Treatment with Tecentriq SC should be withheld if Grade 2 or Grade 3 myositis occurs. Treatment with corticosteroid therapy (1–2 mg/kg/day prednisone or equivalent) should be initiated. Treatment with Tecentriq SC 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. Treatment with Tecentriq SC should be permanently discontinued for Grade 4, or recurrent Grade 3 myositis.

Immune-Mediated Nephritis

Tecentriq can cause nephritis. Patients should be monitored for changes in renal function. Refer to section 4 DOSAGE AND ADMINISTRATION for recommended dose modifications.

Treatment with Tecentriq SC should be withheld for Grade 2 nephritis. Treatment with Tecentriq SC should be permanently discontinued for Grade 3 or 4 nephritis.

Immune-Mediated Neuropathies

Tecentriq can cause myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome, which may be life threatening, and facial palsy, which were observed in patients receiving Tecentriq across tumour types. Patients should be monitored for symptoms of motor and sensory neuropathy. Refer to section 4 DOSAGE AND ADMINISTRATION for recommended dose modifications.

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

Immune-Mediated Pancreatitis

Tecentriq can cause pancreatitis, including increases in serum amylase and lipase levels across tumour types. Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis. Refer to section 4 DOSAGE AND ADMINISTRATION for recommended dose modifications.

Treatment with Tecentriq SC should be withheld for \geq Grade 3 serum amylase or lipase levels increased (> 2.0 ULN), or Grade 2 or 3 pancreatitis, and treatment with 1–2 mg/kg IV methylprednisolone or equivalent per day, should be started. Once symptoms improve, follow with 1–2 mg/kg oral prednisone or equivalent per day. Treatment with Tecentriq SC may be resumed when serum amylase and lipase levels improve to \leq Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Treatment with Tecentriq SC should be permanently discontinued for Grade 4, or any grade of recurrent pancreatitis.

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 8 ADVERSE REACTIONS). Patients should be monitored for clinical signs and symptoms of pericardial disorders. Refer to the 4 DOSAGE AND ADMINISTRATION section for recommended dose modifications.

Immune-Mediated Pneumonitis

Tecentriq can cause pneumonitis, including fatal cases across tumour types. Patients should be monitored for signs and symptoms of pneumonitis. Refer to section 4 DOSAGE AND ADMINISTRATION for recommended dose modifications.

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

Immune-Mediated Skin Reactions

Tecentriq can cause immune-mediated rash. 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 monotherapy or in combination with other anti-cancer

agents. In most cases, patients received concomitant medications known to be associated with severe cutaneous reactions. Monitor patients for rash and other skin reactions and exclude other causes. Based on the severity of the adverse reaction, Tecentriq SC 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. Refer to the 4 DOSAGE AND ADMINISTRATION section for recommended dose modifications.

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

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

Other Immune-Mediated Toxicities

The following additional clinically significant immune-mediated adverse reactions were reported in less than 1% (unless otherwise indicated) in patients treated with Tecentriq for various cancers and/or reported with the use of other PD-1/PD-L1 blocking antibodies: sarcoidosis, vasculitis and aplastic anemia.

Infections

Tecentriq can cause severe infections. Monitor patients for signs and symptoms of infection and treat with antibiotics for suspected or confirmed bacterial infections. Withhold Tecentriq SC for \geq Grade 3 infection. Refer to 4 DOSAGE AND ADMINISTRATION for recommended dose modifications.

Infusion-Related Reactions

Infusion related reactions, including hypersensitivity and anaphylaxis, have been observed in clinical trials with Tecentriq. Monitor for signs and symptoms of infusion-related reactions. Refer to section 4 DOSAGE AND ADMINISTRATION for recommended dose modifications.

The rate of injection should be reduced or treatment should be interrupted in patients with Grade 1 or 2 infusion-related reactions. Patients with Grade 1 or 2 infusion-related reactions may continue to receive Tecentriq SC with close monitoring; premedication with antipyretic and antihistamines may be considered. Treatment with Tecentriq SC should be permanently discontinued in patients with Grade 3 or 4 infusion-related reactions.

Monitoring and Laboratory Tests

Monitor AST, ALT, bilirubin, renal, and thyroid function prior to, periodically during treatment with Tecentriq SC and as indicated based on clinical evaluation. Patients should be closely monitored during treatment for signs and symptoms of immune-mediated adverse reactions, including but not limited to, dyspnea, hypoxia; increased frequency of bowel movements, diarrhea; elevated creatinine levels; rash, pruritus; headache, fatigue, hypotension, mental status changes, visual disturbances; muscle pain or weakness, paresthesias (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

Ophthalmologic

Ocular Inflammatory Toxicity

Tecentriq can cause ocular inflammatory toxicity including optic neuritis, uveitis, keratitis and retinopathy. Withhold Tecentriq SC for moderate and permanently discontinue for severe ocular

inflammatory toxicity. Refer to section 4 DOSAGE AND ADMINISTRATION for recommended dose modifications.

Reproductive Health: Female and Male Potential

- **Fertility**

Based on animal studies, Tecentriq SC may impair fertility in females of reproductive potential while receiving treatment.

7.1 Special Populations

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

7.1.1 Pregnant Women

There are no data on the use of Tecentriq SC in pregnant women. Animal reproductive studies have not been conducted with Tecentriq SC; however, in murine pregnancy models, inhibition of the PD-L1/PD-1 pathway has been demonstrated to disrupt immune system tolerance to the developing fetus resulting in fetal death. Based on these studies, and based on its mechanism of action, the use of Tecentriq SC during pregnancy can cause fetal harm including increased rates of abortion or stillbirth (see 16 NON-CLINICAL TOXICOLOGY).

Tecentriq SC is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. Pregnant women should be advised of the potential risk to the fetus.

Women of Childbearing Potential: For women of childbearing potential, pregnancy status should be established prior to initiating Tecentriq SC. Women should be advised to use highly effective contraception and take active measures to avoid pregnancy while undergoing Tecentriq SC treatment and for at least 5 months after the last dose (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

Nursing Women: There is no information regarding the presence of atezolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from Tecentriq SC, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Tecentriq SC in pediatric patients have not been established; therefore Health Canada has not authorized an indication for pediatric use (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics– Special Populations and Conditions).

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions). Data for patients ≥ 75 years of age are too limited to draw conclusions on this population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

SUBCUTANEOUS FORMULATION (Tecentriq SC)

Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Study BP40657 (IMscin001)

The safety of Tecentriq SC was evaluated in IMscin001, a phase Ib/III, open-label, randomized, multicentre study comparing the pharmacokinetics, efficacy, safety and immunogenicity of atezolizumab subcutaneous with atezolizumab intravenous in patients with locally advanced or metastatic NSCLC who have not been exposed to cancer immunotherapy and for whom prior platinum-based therapy has failed (see 14 CLINICAL TRIALS). Patients received Tecentriq SC (subcutaneous formulation) (n=247) or Tecentriq (intravenous formulation) (n=124) every 3 weeks. The median duration of exposure was 2.2 months to Tecentriq SC (range: 0-15 months) and intravenous Tecentriq (range: 0-16 months). The median number of doses was 4 in both study arms.

The proportions of patients with at least one AE were 86% in the Tecentriq SC arm compared to 84% in the intravenous Tecentriq arm. The most common adverse events of any grade (occurring in ≥10% of patients) in the Tecentriq SC arm were anemia (15%) and fatigue (10%).

Adverse events leading to death occurred in 5.7% of patients receiving Tecentriq SC; these included myocardial infarction, COVID-19 pneumonia, pneumonia aspiration, pneumonia, respiratory tract infection, sepsis, pulmonary embolism, head injury, ischemic stroke, and toxic epidermal necrolysis. Adverse events leading to death occurred in 3.2% of patients receiving Tecentriq (intravenous formulation); these included COVID-19, upper respiratory tract infection, pulmonary embolism, and hypercalcaemia. Of the 14 Grade 5 AEs in the Tecentriq SC arm, 2 were considered by the Investigator as treatment-related (pneumonia aspiration and toxic epidermal necrolysis) versus none in the Tecentriq (intravenous formulation) arm.

Serious adverse events occurred in 15.4% of patients receiving Tecentriq SC and 17.7% of patients receiving Tecentriq (intravenous formulation). The most frequent serious adverse events (>1%) were pneumonia, COVID-19 pneumonia, and myocardial infarction for patients receiving Tecentriq SC and pneumonia, COVID-19, urinary tract infection, pleural effusion and pyrexia for patients receiving Tecentriq (intravenous formulation).

Tecentriq SC was discontinued due to adverse events in 3.2% of patients and included COVID-19 pneumonia, pneumonia, pneumonia aspiration, sepsis, myocardial infarction, ALT increased, AST increased, GGT increased, and ischemic stroke. Tecentriq (intravenous formulation) was discontinued due to adverse events in 4.0% of patients and included COVID-19, asthma, pneumonitis, infusion related reaction, and hypercalcaemia.

Adverse events leading to interruption of Tecentriq SC occurred in 25.1% of patients; the most common (>1%) were COVID-19 (4%), ALT increased (2.0%), AST increased (2.0%), pneumonia (1.6%), respiratory

tract infection viral (1.2%), and anemia (1.2%). Adverse events leading to interruption of Tecentriq (intravenous formulation) occurred in 25.0% of patients; the most common (>1%) were COVID-19 (6.5%), pneumonia (2.4%), bronchitis (1.6%), and hypercreatininaemia (1.6%).

The common adverse reactions ($\geq 10\%$) in patients receiving Tecentriq SC were fatigue (17.0%), musculoskeletal pain (11.3%), and cough (10.9%) (see Table 3).

Treatment-related local injection site reactions (ISR) were reported in patients receiving Tecentriq SC [4.5% Tecentriq SC vs. 0% Tecentriq (intravenous formulation)] including injection site pain and injection site reaction.

INTRAVENOUS FORMULATION (Tecentriq)

Information in this section reports data from a separate Product Monograph for Tecentriq (intravenous formulation).

Extensive-Stage Small Cell Lung Cancer (ES-SCLC)

Study GO30081 (IMpower133) – First-Line Combination Therapy

The safety of Tecentriq (intravenous formulation) was evaluated in study GO30081 (IMpower133), a randomized, multicentre, double-blind, placebo-controlled trial in patients with chemotherapy-naïve ES-SCLC. A total of 403 patients were randomized (1:1) to one of the following treatment arms:

- Arm A: Tecentriq (intravenous formulation) 1200 mg followed by carboplatin and then etoposide every 3 weeks for four cycles, followed by Tecentriq (intravenous formulation) 1200 mg every 3 weeks as maintenance therapy
- Arm B: Placebo followed by carboplatin and then etoposide every 3 weeks for four cycles, followed by placebo every 3 weeks

Among 198 patients treated in the Tecentriq (intravenous formulation) plus carboplatin and etoposide (CE) arm, the median duration of exposure of Tecentriq (intravenous formulation) was 4.7 months (range: 0-21 months). The administration of Tecentriq (intravenous formulation) did not compromise the delivery of standard carboplatin plus etoposide in the Tecentriq (intravenous formulation) plus CE arm. In both treatment arms, patients received a median of 4 doses of carboplatin, and a median of 12 doses of etoposide.

Overall, 198/198 (100%) patients treated with Tecentriq (intravenous formulation) plus CE had at least one adverse event versus 189/196 (96.4%) patients treated with placebo plus CE. Grade 3 to 4 adverse events were experienced by 133 (67.2%) patients treated with Tecentriq (intravenous formulation) plus CE versus 125 (63.8%) patients treated with placebo plus CE. Serious adverse events occurred in 74 (37.4%) patients treated with Tecentriq (intravenous formulation) plus CE versus 68 (34.7%) patients treated with placebo plus CE. Grade 5 adverse events occurred in 4 (2.0%) patients treated with Tecentriq (intravenous formulation) plus CE versus 11 (5.6%) patients treated with placebo plus CE. Adverse events leading to dose modification / interruption occurred in 138 (69.7%) patients treated with Tecentriq (intravenous formulation) plus CE versus 119 (60.7%) patients in the placebo plus CE arm. Adverse events leading to Tecentriq (intravenous formulation) / placebo withdrawal occurred in 21 (10.6%) patients treated with Tecentriq (intravenous formulation) plus CE and 5 (2.6%) patients in the placebo plus CE arm.

The most common adverse reactions ($\geq 10\%$) in patients receiving Tecentriq (intravenous formulation) plus CE were anemia (43.4%), nausea (37.9%), decreased appetite (27.3%), fatigue (27.3%), vomiting

(19.7%), thrombocytopenia (16.7%), platelet count decreased (12.6%), hypothyroidism (10.1%), dyspnea (10.1%), and pyrexia (10.1%).

The common adverse events ($\geq 1\%$) in patients treated with Tecentriq (intravenous formulation) plus CE leading to atezolizumab dose modification / interruption was neutropenia (21.7%), neutrophil count decreased (10.6%), anemia (8.6%), leukopenia (6.6%), thrombocytopenia (5.1%), fatigue (4.0%), infusion related reaction (3.5%), pneumonia (2.0%), platelet count decreased (1.5%), white blood cell count decreased 1.5%), febrile neutropenia (1.5%), ALT increased (1.5%), nausea (1.5%), vomiting (1.0%), acute kidney injury (1.0%), AST increased (1.0%), blood alkaline phosphatase increased (1.0%), hemoptysis (1.0%), hypertension (1.0%), hypothyroidism (1.0%), peripheral neuropathy (1.0%), pyrexia (1.0%), rash maculo-papular (1.0%).

Non-Small Cell Lung Cancer (NSCLC)

Study GO29527 (IMpower010) – Adjuvant Treatment of Early-Stage NSCLC

The safety of Tecentriq (intravenous formulation) was evaluated in IMpower010, a multicentre, open-label, randomized trial for the adjuvant treatment of patients with stage IB (tumours $\geq 4\text{cm}$) – stage IIIA NSCLC, who had complete tumor resection and received up to 4 cycles of cisplatin-based adjuvant chemotherapy. Patients received Tecentriq (intravenous formulation) 1200 mg every 3 weeks (n=495) or best supportive care for 16 cycles, unless disease progression or unacceptable toxicity (see 14 CLINICAL TRIALS). The median duration of exposure to Tecentriq (intravenous formulation) was 10.4 months (0–16 months); the median number of cycles received was 16 (range: 1, 16).

Fatal adverse events occurred in 1.8% of patients receiving Tecentriq (intravenous formulation); these included interstitial lung disease, myocarditis, acute myeloid leukemia, multiple organ dysfunction syndrome, arrhythmia, acute cardiac failure, pneumothorax, cerebrovascular accident, and death of unknown cause (1 patient each).

Serious adverse events occurred in 18% of patients receiving Tecentriq (intravenous formulation). The most frequent serious adverse events ($>1\%$) were pneumonia (1.6%) and pyrexia (1.2%).

Tecentriq (intravenous formulation) was discontinued due to adverse events in 18% of patients; the most common adverse events ($\geq 1\%$) leading to Tecentriq (intravenous formulation) discontinuation were pneumonitis (1.4%), hypothyroidism (1.4%), increased AST (1.4%), and increased ALT (1.0%).

Adverse events leading to interruption of Tecentriq (intravenous formulation) occurred in 29% of patients; the most common ($>1\%$) were hyperthyroidism (2.8%), increased AST (1.6%), pyrexia (1.6%), increased ALT (1.4%), rash (1.4%), upper respiratory tract infection (1.4%), hypothyroidism (1.2%), headache (1.2%), and pneumonia (1.0%).

Adverse reactions (treatment-emergent adverse events) occurring in $\geq 1\%$ of Tecentriq (intravenous formulation) treated patients are shown in Table 5.

Study GO29431 (IMpower110) – First Line Monotherapy

The safety of Tecentriq (intravenous formulation) was evaluated in Study GO29431. Patients received Tecentriq (intravenous formulation) 1200 mg every 3 weeks (n=286) or platinum-based chemotherapy consisting of carboplatin or cisplatin in combination with either pemetrexed or gemcitabine (n=263). The median duration of treatment was 5.3 months in the Tecentriq (intravenous formulation) arm, 3.5 months for pemetrexed, 2.1 months for cisplatin, 2.3 months for carboplatin, 2.6 months for gemcitabine in the chemotherapy arm.

Overall, 258/286 (90.2%) patients treated with Tecentriq (intravenous formulation) in GO29431 had at least one adverse event versus 249/263 (94.7 %) patients treated with chemotherapy. The incidence of Grade 3-4 events was 30.1% in the Tecentriq (intravenous formulation) arm and 52.5% in the chemotherapy arm. Serious adverse reactions occurred in 28.3% patients receiving Tecentriq (intravenous formulation) and 28.5% patients in the chemotherapy arm. The incidence of Grade 5 adverse events was 3.8% (11 patients) in the Tecentriq (intravenous formulation) arm and 4.2% (11 patients) in the chemotherapy arm.

Adverse events leading to dose interruption occurred in 74 (25.9%) patients treated with Tecentriq (intravenous formulation) and 115 (43.7%) patients treated with chemotherapy. The proportion of patients experiencing adverse events leading to any study treatment withdrawal was 6.3% (18 patients) in the Tecentriq (intravenous formulation) arm and 16.3% (43 patients) in the chemotherapy arm.

Adverse reactions occurring in $\geq 1\%$ of Tecentriq (intravenous formulation) treated patients are shown in Table 6.

Study GO29436 (IMpower150) - First-Line Combination Therapy

The safety of Tecentriq (intravenous formulation) in combination with paclitaxel and carboplatin, with bevacizumab, for the treatment of chemotherapy-naïve patients with metastatic, non-squamous NSCLC in study GO29436 (IMpower150) in the first-line (1L) setting is presented in Table 7. Tecentriq (intravenous formulation) at a dose of 1200 mg was administered intravenously every 3 weeks until loss of clinical benefit or unacceptable toxicity (for bevacizumab, carboplatin and paclitaxel dosage information see 14 CLINICAL TRIALS).

The incidence of patients experiencing at least one adverse event of any grade was 98.2% in the Tecentriq (intravenous formulation) + bevacizumab (Bev) + carboplatin and paclitaxel (CP) arm and 99.0% in the Bev + CP arm. The incidence of Grade 3-4 adverse events was 63.6% in the Tecentriq (intravenous formulation) + Bev + CP arm and 58.4%, in the Bev + CP arm. The proportion of patients experiencing serious adverse events was 44.3% in the Tecentriq (intravenous formulation) + Bev + CP arm and 34.3% in the Bev + CP arm.

The incidence of Grade 5 adverse events were 6.1% (n = 24) in the Tecentriq (intravenous formulation) + Bev + CP arm, 5.3% (n = 21) in the Bev + CP arm. The deaths due to adverse events in the Tecentriq (intravenous formulation) + Bev + CP arm were due to: febrile neutropenia (n = 3), hemoptysis (n = 3), pulmonary embolism (n = 2), pulmonary hemorrhage (n = 2), death (n = 2), cardiac arrest (n = 2), cerebrovascular accident (n = 2), chronic obstructive pulmonary disease (n = 1), pneumonia aspiration (n = 1), pneumonia (n = 1), intracranial hemorrhage (n = 1), intestinal angina (n = 1), intestinal obstruction (n = 1), intestinal ischemia (n = 1) and aortic dissection (n = 1). Eleven Grade 5 events were related to any study treatment; cerebrovascular accident (n = 1), intestinal obstruction (n = 1), febrile neutropenia (n = 3), haemoptysis (n = 3), pulmonary haemorrhage (n = 2) and aortic dissection (n = 1).

The deaths due to adverse events in the Bev + CP arm were due to: pneumonia (n = 3), sepsis (n = 2), pulmonary embolism (n = 2), pulmonary hemorrhage (n = 2), intestinal perforation (n = 2), death (n = 2), hemoptysis (n = 1), thrombosis (n = 1), respiratory tract infection (n = 1), acute myocardial infarction (n = 1), myocardial infarction (n = 1), pericarditis (n = 1), cerebral infarction (n = 1) and posterior reversible encephalopathy syndrome (n = 1). Nine Grade 5 events were related to any study treatment: intestinal perforation (n = 2), pulmonary embolism (n = 2), pulmonary hemorrhage (n = 2), pneumonia (n = 1), sepsis (n = 1) and posterior reversible encephalopathy syndrome (n = 1). The proportion of patients experiencing adverse events leading to any dose modification or interruption was 62.6% in the Tecentriq (intravenous formulation) + Bev + CP arm and 47.7 % in the Bev + CP arm.

The most common adverse events in patients treated with Tecentriq (intravenous formulation) (reported by $\geq 10\%$ patients) were: neuropathy peripheral (23.7%), peripheral sensory neuropathy (16.5%), nausea (39.2%) anemia (29.3%), neutropenia (18.6%), neutrophil count decreased (12.2%), febrile neutropenia (10.2%), rash (16.5%), fatigue (33.1%), constipation (29.8%), decreased appetite (28.8%), diarrhea (32.1%), thrombocytopenia (13.5%), platelet count decreased (14.0%), arthralgia (26.2%), asthenia (20.6%), cough (19.6%), dyspnea (13.5%), vomiting (18.6%), pyrexia (18.6%), pruritus (12.7%), hypothyroidism (11.5%), back pain (12.2%), hypomagnesemia (13.0%), hepatitis (lab abnormality) (12.2%), stomatitis (13.0%), musculoskeletal pain (10.9%) and febrile neutropenia (10.2%).

The most common adverse events in patients treated with Tecentriq (intravenous formulation), bevacizumab and CP leading to dose modification/interruption were neutropenia (7.6%), thrombocytopenia 5.6%), anemia (3.1%), febrile neutropenia (4.1%), platelet count decreased (7.1%), neutrophil count decreased (4.6%), peripheral neuropathy (3.6%), peripheral sensory neuropathy (2.5%), weight decreased (5.1%), pneumonia (3.1%), asthenia (3.6%), fatigue (3.3%), pyrexia (2.0%), diarrhea (5.1%), dyspnea (1.3%), hypothyroidism (2.8%), proteinuria (6.4%) and infusion related reaction (1.3%).

Metastatic Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Study GO29537 (IMpower130) - First-Line Combination Therapy

The safety of Tecentriq (intravenous formulation) in combination with nab-paclitaxel and carboplatin for the treatment of chemotherapy-naïve patients with metastatic, non-squamous NSCLC in study GO29537 (IMpower130) in the first-line (1L) setting is presented in Table 8. Tecentriq (intravenous formulation) at a dose of 1200 mg was administered intravenously every 3 weeks until loss of clinical benefit or unacceptable toxicity (for carboplatin and nab-paclitaxel (CnP) dosage information see 14 CLINICAL TRIALS).

The majority of patients in both treatment arms experienced at least one AE of any grade (Tecentriq (intravenous formulation) + CnP 99.6% vs. CnP 99.1%). The incidence of Grade ≥ 3 AEs was 85.8% in the Tecentriq (intravenous formulation) + CnP arm and 76.3% in the CnP arm. The incidence of Grade 5 AEs was 5.3% in the Tecentriq (intravenous formulation) + CnP versus 5.6% in the CnP arm. Overall, 8 of the Grade 5 AEs in the Tecentriq (intravenous formulation) + CnP arm and 1 Grade 5 AE in the CnP arm were considered by the investigator as related to any study treatment component. The proportion of patients who experienced SAEs was 50.7% in the Tecentriq (intravenous formulation) + CnP arm and 37.9% in the CnP arm. AEs led to withdrawal of any study treatment during the overall study period in 26.4% in the Tecentriq + CnP arm and 22.0% in the CnP arm. The proportion of patients experiencing AEs leading to any dose modification/interruption was 85.0% in the Tecentriq (intravenous formulation) + CnP arm and 80.2% in the CnP arm.

The most common adverse events in patients treated with Tecentriq (intravenous formulation) + CnP (reported by $\geq 10\%$ patients) were: anemia (52.4%), neutropenia (46.1%), nausea (43.8%), fatigue (39.1%), diarrhea (31.7%), alopecia (30.7%), thrombocytopenia (26.8%), decreased appetite (22.6%), platelet count decrease (22.2%), vomiting (20.9%), neutrophil count decrease (19.7%), constipation (15.4%), hypomagnesaemia (13.1%), asthenia (12.9%), white blood cell count decrease (10.8%), dysgeusia (10.8%), peripheral sensory neuropathy (10.6%), neuropathy peripheral (10.4%), hypothyroidism (10.4%) and leukopenia (10.1%).

The most common adverse events in patients treated with Tecentriq (intravenous formulation) + CnP leading to dose modification/interruption were neutropenia (38.5%), thrombocytopenia (19.7%),

anemia (16.3%), platelet count decrease (15.0%), neutrophil count decrease (14.4%), diarrhea (9.1%), fatigue (7.4%), leukopenia (5.7%), white blood cell count decrease (5.7%), pyrexia (4.9%), nausea (4.4%), pneumonia (3.8%), dyspnea (3.6%), vomiting (3.2%), pneumonitis (2.7%), dehydration (2.5%), blood creatinine increased (2.3%), decreased appetite (2.3%), asthenia (2.1%) and febrile neutropenia (1.5%).

Study GO28915 (OAK) - Second Line Monotherapy

The safety of Tecentriq (intravenous formulation), as presented in Table 9, is based on use in 1187 patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC), who had progressed during or following a platinum-containing regimen. These patients were enrolled in the phase III pivotal trial study GO28915 (OAK), in which 609 patients received Tecentriq (intravenous formulation) 1200 mg administered intravenously every 3 weeks until loss of clinical benefit or unacceptable toxicity vs. 578 patients who received docetaxel 75 mg/m² administered intravenously every 3 weeks until unacceptable toxicity or disease progression.

Overall, 573/609 (94.1%) patients treated with Tecentriq (intravenous formulation) in GO28915 (OAK), had at least one adverse event versus 555/578 (96.0%) patients treated with docetaxel. Grade 3-4 events were experienced by 227 (37.3%) patients treated with Tecentriq versus 310 (53.6%) patients treated with docetaxel. Serious adverse events occurred in 194 (31.9%) patients treated with Tecentriq (intravenous formulation) versus 181 (31.3%) patients treated with docetaxel. Grade 5 adverse events occurred in 10 (1.6%) patients treated with Tecentriq (intravenous formulation) versus 14 (2.4%) patients treated with docetaxel. There were no deaths related to Tecentriq (intravenous formulation) and one related to docetaxel (respiratory tract infection). Adverse events leading to dose interruption occurred in 152 (25.0%) patients treated with Tecentriq (intravenous formulation) versus 210 (36.3%) patients treated with docetaxel and withdrawal from Tecentriq (intravenous formulation) due to adverse events occurred in 46 (7.6%) patients versus 108 (18.7%) patients treated with docetaxel.

The most common adverse events in patients treated with Tecentriq (intravenous formulation) (reported by ≥10% patients) were: fatigue (26.8%), asthenia (19.0%), pyrexia (17.7%), nausea (17.7%), diarrhea (15.4%), constipation (17.6%), vomiting (12.2%), cough (23.2%), dyspnea (19.4%), arthralgia (12.0%), decreased appetite (23.5%), anemia (11.5%), musculoskeletal pain (10.5%) and back pain (11.0%).

The most common adverse events in patients treated with Tecentriq (intravenous formulation) leading to dose interruption were pneumonia (2.1%), respiratory tract infection (1.0%), fatigue (1.1%), pyrexia (1.0%), dyspnea (1.6%), and back pain (1.3%).

The safety of Tecentriq (intravenous formulation) in NSCLC was also investigated in four additional supporting studies: Phase II global multi-centered open-label randomized controlled study GO28753 (POPLAR), two phase II global multi-centered single arm studies GO28754 (BIRCH) and GO28625 (FIR), and phase I multi-centered open-label study PCD4989g with a NSCLC cohort. The total number of locally advanced or metastatic NSCLC patients who were treated with Tecentriq (intravenous formulation) in clinical trials was 1636.

Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

Study YO40245 (IMbrave150) -First-Line Combination Therapy

The safety of Tecentriq (intravenous formulation) in combination with bevacizumab was evaluated in YO40245 (IMbrave150), a multicentre, international, randomized, open-label first-line trial in patients with unresectable or metastatic hepatocellular carcinoma not amenable to curative or localized therapies who require systemic treatment (see 14 CLINICAL TRIALS). Patients received 1200 mg of Tecentriq (intravenous formulation) intravenously, followed by 15 mg/kg bevacizumab (n=329) on the same day, every 3 weeks until loss of clinical benefit or unacceptable toxicity or 400 mg of sorafenib (n=156) given orally twice daily, until loss of clinical benefit or unacceptable toxicity. The median duration of exposure to Tecentriq (intravenous formulation) was 7.4 months (range: 0-16 months) and to bevacizumab was 6.9 months (range: 0-16 months) in the Tecentriq (intravenous formulation) and bevacizumab arm.

Fatal adverse reactions occurred in 4.6% of patients in the Tecentriq (intravenous formulation) and bevacizumab arm. These most common adverse events leading to death were gastrointestinal and esophageal varices hemorrhage (1.2%) and infections (1.2%). Other fatal events included liver injury, hepatic function abnormal, gastric ulcer perforation, sepsis, multiple organ dysfunction syndrome, respiratory distress, empyema, and cardiac arrest (0.3% each).

Serious adverse reactions occurred in 38% of patients in the Tecentriq (intravenous formulation) and bevacizumab arm. The most frequent serious adverse reactions ($\geq 2\%$) were hemorrhages (7.3%), infections (7.3%), and pyrexia (2.1%).

Adverse reactions leading to discontinuation of Tecentriq (intravenous formulation) occurred in 8.5% of patients in the Tecentriq (intravenous formulation) and bevacizumab arm. The most common adverse reactions leading to Tecentriq (intravenous formulation) discontinuation were hemorrhage (1.2%), aspartate aminotransferase or bilirubin increased (1.2%), infusion-related reaction or cytokine release syndrome (0.9%), and autoimmune hepatitis (0.6%).

Adverse reactions leading to interruption of Tecentriq (intravenous formulation) occurred in 41% of patients in the Tecentriq (intravenous formulation) and bevacizumab arm; the most common ($\geq 2\%$) were aspartate aminotransferase increased (5.2%), alanine aminotransferase increased (3.3%), hyperthyroidism (2.7%), platelet count decreased (2.1%), and pyrexia (2.1%).

Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 12.2% of patients in the Tecentriq (intravenous formulation) and bevacizumab arm.

Table 10 and Table 18 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received Tecentriq (intravenous formulation) and bevacizumab in Study YO40245 (IMbrave150).

Locally Advanced or Metastatic Triple-Negative Breast Cancer (TNBC)

Study WO29522 (IMpassion130) - First-Line Combination Therapy

The safety of Tecentriq (intravenous formulation) in combination with nab-paclitaxel was evaluated in WO29522 (IMpassion130), a multicentre, international, randomized, double-blinded placebo controlled trial in patients with locally advanced or metastatic TNBC who had not received prior chemotherapy for metastatic disease (see 14 CLINICAL TRIALS). Patients received 840 mg of Tecentriq (intravenous formulation) (n=460) or placebo (n=430) intravenously followed by nab-paclitaxel (100 mg/m²) intravenously. For each 28-day cycle, Tecentriq (intravenous formulation) was administered on days 1

and 15 and nab-paclitaxel was administered on days 1, 8, and 15 until radiographic disease progression per RECIST v1.1, or unacceptable toxicity. In the safety-evaluable population, the median duration of exposure to Tecentriq (intravenous formulation) was 5.5 months (range: 0–55.6 months) and nab-paclitaxel was 5.1 months (range: 0 – 55.6 months) in the Tecentriq (intravenous formulation) plus nab-paclitaxel arm. The median duration of exposure to placebo was 5.1 months (range: 0–26.9 months) and nab-paclitaxel was 4.9 months (range: 0–38.2 months) in the nab-paclitaxel arm. The addition of Tecentriq (intravenous formulation) did not compromise the patient’s ability to receive nab-paclitaxel. The mean dose intensity was 85.9% in the Tecentriq (intravenous formulation) plus nab-paclitaxel arm and 90.1% in the placebo arm.

Overall, 457 (99.3%) patients treated with Tecentriq (intravenous formulation) in combination with nab-paclitaxel had at least one adverse event versus 421 (97.9%) patients treated with placebo plus nab-paclitaxel. Grade 3 to 4 adverse events were experienced by 233 (50.7%) patients treated with Tecentriq (intravenous formulation) in combination with nab-paclitaxel versus 183 (42.6%) patients treated with placebo plus nab-paclitaxel. Serious adverse events occurred in 110 (23.9%) patients treated with Tecentriq (intravenous formulation) in combination with nab-paclitaxel versus 80 (18.6%) patients treated with placebo plus nab-paclitaxel. The most frequent of these serious adverse events ($\geq 1\%$) were pneumonia (2.6%), cellulitis (1.1%), urinary tract infection (1.1%), pulmonary embolism (1.1%), dyspnea (1.1%), pyrexia (1.1%) and febrile neutropenia (1.1%). Grade 5 adverse events occurred in 6 (1.3%) patients treated with Tecentriq (intravenous formulation) in combination with nab-paclitaxel versus 3 (0.7%) patients treated with placebo plus nab-paclitaxel. Adverse events leading to Tecentriq (intravenous formulation)/placebo discontinuation occurred in 37 (8.0%) patients treated with Tecentriq (intravenous formulation) in combination with nab-paclitaxel and 4 (0.9%) patients in the placebo plus nab-paclitaxel arm. Dose reductions of Tecentriq (intravenous formulation)/placebo were not permitted by the protocol.

The most common adverse events leading to Tecentriq (intravenous formulation) discontinuation were peripheral neuropathies (1.3%). Overall, the most common ($\geq 1\%$ of patients in either arm) adverse events leading to nab-paclitaxel withdrawal were peripheral neuropathies (9.3% Tecentriq (intravenous formulation) + nab-paclitaxel vs. 4% placebo + nab-paclitaxel), and fatigue (1.7% vs. 1.4%).

Adverse events leading to interruption of Tecentriq (intravenous formulation)/placebo occurred in 160 (34.8%) patients treated with Tecentriq (intravenous formulation) in combination with nab-paclitaxel and 102 (23.7%) patients in the placebo plus nab-paclitaxel arm. The most common adverse events leading to interruption of Tecentriq (intravenous formulation)/placebo ($\geq 2\%$) were neutropenia (3.9% Tecentriq (intravenous formulation) + nab-paclitaxel vs. 1.9% placebo + nab-paclitaxel), neutrophil count decreased (2.6% vs. 1.4%), hyperthyroidism (2.2% vs. 0%), pyrexia (2.2% vs. 0.5%), pneumonitis (2.0% vs 0%) and dyspnea (2.0% vs 1.6%). Adverse events leading to dose modification/interruption of nab-paclitaxel occurred in 206 (44.8%) patients treated with Tecentriq in combination with nab-paclitaxel and 170 (39.5%) patients in the placebo plus nab-paclitaxel arm.

The common adverse reactions ($\geq 10\%$) in patients receiving Tecentriq (intravenous formulation) in combination with nab-paclitaxel were alopecia (57.2%), fatigue (47.0%), nausea (46.7%), peripheral neuropathies (43.0%), rash (35.9%), neutropenia (33.5%), diarrhea (32.8%), anemia (28.3%), cough (27.4%), constipation (25.4%), headache (25.2%), musculoskeletal pain (24.6%), pyrexia (20.2%), vomiting (20.0%), decreased appetite (20.0%), arthralgia (19.3%), hypothyroidism (18.3%), nasopharyngitis (17.4%), dyspnea (16.3%), back pain (16.1%), edema peripheral (15.9%), pruritus (15.9%), urinary tract infection (15.9%), dizziness (15.0%), leukopenia (14.6%), asthenia (13.0%), ALT increased (11.7%), abdominal pain (11.5%), dysgeusia (11.3%), lung infections (11.3%), AST increased (10.9%), stomatitis (10.7%) (see Table 11).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

SUBCUTANEOUS FORMULATION (Tecentriq SC)

Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Study BP40657 (IMscin001)

The information provided in Table 3 summarizes the adverse drug reactions that occurred in $\geq 1\%$ of adult patients with locally advanced or metastatic NSCLC in the Tecentriq SC arm and in the Tecentriq (intravenous formulation) arm.

Table 3 **Adverse Drug Reactions^a Occurring in $\geq 1\%$ of Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer in either Treatment Arm in Study BP40657 (IMscin001)**

Adverse Drug Reaction (MedDRA) System Organ Class (SOC)	Tecentriq (intravenous formulation) (n = 124)		Tecentriq SC (n = 247)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Endocrine Disorders				
Hypothyroidism ^b	5 (4.0)	0	17 (6.9)	0
Hyperthyroidism	1 (0.8)	0	6 (2.4)	0
Gastrointestinal disorders				
Abdominal Pain ^c	3 (2.4)	1 (0.8)	13 (5.3)	0
Diarrhoea	3 (2.4)	0	11 (4.5)	0
Vomiting	4 (3.2)	1 (0.8)	7 (2.8)	0
General Disorders and Administration Site Conditions				
Fatigue ^d	23 (18.5)	1 (0.8)	42 (17.0)	2 (0.8)
Edema ^e	1 (0.8)	0	5 (2.0)	0
Injection Site Reactions ^f	0	0	11 (4.5)	0
Infections and infestations				
Respiratory Tract Infection ^g	10 (8.1)	6 (4.8)	23 (9.3)	3 (1.2)
Urinary tract infection ^h	10 (8.1)	3 (2.4)	8 (3.2)	0
Metabolism and nutrition disorders				
Decreased appetite	10 (8.1)	0	24 (9.7)	0
Hyperglycemia	10 (8.1)	0	7 (2.8)	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain ⁱ	11 (8.9)	3 (2.4)	28 (11.3)	1 (0.4)
Nervous System Disorder				
Neuropathy peripheral ^j	4 (3.2)	0	8 (3.2)	0
Respiratory, thoracic and mediastinal disorders				
Cough ^k	8 (6.5)	0	27 (10.9)	0
Dyspnoea ^l	16 (12.9)	1 (0.8)	24 (9.7)	1 (0.4)
Embolism ^m	2 (1.6)	1 (0.8)	2 (0.8)	0
Skin and subcutaneous tissue disorders				
Rash ⁿ	11 (8.9)	0	15 (6.1)	3 (1.2)

^a ADRs known to be associated with atezolizumab monotherapy and combination therapy

^b Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, blood thyroid stimulating hormone decreased and thyroiditis.

^c Includes reports of abdominal pain, abdominal pain upper and flank pain.

^d Includes reports of fatigue, asthenia and malaise.

^e Includes reports of oedema peripheral, oedema and peripheral swelling.

^f Includes reports of injection site reaction, injection site pain, injection site erythema and injection site rash.

^g Includes reports of pneumonia, bronchitis, upper respiratory tract infection, and respiratory tract infection.

^h Includes reports of urinary tract infection and cystitis pyelonephritis.

ⁱ Includes reports of back pain, myalgia, musculoskeletal chest pain and neck pain.

^j Includes reports of paraesthesia, polyneuropathy, hypoaesthesia, neuropathy peripheral and peripheral sensory neuropathy.

^k Includes reports of cough and productive cough.

^l Includes reports of dyspnoea and dyspnoea exertional.

^m Includes reports of pulmonary embolism and embolism.

ⁿ Includes reports of rash, rash maculo-papular, dermatitis, rash pruritic, dermatitis allergic, erythema, rash erythematous, rash macular, rash pustular and skin toxicity.

INTRAVENOUS FORMULATION (Tecentriq)

Information in this section reports data from a separate Product Monograph for Tecentriq intravenous formulation (IV).

Extensive-Stage Small Cell Lung Cancer (ES-SCLC)

Study GO30081 (IMpower133) – First-Line Combination Therapy

Table 4 summarizes adverse reactions that occurred in $\geq 1\%$ of patients in the Tecentriq (intravenous formulation) in combination with carboplatin and etoposide arm and in the placebo with carboplatin and etoposide arm. Table 13 summarizes selected laboratory abnormalities worsening from baseline that occurred in $\geq 1\%$ of patients in the Tecentriq (intravenous formulation) with carboplatin and etoposide arm and at a higher incidence than in the placebo with carboplatin and etoposide arm.

Table 4 Adverse Drug Reactions Occurring in $\geq 1\%$ of Patients with First-Line Extensive-Stage Small Cell Lung Cancer (ES-SCLC) treated with Tecentriq (intravenous formulation) plus Carboplatin plus Etoposide vs. Carboplatin plus Etoposide in Pivotal Study GO30081 (IMpower133)

System Organ Class ADR (MedDRA v22.0)	Tecentriq (intravenous formulation) + carboplatin + etoposide (n=198)		Placebo + carboplatin + etoposide (n=196)	
	All Grades n (%)	Grades 3 – 4 n (%)	All Grades n (%)	Grades 3 – 4 n (%)
Blood and Lymphatic System Disorders				
Anemia	86 (43.4)	31 (15.7)	69 (35.2)	26 (13.3)
Thrombocytopenia ^a	56 (28.3)	27 (13.6)	58 (29.6)	25 (12.8)
Endocrine Disorders				
Hypothyroidism ^b	25 (12.6)	0	1 (0.5)	0
Hyperthyroidism	11 (5.6)	0	5 (2.6)	0
Adrenal insufficiency ^c	0	0	3 (1.5)	0
Gastrointestinal Disorders				
Nausea	75 (37.9)	1 (0.5)	64 (32.7)	1 (0.5)
Vomiting	39 (19.7)	3 (1.5)	33 (16.8)	5 (2.6)
Diarrhea	35 (17.7)	4 (2.0)	31 (15.8)	2 (1.0)
Abdominal pain ^d	14 (7.1)	1 (0.5)	17 (8.7)	0
Oropharyngeal pain	12 (6.1)	0	5 (2.6)	0
Dysphagia	4 (2.0)	0	3 (1.5)	0
Pancreatitis ^e	2 (1.0)	2 (1.0)	2 (1.0)	2 (1.0)
Colitis ^f	3 (1.5)	2 (1.0)	0	0
General Disorders and Administration Site Conditions				
Fatigue ^g	84 (42.4)	10 (5.1)	68 (34.7)	5 (2.6)
Pyrexia	20 (10.1)	0	16 (8.2)	0
Infusion related reaction ^h	12 (6.1)	5 (2.5)	12 (6.1)	1 (0.5)
Influenza like illness	2 (1.0)	0	3 (1.5)	0
Chills	3 (1.5)	0	0	0
Hepatobiliary Disorder				
AST increased	9 (4.5)	0	6 (3.1)	0
ALT increased	7 (3.5)	1 (0.5)	7 (3.6)	0
Infections and infestations				
Urinary Tract Infection ⁱ	14 (7.1)	2 (1.0)	7 (3.6)	2 (1.0)

System Organ Class ADR (MedDRA v22.0)	Tecentriq (intravenous formulation) + carboplatin + etoposide (n=198)		Placebo + carboplatin + etoposide (n=196)	
	All Grades n (%)	Grades 3 – 4 n (%)	All Grades n (%)	Grades 3 – 4 n (%)
Metabolism and Nutrition Disorders				
Decreased Appetite ^j	54 (27.3)	2 (1.0)	37 (18.9)	0
Hypokalaemia	8 (4.0)	0	18 (9.2)	3 (1.5)
Hyponatraemia	11 (5.6)	9 (4.5)	14 (7.1)	13 (6.6)
Hyperglycaemia	11 (5.6)	4 (2.0)	4 (2.0)	1 (0.5)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain ^k	37 (18.7)	1 (0.5)	43 (21.9)	2 (1.0)
Arthralgia	18 (9.1)	0	13 (6.6)	1 (0.5)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough ^l	28 (14.1)	1 (0.5)	31 (15.8)	2 (1.0)
Dyspnea ^m	20 (10.1)	3 (1.5)	21 (10.7)	4 (2.0)
Pneumonitis	4 (2.0)	1 (0.5)	5 (2.6)	2 (1.0)
Nasopharyngitis ⁿ	6 (3.0)	0	2 (1.0)	0
Hypoxia	2 (1.0)	1 (0.5)	2 (1.0)	0
Skin and Subcutaneous Tissue Disorders				
Rash ^o	36 (18.2)	4 (2.0)	20 (10.2)	0
Pruritus	12 (6.1)	0	9 (4.6)	0
Severe Cutaneous Adverse Reactions ^p	2 (1.0)	0	0	0
Vascular Disorders				
Hypotension	8 (4.0)	0	9 (4.6)	0

^a Includes reports of thrombocytopenia and platelet count decreased

^b Includes reports of autoimmune hypothyroiditis, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, hypothyroidism, thyroiditis, thyroxine free increased and tri-iodothyronine free increased

^c Includes reports of adrenal insufficiency and cortisol decreased

^d Includes reports of abdominal pain, abdominal pain upper and flank pain

^e Includes reports of lipase increased, pancreatic enzymes increased, pancreatitis and pancreatitis acute

^f Includes reports of colitis and autoimmune colitis

^g Includes reports of asthenia, fatigue, lethargy and malaise

^h Includes reports of anaphylactic reaction, hypersensitivity and infusion related reaction

ⁱ Includes reports of cystitis, urinary tract infection and urinary tract infection enterococcal

^j Includes reports of decreased appetite, early satiety and hypophagia

^k Includes reports of back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia and neck pain

^l Includes reports of cough, productive cough and upper airway cough syndrome

^m Includes reports of dyspnea and dyspnea exertional

ⁿ Includes reports of nasopharyngitis and nasal congestion

^o Includes reports of dermatitis, dermatitis acneiform, drug eruption, erythema, folliculitis, rash, rash erythematous, rash follicular, rash maculo-papular, rash papular, rash pruritic, rash pustular, skin toxicity and skin ulcer

^p Includes reports of dermatitis bullous and toxic skin eruption

Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Study GO29527 (IMpower010) – Adjuvant Treatment of Early-Stage NSCLC

Table 5 summarizes adverse drug reactions in patients included in study GO29527 (IMpower010) during treatment with Tecentriq (intravenous formulation) 1200 mg every 3 weeks (n=495) or best supportive care (BSC, n=495).

Table 5 Adverse Drug Reactions* Occurring in ≥1 % of Patients with Non-Small Cell Lung Cancer Receiving Tecentriq (intravenous formulation) vs. Best Supportive Care in Study GO29527 (IMpower010)

ADR (MedDRA v22.0) System Organ Class Preferred Term	Tecentriq (intravenous formulation) (n=495)		Best Supportive Care (n=495)	
	All grades n (%)	Grade 3–4 n (%)	All grades n (%)	Grade 3–4 n (%)
Gastrointestinal				
Nausea	30 (6.1)	0	16 (3.2)	0
Constipation	23 (4.6)	0	8 (1.6)	0
Diarrhoea	37 (7.5)	1 (0.2)	9 (1.8)	1 (0.2)
Vomiting	20 (4.0)	3 (0.6)	9 (1.8)	0
Abdominal pain ^a	28 (5.7)	1 (0.2)	14 (2.8)	0
Stomatitis	10 (2.0)	0	2 (0.4)	0
Gastroesophageal reflux disease	8 (1.6)	0	9 (1.8)	0
Dry mouth	14 (2.8)	0	0	0
Abdominal distension	5 (1.0)	0	1 (0.2)	0
General disorders and administration site conditions				
Fatigue ^c	70 (14.1)	3 (0.6)	27 (5.5)	1 (0.2)
Edema ^d	21 (4.2)	1 (0.2)	12 (2.4)	0
Pyrexia	65 (13.1)	4 (0.8)	11 (2.2)	1 (0.2)
Chest pain	8 (1.6)	0	13 (2.6)	1 (0.2)
Influenza like illness	7 (1.4)	0	11 (2.2)	1 (0.2)
Chills	11 (2.2)	0	0	0
Chest discomfort	6 (1.2)	0	2 (0.4)	0
Blood and lymphatic system disorders				
Neutropenia ^e	29 (5.9)	5 (1.0)	8 (1.6)	2 (0.4)
Anaemia	38 (7.7)	2 (0.4)	30 (6.1)	1 (0.2)
Leukopenia	5 (1.0)	2 (0.4)	5 (1.0)	0
Thrombocytopenia	9 (1.8)	1 (0.2)	6 (1.2)	0
Investigations				
ALT increased	53 (10.7)	8 (1.6)	16 (3.2)	1 (0.2)
AST increased	53 (10.7)	7 (1.4)	16 (3.2)	0
Blood creatinine increased	29 (5.9)	1 (0.2)	15 (3.0)	0
White blood cell count decreased	6 (1.2)	0	1 (0.2)	0
Platelet count decreased	10 (2.0)	0	1 (0.2)	0

ADR (MedDRA v22.0) System Organ Class Preferred Term	Tecentriq (intravenous formulation) (n=495)		Best Supportive Care (n=495)	
	All grades n (%)	Grade 3–4 n (%)	All grades n (%)	Grade 3–4 n (%)
Weight decreased	8 (1.6)	0	1 (0.2)	0
Weight increased	17 (3.4)	0	7 (1.4)	0
Blood alkaline phosphatase increased	11 (2.2)	0	1 (0.2)	0
Gamma-glutamyltransferase increased	5 (1.0)	2 (0.4)	3 (0.6)	0
Blood lactate dehydrogenase increased	8 (1.6)	0	0	0
Blood creatine phosphokinase increased	8 (1.6)	2 (0.4)	2 (0.4)	0
Metabolism and nutrition disorders				
Decreased appetite	22 (4.4)	1 (0.2)	7 (1.4)	0
Dehydration	6 (1.2)	0	1 (0.2)	0
Hyperglycaemia	8 (1.6)	1 (0.2)	7 (1.4)	1 (0.2)
Hypomagnesaemia	6 (1.2)	0	3 (0.6)	0
Hypokalaemia	9 (1.8)	1 (0.2)	1 (0.2)	0
Hyperkalaemia	12 (2.4)	3 (0.6)	5 (1.0)	1 (0.2)
Hyperuricaemia	7 (1.4)	0	4 (0.8)	1 (0.2)
Hypertriglyceridaemia	5 (1.0)	1 (0.2)	4 (0.8)	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea ^f	36 (7.3)	1 (0.2)	37 (7.5)	4 (0.8)
Cough ^g	79 (16.0)	0	53 (10.7)	0
Oropharyngeal pain	13 (2.6)	0	7 (1.4)	0
Rhinorrhoea	9 (1.8)	0	3 (0.6)	0
Pneumonitis	12 (2.4)	2 (0.4)	1 (0.2)	0
Interstitial lung disease	6 (1.2)	2 (0.4)	0	0
Infections and infestations				
Respiratory tract infection ^h	70 (14.1)	9 (1.8)	41 (8.3)	5 (1.0)
Nasopharyngitis ⁱ	37 (7.5)	0	51 (10.3)	0
Urinary tract infection ^j	20 (4.0)	3 (0.6)	14 (2.8)	1 (0.2)
Influenza	15 (3.0)	2 (0.4)	9 (1.8)	0
Respiratory tract infection viral	8 (1.6)	0	7 (1.4)	0
Sinusitis	8 (1.6)	0	5 (1.0)	0
Pharyngitis	6 (1.2)	0	3 (0.6)	1 (0.2)
Viral infection	5 (1.0)	0	0	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain ^l	47 (9.5)	4 (0.8)	28 (5.7)	0

ADR (MedDRA v22.0) System Organ Class Preferred Term	Tecentriq (intravenous formulation) (n=495)		Best Supportive Care (n=495)	
	All grades n (%)	Grade 3–4 n (%)	All grades n (%)	Grade 3–4 n (%)
Arthralgia	52 (10.5)	2 (0.4)	26 (5.3)	0
Pain in extremity	20 (4.0)	0	9 (1.8)	0
Bone pain	5 (1.0)	0	4 (0.8)	1 (0.2)
Muscle spasms	9 (1.8)	0	5 (1.0)	0
Muscular weakness	5 (1.0)	1 (0.2)	2 (0.4)	0
Nervous system disorders				
Neuropathy peripheral ^m	60 (12.1)	2 (0.4)	35 (7.1)	1 (0.2)
Headache	28 (5.7)	0	20 (4.0)	0
Dizziness	18 (3.6)	0	15 (3.0)	0
Skin and subcutaneous tissue disorders				
Rash ⁿ	91 (18.4)	7 (1.4)	11 (2.2)	0
Alopecia	6 (1.2)	0	10 (2.0)	0
Pruritus	51 (10.3)	0	3 (0.6)	0
Dry skin	9 (1.8)	0	0	0
Psoriasis	6 (1.2)	1 (0.2)	0	0
Endocrine disorders				
Hypothyroidism ^o	86 (17.4)	0	3 (0.6)	0
Hyperthyroidism ^p	32 (6.5)	2 (0.4)	4 (0.8)	0
Adrenal insufficiency	5 (1.0)	1 (0.2)	0	0
Vascular disorders				
Hypertension	18 (3.6)	5 (1.0)	9 (1.8)	2 (0.4)
Hypotension	7 (1.4)	1 (0.2)	1 (0.2)	0
Embolism ^q	5 (1.0)	3 (0.6)	5 (1.0)	2 (0.4)
Psychiatric disorders				
Insomnia	21 (4.2)	0	6 (1.2)	0
Anxiety	10 (2.0)	0	5 (1.0)	0
Ear and labyrinth disorders				
Tinnitus	6 (1.2)	0	6 (1.2)	0
Vertigo	5 (1.0)	0	3 (0.6)	0
Injury, poisoning and procedural complications				
Fall	6 (1.2)	0	2 (0.4)	0
Infusion related reaction	7 (1.4)	1 (0.2)	0	0
Cardiac disorders				
Tachycardia	6 (1.2)	0	1 (0.2)	0
Atrial fibrillation	5 (1.0)	1 (0.2)	0	0

*treatment-emergent adverse events

ADR (MedDRA v22.0) System Organ Class Preferred Term	Tecentriq (intravenous formulation) (n=495)		Best Supportive Care (n=495)	
	All grades n (%)	Grade 3–4 n (%)	All grades n (%)	Grade 3–4 n (%)

^a Includes reports of abdominal pain, abdominal pain upper, abdominal pain lower, flank pain

^c Includes reports of fatigue, asthenia, lethargy, malaise

^d Includes reports of localized oedema, oedema, oedema peripheral, peripheral swelling, swelling

^e Includes reports of neutropenia, neutrophil count decreased

^f Includes reports of dyspnoea, dyspnoea exertional

^g Includes reports of cough, productive cough, upper-airway cough syndrome

^h Includes reports of bronchitis, pneumonia, respiratory tract infection, upper respiratory tract infection

ⁱ Includes reports of nasal congestion, nasopharyngitis

^j Includes reports of cystitis, kidney infection, pyelonephritis, urinary tract infection

^l Includes reports of back pain, musculoskeletal pain, musculoskeletal chest pain, myalgia, neck pain

^m Includes reports of herpes zoster, hypoaesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy

ⁿ Includes reports of acne, dermatitis, dermatitis acneiform, dermatitis allergic, drug eruption, eczema, erythema, erythema of eye lid, hand dermatitis, furuncle, rash, Palmar-plantar erythrodysesthesia syndrome, rash erythematous, rash maculo-papular, rash pruritic, rash papular, skin exfoliation, skin ulcer

^o Includes reports of anti-thyroid antibody positive, autoimmune thyroiditis, autoimmune hypothyroidism, hypothyroidism, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, goiter, immune-mediated thyroiditis, myxedema, primary hypothyroidism, thyroid disorder, thyroiditis, thyroxine free decreased, thyroxine free increased, thyroxine increased, tri-iodothyronine free decreased, tri-iodothyronine decreased, tri-iodothyronine increased

^p Includes reports of Basedow's disease, hyperthyroidism

^q Includes reports of deep vein thrombosis, embolism pulmonary embolism, venous thrombosis

Study GO29431 (IMpower110) – First Line Monotherapy

The information provided in Table 6 and **Listing 4** summarizes the adverse drug reactions observed in patients included in study GO29431 (IMpower110) during treatment with Tecentriq (intravenous formulation) 1200 mg every 3 weeks (n=286) or platinum-based chemotherapy consisting of carboplatin or cisplatin in combination with either pemetrexed or gemcitabine (n=263).

Table 6 Adverse Drug Reactions Occurring in ≥ 1% of Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) Treated with Tecentriq (intravenous formulation) vs. Platinum Agent in Combination with Pemetrexed or Gemcitabine in the Study GO29431 (IMpower110)

ADR (MedDRA v22.0) System Organ Class Preferred Term	Tecentriq (intravenous formulation) (n=286)		Platinum Agent in Combination with Pemetrexed or Gemcitabine (n=263)	
	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)
Gastrointestinal				
Nausea	39 (13.6)	1 (0.3)	89 (33.8)	5 (1.9)
Constipation	35 (12.2)	3 (1.0)	57 (21.7)	2 (0.8)
Diarrhoea	32 (11.2)	0	31 (11.8)	2 (0.8)
Vomiting	18 (6.3)	1 (0.3)	34 (12.9)	2 (0.8)
Stomatitis	8 (2.8)	0	14 (5.3)	2 (0.8)

ADR (MedDRA v22.0) System Organ Class Preferred Term	Tecentriq (intravenous formulation) (n=286)		Platinum Agent in Combination with Pemetrexed or Gemcitabine (n=263)	
	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)
Dry mouth	12 (4.2)	0	1 (0.4)	0
Abdominal pain ^a	12 (4.2)	0	11 (4.2)	0
Dyspepsia	6 (2.1)	0	6 (2.3)	0
Dysphagia	5 (1.7)	0	5 (1.9)	0
Colitis ^b	3 (1.0)	2 (0.7)	0	0
Haemorrhoids	3 (1.0)	0	2 (0.8)	0
Gastritis	3 (1.0)	0	1 (0.4)	0
General				
Fatigue ^c	75 (26.2)	4 (1.4)	95 (36.1)	11 (4.2)
Pyrexia	39 (13.6)	0	23 (8.7)	1 (0.4)
Oedema ^d	19 (6.6)	1 (0.3)	18 (6.8)	2 (0.8)
Chest pain	17 (5.9)	2 (0.7)	10 (3.8)	1 (0.4)
Mucosal inflammation	4 (1.4)	0	11 (4.2)	1 (0.4)
Chills	6 (2.1)	0	3 (1.1)	0
Pain	6 (2.1)	0	2 (0.8)	0
Influenza like illness	7 (2.4)	2 (0.7)	0	0
Blood and lymphatic system disorders				
Anaemia	44 (15.4)	5 (1.7)	125 (47.5)	48 (18.3)
Neutropenia ^e	4 (1.4)	2 (0.7)	90 (34.2)	55 (20.9)
Thrombocytopenia	7 (2.4)	1 (0.3)	44 (16.7)	19 (7.2)
Leukopenia	3 (1.0)	1 (0.3)	21 (8.0)	4 (1.5)
Lymphopenia	6 (2.1)	1 (0.3)	3 (1.1)	0
Thrombocytosis	3 (1.0)	0	3 (1.1)	1 (0.4)
Metabolism and nutrition disorders				
Decreased appetite	44 (15.4)	2 (0.7)	50 (19.0)	0
Hyponatraemia	17 (5.9)	6 (2.1)	12 (4.6)	6 (2.3)
Hyperglycaemia	12 (4.2)	1 (0.3)	13 (4.9)	4 (1.5)
Hyperkalaemia	12 (4.2)	6 (2.1)	8 (3.0)	3 (1.1)
Hypomagnesaemia	8 (2.8)	0	11 (4.2)	1 (0.4)
Hypokalaemia	4 (1.4)	0	10 (3.8)	3 (1.1)
Hypoalbuminaemia	8 (2.8)	0	5 (1.9)	2 (0.8)
Hypercalcaemia	7 (2.4)	4 (1.4)	2 (0.8)	0
Hypocalcaemia	4 (1.4)	0	4 (1.5)	1 (0.4)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea ^f	41 (14.3)	3 (1.0)	30 (11.4)	0

ADR (MedDRA v22.0) System Organ Class Preferred Term	Tecentriq (intravenous formulation) (n=286)		Platinum Agent in Combination with Pemetrexed or Gemcitabine (n=263)	
	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)
Cough ^g	38 (13.3)	1 (0.3)	26 (9.9)	0
Haemoptysis	21 (7.3)	0	12 (4.6)	2 (0.8)
Chronic obstructive pulmonary disease	11 (3.8)	4 (1.4)	2 (0.8)	0
Pneumonitis	9 (3.1)	2 (0.7)	1 (0.4)	0
Oropharyngeal pain	8 (2.8)	0	1 (0.4)	0
Pleurisy	4 (1.4)	0	2 (0.8)	0
Infections and infestations				
Respiratory tract infection ^h	40 (14.0)	10 (3.5)	29 (11.0)	10 (3.8)
Nasopharyngitis ⁱ	21 (7.3)	0	6 (2.3)	0
Urinary tract infection ^j	8 (2.8)	1 (0.3)	12 (4.6)	3 (1.1)
Conjunctivitis	3 (1.0)	0	8 (3.0)	0
Influenza	7 (2.4)	0	4 (1.5)	0
Lower respiratory tract infection	3 (1.0)	1 (0.3)	6 (2.3)	3 (1.1)
Lung infection	5 (1.7)	2 (0.7)	3 (1.1)	2 (0.8)
Respiratory tract infection viral	4 (1.4)	0	4 (1.5)	0
Pharyngitis	5 (1.7)	1 (0.3)	1 (0.4)	0
Infection	3 (1.0)	0	0	0
Oral fungal infection ^k	3 (1.0%)	0	3 (1.1)	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain ^l	44 (15.4)	2 (0.7)	26 (9.9)	3 (1.1)
Arthralgia	18 (6.3)	2 (0.7)	6 (2.3)	0
Pain in extremity	10 (3.5)	2 (0.7)	11 (4.2)	1 (0.4)
Spinal pain	4 (1.4)	0	3 (1.1)	0
Muscular weakness	4 (1.4)	0	0	0
Nervous system disorders				
Headache	26 (9.1)	0	18 (6.8)	0
Neuropathy peripheral ^m	21 (7.3)	0	13 (4.9)	1 (0.4)
Dizziness	9 (3.1)	0	13 (4.9)	0
Dysgeusia	6 (2.1)	0	8 (3.0)	0
Somnolence	6 (2.1)	0	2 (0.8)	1 (0.4)
Cerebral ischaemia	3 (1.0)	1 (0.3)	2 (0.8)	0
Tremor	4 (1.4)	0	1 (0.4)	0
Skin and subcutaneous tissue disorders				
Rash ⁿ	43 (15.0)	3 (1.0)	19 (7.2)	2 (0.8)

ADR (MedDRA v22.0) System Organ Class Preferred Term	Tecentriq (intravenous formulation) (n=286)		Platinum Agent in Combination with Pemetrexed or Gemcitabine (n=263)	
	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)
Pruritus	19 (6.6)	0	4 (1.5)	0
Alopecia	3 (1.0)	0	15 (5.7)	0
Dry skin	8 (2.8)	0	4 (1.5)	0
Hyperhidrosis	4 (1.4)	0	2 (0.8)	0
Psychiatric disorders				
Insomnia	20 (7.0)	0	15 (5.7)	0
Anxiety	9 (3.1)	0	2 (0.8)	0
Depression	8 (2.8)	0	3 (1.1)	0
Confusional state	4 (1.4)	0	0	0
Endocrine disorders				
Hypothyroidism ^p	27 (9.4)	0	4 (1.5)	0
Hyperthyroidism ^p	13 (4.5)	0	2 (0.8)	0
Renal and urinary disorders				
Renal impairment	3 (1.0)	0	7 (2.7)	1 (0.4)
Dysuria	4 (1.4)	0	0	0
Haematuria	4 (1.4)	1 (0.3)	0	0
Urinary retention	3 (1.0)	0	1 (0.4)	0
Vascular disorders				
Hypertension	5 (1.7)	2 (0.7)	9 (3.4)	3 (1.1)
Embolism ^q	10 (3.5)	4 (1.4)	4 (1.5)	2 (0.8)
Cardiac disorders				
Atrial fibrillation	3 (1.0)	0	3 (1.1)	0
Tachycardia	4 (1.4)	0	2 (0.8)	0
Ear and labyrinth disorders				
Vertigo	3 (1.0)	0	4 (1.5)	0
Eye disorders				
Vision blurred	3 (1.0)	0	3 (1.1)	0
Injury, poisoning and procedural complications				
Infusion related reaction	4 (1.4)	0	0	0

^a Includes reports of abdominal pain, abdominal pain lower, abdominal pain upper, flank pain

^b Includes reports of autoimmune colitis, colitis

^c Includes reports of asthenia, fatigue, lethargy, malaise

^d Includes reports of lymphoedema, oedema, oedema peripheral, peripheral swelling, swelling

^e Includes reports of neutropenia, neutrophil count decreased

^f Includes reports of dyspnoea, dyspnoea exertional

^g Includes reports of cough, productive cough, upper-airway cough syndrome

^h Includes reports of bronchitis, pneumonia, respiratory tract infection, upper respiratory tract infection

ADR (MedDRA v22.0) System Organ Class Preferred Term	Tecentriq (intravenous formulation) (n=286)		Platinum Agent in Combination with Pemetrexed or Gemcitabine (n=263)	
	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)

ⁱ Includes reports of nasal congestion, nasopharyngitis

^j Includes reports of cystitis, urinary tract infection

^k Includes reports of oral candidiasis, oral fungal infection

^l Includes reports of back pain, musculoskeletal pain, musculoskeletal chest pain, myalgia, neck pain

^m Includes reports of herpes zoster, hypoaesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy

ⁿ Includes reports of acne, blister, dermatitis, dermatitis acneiform, dermatitis allergic, drug eruption, eczema, erythema, folliculitis, rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation, skin ulcer

^o Includes reports of hypothyroidism, blood thyroid stimulating hormone decreased, myxedema, thyroxine free decreased

^p Includes reports of exophthalmos, hyperthyroidism

^q Includes reports of deep vein thrombosis, pulmonary embolism

Study GO29436 (IMpower150) (First-Line Combination Therapy)

The information provided in Table 7 and **Listing 5** summarizes the adverse drug reactions observed in patients included in study GO29436 (IMpower150) (n=1202) in chemotherapy-naïve patients with metastatic, non-squamous NSCLC in the first-line (1L) setting.

In the first-line NSCLC study (IMpower150), an overall higher frequency of adverse events was observed in the four-drug regimen of atezolizumab, bevacizumab, paclitaxel, and carboplatin compared to atezolizumab, paclitaxel and carboplatin. Nausea, diarrhea, stomatitis, fatigue, pyrexia, mucosal inflammation, decreased appetite, weight decreased, hypertension and proteinuria were reported higher ($\geq 5\%$ difference) in patients receiving intravenous atezolizumab in combination with bevacizumab, paclitaxel and carboplatin. Other clinically significant adverse events which were observed more frequently in the atezolizumab, bevacizumab, paclitaxel, and carboplatin arm were epistaxis, hemoptysis, cerebrovascular accident, including fatal events.

Table 7 Adverse Drug Reactions Occurring in $\geq 1\%$ of Patients with NSCLC Treated with Tecentriq (intravenous formulation) in Combination with bevacizumab, Paclitaxel and Carboplatin in the Pivotal Study GO29436 (IMpower150)

ADR (MedDRA v20.1) System Organ Class Preferred Term	Arm B: TECENTRIQ (Intravenous Formulation) + bevacizumab + paclitaxel + carboplatin (n=393) (Frequency rate %)		Arm C: bevacizumab + paclitaxel + carboplatin (n=394) (Frequency rate %)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Gastrointestinal disorders				
Diarrhea ^a	127 (32.3)	18 (4.6)	97 (24.6)	2 (0.5)
Vomiting	73 (18.6)	7 (1.8)	69 (17.5)	5 (1.3)
Abdominal Pain ^b	53 (13.5)	7 (1.8)	39 (9.9)	4 (1.0)
Colitis ^c	11 (2.8)	7 (1.8)	2 (0.5)	2 (0.5)

ADR (MedDRA v20.1) System Organ Class Preferred Term	Arm B: TECENTRIQ (Intravenous Formulation) + bevacizumab + paclitaxel + carboplatin (n=393) (Frequency rate %)		Arm C: bevacizumab + paclitaxel + carboplatin (n=394) (Frequency rate %)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
General disorders & administration site conditions				
Fatigue ^d	222 (56.5)	24 (6.1)	192 (48.7)	25 (6.3)
Pyrexia	73 (18.6)	1 (0.3)	34 (8.6)	2 (0.5)
Edema ^e	41 (10.4)	1 (0.3)	26 (6.6)	2 (0.5)
Hepatobiliary disorders				
Liver Function Test Abnormality	35 (8.9)	10 (2.5)	26 (6.6)	2 (0.5)
Alanine Aminotransferase Increased	30 (7.6)	9 (2.3)	20 (5.1)	2 (0.5)
Blood Alkaline Phosphatase Increased	11 (2.8)	2 (0.5)	9 (2.3)	0
Blood Bilirubin Increased	4 (1.0)	1 (0.3)	1 (0.3)	0
Infections & infestations				
Respiratory Tract Infection ^f	107 (27.2)	31 (7.9)	67 (17.0)	18 (4.6)
Urinary Tract Infection ^g	42 (10.7)	5 (1.3)	30 (7.6)	4 (1.0)
Oral Fungal Infection ^h	7 (1.8)	0	5 (1.3)	0
Sepsis ⁱ	5 (1.3)	5 (1.3)	5 (1.3)	3 (0.8)
Metabolism disorders				
Decreased Appetite ^j	114 (29.0)	14 (3.6)	84 (21.3)	3 (0.8)
Dehydration	34 (8.7)	8 (2.0)	21 (5.3)	7 (1.8)

ADR (MedDRA v20.1) System Organ Class Preferred Term	Arm B: TECENTRIQ (Intravenous Formulation) + bevacizumab + paclitaxel + carboplatin (n=393) (Frequency rate %)		Arm C: bevacizumab + paclitaxel + carboplatin (n=394) (Frequency rate %)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain ^k	153 (38.9)	8 (2.0)	117 (29.7)	8 (2.0)
Nervous System Disorders				
Neuropathy Peripheral ^l	224 (57.0)	14 (3.6)	190 (48.2)	13 (3.3)
Psychiatric disorders				
Insomnia	39 (9.9)	0	37 (9.4)	0
Confusional State ^m	9 (2.3)	1 (0.3)	10 (2.5)	4 (1.0)
Renal & urinary disorders				
Blood Creatinine Increased	11 (2.8)	0	9 (2.3)	0
Hematuria	13 (3.3)	0	7 (1.8)	1 (0.3)
Acute Kidney Injury	7 (1.8)	1 (0.3)	6 (1.5)	4 (1.0)
Respiratory, thoracic and mediastinal disorders				
Cough ⁿ	86 (21.9)	3 (0.8)	79 (20.1)	1 (0.3)
Dyspnea ^o	58 (14.8)	4 (1.0)	64 (16.2)	7 (1.8)
Skin & subcutaneous disorders				
Rash ^p	114 (29.0)	9 (2.3)	52 (13.2)	2 (0.5)
Severe Cutaneous Adverse Reactions ^q	4 (1.0)	0	2 (0.5)	0
Vascular Disorders				
Embolism ^r	23 (5.9)	10 (2.5)	22 (5.6)	13 (3.3)

^a Includes reports of diarrhea and frequent bowel movements

^b Includes reports of abdominal pain, abdominal pain lower, abdominal pain upper and flank pain

^c Includes reports of colitis, colitis ischemic and immune-mediated enterocolitis

^d Includes reports of asthenia, fatigue, lethargy and malaise

^e Includes reports of edema, edema peripheral, localized edema, lymphedema, peripheral swelling and swelling

^f Includes reports of bronchitis, pneumonia, respiratory tract infection and upper respiratory tract infection

^g Includes reports of cystitis, emphysematous cystitis, pyelonephritis and urinary tract infection

^h Includes reports of oral candidiasis and oral fungal infection

ⁱ Includes reports of bacteremia, sepsis and urosepsis

^j Includes reports of decreased appetite, early satiety and hypophagia

^k Includes reports of back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia and neck pain

^l Includes reports of brachial plexopathy, herpes zoster, hypoaesthesia, neuralgia, neuralgic amyotrophy, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy and toxic neuropathy

^m Includes reports of confusional state and mental status changes

ⁿ Includes reports of cough, productive cough and upper airway cough syndrome

^o Includes reports of dyspnea and dyspnea exertional

^p Includes reports of acne, blister dermatitis, dermatitis acneiform, dermatitis allergic, drug eruption, eczema, eczema infected, erythema, folliculitis, furuncle, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, rash pustular, seborrheic dermatitis, skin exfoliation, skin toxicity and skin ulcer

^q Includes reports of erythema multiforme, exfoliative rash, toxic skin eruption and dermatitis exfoliative generalised

^r Includes reports of deep vein thrombosis, embolism, embolism venous and pulmonary embolism

Metastatic Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Study GO29537 (IMpower130) – First-Line Combination Therapy

The information provided in Table 8 and **Listing 6** summarizes the adverse drug reactions observed in patients included in study GO29537 (IMpower130) (n=705) in chemotherapy-naïve patients with metastatic, non-squamous non-small cell lung cancer (NSCLC) who received intravenous atezolizumab in the first-line (1L) setting.

Table 8 Adverse Drug Reactions Occurring in ≥ 1% of Patients with NSCLC Treated with Tecentriq (intravenous formulation) in Combination with nab-Paclitaxel and Carboplatin in the Pivotal Study GO29537 (IMpower130)

ADR (MedDRA v20.1) System Organ Class Preferred Term	TECENTRIQ (intravenous formulation) + nab-paclitaxel + carboplatin (n=473) (Frequency rate %)		nab-paclitaxel + carboplatin (n=232) (Frequency rate %)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Gastrointestinal disorders				
Diarrhea ^a	202 (42.7)	25 (5.3)	73 (31.5)	14 (6.0)
Vomiting	128 (27.1)	13 (2.7)	45 (19.4)	5 (2.2)
Abdominal Pain ^b	82 (17.3)	6 (1.3)	28 (12.1)	3 (1.3)
General disorders & administration site conditions				
Fatigue ^c	294 (62.2)	52 (11.0)	140 (60.3)	19 (8.2)
Pyrexia	82 (17.3)	1 (0.2)	23 (9.9)	0
Edema ^d	72 (15.2)	3 (0.6)	33 (14.2)	2 (0.9)
Infections & infestations				
Respiratory Tract Infection ^e	132 (27.9)	47 (9.9)	39 (16.8)	13 (5.6)
Urinary Tract Infection ^f	69 (14.6)	8 (1.7)	24 (10.3)	2 (0.9)
Oral Fungal Infection ^g	10 (2.1)	0	7 (3.0)	0
Sepsis ^h	11 (2.3)	10 (2.1)	3 (1.3)	1 (0.4)
Investigations				
Alanine Aminotransferase Increased	25 (5.3)	6 (1.3)	14 (6.0)	4 (1.7)
Blood Alkaline Phosphatase Increased	20 (4.2)	4 (0.8)	10 (4.3)	0
Metabolism disorders				
Decreased Appetite ⁱ	143 (30.2)	10 (2.1)	60 (25.9)	5 (2.2)
Dehydration	49 (10.4)	6 (1.3)	25 (10.8)	2 (0.9)
Musculoskeletal and Connective Tissue disorders				
Musculoskeletal Pain ^j	158 (33.4)	12 (2.5)	41 (17.7)	1 (0.4)
Nervous System Disorders				
Neuropathy Peripheral ^k	167 (35.3)	14 (3.0)	65 (28.0)	6 (2.6)
Psychiatric disorders				
Insomnia	68 (14.4)	0	31 (13.4)	0
Confusional State ^l	19 (4.0)	8 (1.7)	1 (0.4)	0
Renal & urinary disorders				
Blood Creatinine Increased	26 (5.5)	2 (0.4)	7 (3.0)	0
Hematuria	16 (3.4)	2 (0.4)	5 (2.2)	0
Acute Kidney Injury	9 (1.9)	4 (0.8)	3 (1.3)	1 (0.4)

ADR (MedDRA v20.1) System Organ Class Preferred Term	TECENTRIQ (intravenous formulation) + nab-paclitaxel + carboplatin (n=473) (Frequency rate %)		nab-paclitaxel + carboplatin (n=232) (Frequency rate %)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Respiratory, thoracic and mediastinal disorders				
Cough ^m	149 (31.5)	3 (0.6)	45 (19.4)	0
Dyspnea ⁿ	148 (31.3)	23 (4.9)	56 (24.1)	3 (1.3)
Skin & subcutaneous disorders				
Rash ^o	112 (23.7)	5 (1.1)	36 (15.5)	2 (0.9)
Vascular disorders				
Embolism ^p	34 (7.2)	19 (4.0)	15 (6.5)	8 (3.4)

^a Includes reports of diarrhea and frequent bowel movements

^b Includes reports of abdominal pain, abdominal pain lower, abdominal pain upper and flank pain

^c Includes reports of asthenia, fatigue, lethargy and malaise

^d Includes reports of edema, edema peripheral, localized edema, lymphedema, peripheral swelling and swelling

^e Includes reports of bronchitis, pneumonia, respiratory tract infection and upper respiratory tract infection

^f Includes reports of cystitis, urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal and urinary tract infection pseudomonal

^g Includes reports of fungal esophagitis and oral candidiasis

^h Includes reports of bacteremia, pulmonary sepsis, sepsis and urosepsis

ⁱ Includes reports of decreased appetite and hypophagia

^j Includes reports of back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia and neck pain

^k Includes reports of autoimmune neuropathy, herpes zoster, hypoaesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy and toxic neuropathy

^l Includes reports of confusional state and mental status changes

^m Includes reports of cough, productive cough and upper airway cough syndrome

ⁿ Includes reports of dyspnea and dyspnea exertional

^o Includes reports of acne, blister, dermatitis, dermatitis acneiform, dermatitis allergic, drug eruption, eczema, erythema, folliculitis, furuncle, palmar-plantar erythrodysesthesia syndrome, pemphigoid, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, seborrheic dermatitis, skin exfoliation and skin ulcer

^p Includes reports of deep vein thrombosis, embolism, embolism venous, pulmonary embolism and venous thrombosis

Study GO28915 (OAK) – Second Line Monotherapy

The information provided in Table 9 and **Listing 7** summarizes the adverse drug reactions observed in patients included in study GO28915 (OAK) (n=1187), during treatment with Tecentriq (intravenous formulation) compared to treatment with docetaxel.

Table 9 Adverse Drug Reactions Occurring in ≥ 1% of Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with Tecentriq (intravenous formulation) vs. Docetaxel in the Pivotal Study GO28915 (OAK)

Adverse Drug Reaction (MedDRA) System Organ Class (SOC)	Tecentriq (intravenous formulation) n = 609 (Frequency rate %)		Docetaxel n = 578 (Frequency rate %)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
All Adverse Drug Reactions	511 (83.9)	104 (17.1)	480 (83.0)	95 (16.4)
Blood and Lymphatic System Disorders				
Thrombocytopenia	8 (1.3)	1 (0.2)	8 (1.4)	1 (0.2)
Cardiac Disorders				
Pericardial disorders ^a	8 (1.3)	5 (0.8)	4 (0.7)	0
Endocrine Disorders				
Hypothyroidism ^b	27 (4.4)	0	2 (0.3)	0
Hyperthyroidism ^c	9 (1.5)	0	0	0
Gastrointestinal Disorders				
Nausea	109 (17.9)	4 (0.7)	132 (22.8)	2 (0.3)
Diarrhea	94 (15.4)	4 (0.7)	141 (24.4)	11 (1.9)
Vomiting	74 (12.2)	2 (0.3)	63 (10.9)	5 (0.9)
Abdominal pain ^d	44 (7.2)	3 (0.5)	57 (9.9)	6 (1.0)
Dry Mouth	16 (2.6)	0	11 (1.9)	0
Dysphagia	13 (2.1)	2 (0.3)	11 (1.9)	1 (0.2)
General Disorders and Administration				
Fatigue ^e	271 (44.5)	25 (4.1)	329 (56.9)	35 (6.1)
Pyrexia	109 (17.9)	2 (0.3)	77 (13.3)	1 (0.2)
Chills	22 (3.6)	1 (0.2)	9 (1.6)	0
Influenza like illness	32 (5.3)	0	14 (2.4)	0
Hepatobiliary Disorders				
AST increased	38 (6.2)	5 (0.8)	12 (2.1)	2 (0.3)
ALT increased	35 (5.7)	6 (1.0)	14 (2.4)	2 (0.3)
Immune System Disorders				
Hypersensitivity	6 (1.0)	1 (0.2)	11 (1.9)	0
Metabolism and Nutrition Disorders				
Decreased appetite ^f	145 (23.8)	2 (0.3)	138 (23.9)	9 (1.6)
Hyponatremia	26 (4.3)	11 (1.8)	18 (3.1)	4 (0.7)
Hypokalemia	25 (4.1)	4 (0.7)	24 (4.2)	6 (1.0)
Hyperglycemia ^g	19 (3.1)	7 (1.1)	26 (4.5)	5 (0.9)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain ^h	170 (27.9)	16 (2.6)	152 (26.3)	9 (1.6)
Arthralgia	73 (12.0)	3 (0.5)	58 (10.0)	1 (0.2)
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea ⁱ	134 (22.0)	17 (2.8)	123 (21.3)	15 (2.6)
Nasopharyngitis ^j	42 (6.9)	0	26 (4.5)	0
Pneumonitis ^k	14 (2.3)	5 (0.8)	4 (0.7)	2 (0.3)
Hypoxia	10 (1.6)	4 (0.7)	11 (1.9)	6 (1.0)

Adverse Drug Reaction (MedDRA) System Organ Class (SOC)	Tecentriq (intravenous formulation) n = 609 (Frequency rate %)		Docetaxel n = 578 (Frequency rate %)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Skin and Subcutaneous Tissue Disorders				
Rash ^l	103 (16.9)	5 (0.8)	87 (15.1)	1 (0.2)
Pruritus	50 (8.2)	3 (0.5)	18 (3.1)	0
Vascular Disorders				
Hypotension	17 (2.8)	2 (0.3)	23 (4.0)	3 (0.5)

^a Includes reports of pericardial effusion, cardiac tamponade and pericarditis

^b Includes reports of blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, hypothyroidism, thyroid function test abnormal and thyroiditis

^c Includes reports of endocrine ophthalmopathy, exophthalmos and hyperthyroidism

^d Includes reports of abdominal pain, abdominal pain lower, abdominal pain upper and flank pain

^e Includes reports of asthenia, fatigue, lethargy and malaise

^f Includes reports of decreased appetite and hypophagia

^g Includes reports of glucose tolerance impaired and hyperglycemia

^h Includes reports of back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia and neck pain

ⁱ Includes reports of dyspnea and dyspnea exertional

^j Includes reports of nasal congestion and nasopharyngitis

^k Includes reports of interstitial lung disease, lung infiltration, radiation pneumonitis, pneumonitis and bronchiolitis

^l Includes reports of acne, blister, dermatitis, dermatitis acneiform, drug eruption, eczema, epidermolysis, erythema, erythema of eyelid, folliculitis, palmar-plantar erythrodysesthesia syndrome, pemphigoid, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, rash pustular, seborrheic dermatitis, skin exfoliation, skin toxicity and skin ulcer

Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

Study YO40245 (IMbrave150) - First-Line Combination Therapy

The information provided in Table 10 and **Listing 8** summarizes the adverse drug reactions observed in Study YO40245 (IMbrave150) in adult patients who received 1200 mg of Tecentriq (intravenous formulation) intravenously, followed by 15 mg/kg bevacizumab (n=329), every 3 weeks until loss of clinical benefit or unacceptable toxicity or 400 mg of sorafenib (n=156) given orally twice daily.

Table 10 Adverse Reactions Occurring in ≥1% of Patients with Unresectable or Metastatic HCC Receiving Tecentriq (intravenous formulation) in Combination with Bevacizumab Compared to Sorafenib in YO40245

Adverse Reaction	Tecentriq in combination with bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades n (%)	Grades 3–4 n (%)	All Grades n (%)	Grades 3–4 n (%)
Blood and Lymphatic System Disorders				
Anemia	30 (9.1)	9 (2.7)	15 (9.6)	4 (2.6)
Neutropenia ^a	28 (8.5)	6 (1.8)	7 (4.5)	1 (0.6)
Thrombocytopenia	27 (8.2)	6 (1.8)	8 (5.1)	3 (1.9)
Leukopenia	19 (5.8)	3 (0.9)	4 (2.6)	0

Adverse Reaction	Tecentriq in combination with bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades n (%)	Grades 3–4 n (%)	All Grades n (%)	Grades 3–4 n (%)
Leukocytosis	5 (1.5)	0	1 (0.6)	0
Endocrine Disorders				
Hypothyroidism ^b	36 (10.9)	0	4 (2.6)	0
Hyperthyroidism	15 (4.6)	1 (0.3)	0	0
Eye Disorders				
Cataract	0	0	2 (1.3)	0
Gastrointestinal Disorders				
Diarrhoea ^c	62 (18.8)	6 (1.8)	77 (49.4)	8 (5.1)
Abdominal Pain ^d	57 (17.3)	5 (1.5)	32 (20.5)	5 (3.2)
Constipation	44 (13.4)	0	22 (14.1)	0
Nausea	40 (12.2)	1 (0.3)	25 (16)	1 (0.6)
Vomiting ^e	33 (10)	2 (0.6)	13 (8.3)	1 (0.6)
Ascites	23 (7)	6 (1.8)	9 (5.8)	2 (1.3)
Abdominal distension	23 (7)	1 (0.3)	5 (3.2)	2 (1.3)
Stomatitis	19 (5.8)	3 (0.9)	7 (4.5)	1 (0.6)
Gingival bleeding	9 (2.7)	0	0	0
Pancreatitis ^f	9 (2.7)	3 (0.9)	6 (3.8)	5 (3.2)
Dyspepsia	8 (2.4)	0	3 (1.9)	2 (1.3)
Gastrointestinal hemorrhage	8 (2.4)	4 (1.2)	3 (1.9)	3 (1.9)
Oesophageal varices haemorrhage	8 (2.4)	6 (1.8)	1 (0.6)	1 (0.6)
Gastrooesophageal reflux disease	6 (1.8)	1 (0.3)	3 (1.9)	0
Colitis	6 (1.8)	2 (0.6)	1 (0.6)	1 (0.6)
Dysphagia	6 (1.8)	0	1 (0.6)	2 (1.3)
Haemorrhoids	5 (1.5)	0	5 (3.2)	1 (0.6)
Dry mouth	5 (1.5)	0	3 (1.9)	0
Rectal haemorrhage	5 (1.5)	1 (0.3)	3 (1.9)	0
Flatulence	4 (1.2)	0	3 (1.9)	0
Mouth ulceration	4 (1.2)	0	2 (1.3)	0
Upper gastrointestinal haemorrhage	4 (1.2)	2 (0.6)	2 (1.3)	2 (1.3)
General Disorders and Administration Site Conditions				
Fatigue ^g	95 (28.9)	8 (2.4)	55 (35.3)	10 (6.4)
Pyrexia	59 (17.9)	4 (1.2)	15 (9.6)	2 (1.3)
Edema ^h	38 (11.6)	0	6 (3.8)	0
Pain	8 (2.4)	0	1 (0.6)	0
Chills	7 (2.1)	0	2 (1.3)	0
Influenza like illness	7 (2.1)	0	0	0
Mucosal inflammation	5 (1.5)	0	5 (3.2)	0
Chest pain	4 (1.2)	2 (0.6)	3 (1.9)	0
Hepatobiliary Disorders				
Hepatic function abnormal	7 (2.1)	2 (0.6)	5 (3.2)	2 (1.3)
Hyperbilirubinaemia	6 (1.8)	3 (0.9)	3 (1.9)	1 (0.6)
Hepatic pain	5 (1.5)	1 (0.3)	2 (1.3)	0
Cholangitis	5 (1.5)	4 (1.2)	1 (0.6)	1 (0.6)
Infections and Infestations				
Upper Respiratory tract infection ⁱ	31 (9.4)	7 (2.1)	4 (2.6)	1 (0.6)

Adverse Reaction	Tecentriq in combination with bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades n (%)	Grades 3–4 n (%)	All Grades n (%)	Grades 3–4 n (%)
Urinary tract infection ^j	17 (5.2)	2 (0.6)	3 (1.9)	0
Periodontitis	7 (2.1)	0	0	0
Gingivitis	5 (1.5)	1 (0.3)	1 (0.6)	0
Oral fungal infection ^k	6 (1.8)	0	1 (0.6)	0
Sepsis ^l	6 (1.8)	4 (1.2)	0	0
Sinusitis	4 (1.2)	0	1 (0.6)	0
Injury, Poisoning and Procedural Complications				
Infusion related reaction	37 (11.2)	8 (2.4)	0	0
Fall	4 (1.2)	0	0	0
Metabolism and Nutrition Disorders				
Decreased appetite ^m	58 (17.6)	4 (1.2)	38 (24.4)	6 (3.8)
Hypoalbuminaemia	24 (7.3)	1 (0.3)	12 (7.7)	0
Hyponatraemia	19 (5.8)	9 (2.7)	9 (5.8)	3 (1.9)
Hyperglycemia	16 (4.9)	2 (0.6)	4 (2.6)	2 (1.3)
Hyperkalaemia	11 (3.3)	4 (1.2)	4 (2.6)	0
Hypokalaemia	9 (2.7)	2 (0.6)	10 (6.4)	4 (2.6)
Diabetes mellitus	8 (2.4)	1 (0.3)	0	0
Hypophosphataemia	7 (2.1)	2 (0.6)	11 (7.1)	6 (3.8)
Hypoglycaemia	5 (1.5)	3 (0.9)	3 (1.9)	2 (1.3)
Hypercalcaemia	4 (1.2)	0	0	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain ⁿ	54 (16.4)	2 (0.6)	16 (10.3)	3 (1.9)
Arthralgia	32 (9.7)	0	8 (5.1)	1 (0.6)
Pain in extremity	8 (2.4)	0	6 (3.8)	0
Muscle spasms	7 (2.1)	0	5 (3.2)	0
Muscular weakness	5 (1.5)	1 (0.3)	0	0
Nervous System Disorders				
Headache	27 (8.2)	0	11 (7.1)	1 (0.6)
Dizziness	10 (3.0)	0	1 (0.6)	1 (0.6)
Neuropathy peripheral ^o	8 (2.4)	0	4 (2.6)	0
Dysgeusia	6 (1.8)	0	3 (1.9)	0
Hepatic encephalopathy	5 (1.5)	2 (0.6)	3 (1.9)	2 (1.3)
Tremor	4 (1.2)	0	0	0
Psychiatric Disorders				
Insomnia	28 (8.5)	1 (0.3)	11 (7.1)	0
Confusional state ^p	6 (1.8)	3 (0.9)	0	0
Renal and Urinary Disorders				
Proteinuria	66 (20.1)	10 (3.0)	11 (7.1)	1 (0.6)
Haematuria	10 (3.0)	1 (0.3)	0	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough ^q	45 (13.7)	0	17 (10.9)	1 (0.6)
Epistaxis	34 (10.3)	0	7 (4.5)	1 (0.6)
Dyspnoea ^r	32 (9.7)	4 (1.2)	9 (5.8)	3 (1.9)
Dysphonia	28 (8.5)	0	11 (7.1)	0
Nasopharyngitis ^s	18 (5.5)	0	4 (2.6)	0

Adverse Reaction	Tecentriq in combination with bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades n (%)	Grades 3–4 n (%)	All Grades n (%)	Grades 3–4 n (%)
Rhinorrhoea	10 (3.0)	0	3 (1.9)	0
Oropharyngeal pain	8 (2.4)	0	4 (2.6)	0
Pleural effusion	7 (2.1)	2 (0.6)	2 (1.3)	1 (0.6)
Productive cough	7 (2.1)	0	2 (1.3)	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	64 (19.5)	0	15 (9.6)	0
Rash ^t	64 (19.5)	2 (0.6)	96 (61.5)	20 (12.8)
Dry Skin	13 (4.0)	0	4 (2.6)	1 (0.6)
Urticaria	6 (1.8)	0	0	0
Alopecia	4 (1.2)	0	22 (14.1)	0
Vascular Disorders				
Hypertension	98 (29.8)	50 (15.2)	38 (24.4)	19 (12.2)
Embolism ^u	9 (2.7)	5 (1.5)	5 (3.2)	3 (1.9)
Hypotension	7 (2.1)	1 (0.3)	1 (0.6)	1 (0.6)

^a Includes reports of neutropenia and neutrophil count decreased

^b Includes reports of blood thyroid stimulating hormone increased, hypothyroidism, thyroid disorder, thyroxine free increased and tri-iodothyronine free increased

^c Includes reports of diarrhea and frequent bowel movements

^d Includes reports of abdominal pain, abdominal pain lower, abdominal pain upper and flank pain

^e Includes reports of retching and vomiting

^f Includes reports of amylase increased, lipase increased, pancreatic enzymes increased and pancreatitis

^g Includes reports of asthenia, fatigue, lethargy and malaise

^h Includes reports of edema, edema peripheral, peripheral swelling and swelling

ⁱ Includes reports of bronchitis, pneumonia, respiratory tract infection and upper respiratory tract infection

^j Includes reports of cystitis and urinary tract infection

^k Includes reports of oral candidiasis and oral fungal infection

^l Includes reports of pulmonary sepsis and sepsis

^m Includes reports of decreased appetite and early satiety

ⁿ Includes reports of back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia and neck pain

^o Includes reports of hypoaesthesia, neuropathy peripheral, paraesthesia and peripheral sensory neuropathy

^p Includes reports of confusional state and mental status changes

^q Includes reports of cough and productive cough

^r Includes reports of dyspnea and dyspnea exertional

^s Includes reports of nasal congestion and nasopharyngitis

^t Includes reports of blister, dermatitis, dermatitis acneiform, dermatitis allergic, drug eruption, erythema, folliculitis, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, skin exfoliation, skin toxicity and skin ulcer

^u Includes reports of deep vein thrombosis, embolism, embolism venous and pulmonary embolism

Locally Advanced or Metastatic Triple-Negative Breast Cancer (TNBC)

Study WO29522 (IMpassion130) – First-Line Combination Therapy

The information provided in Table 11 and **Listing 9** summarizes the adverse drug reactions observed in patients included in study WO29522 (n=890), during treatment with Tecentriq (intravenous formulation) + nab-paclitaxel compared to treatment with placebo + nab-paclitaxel.

Table 11 Adverse Drug Reactions^a Occurring in ≥ 1% of Patients with Triple Negative Breast Cancer (TNBC) Treated with Tecentriq (intravenous formulation) + Nab-paclitaxel versus Placebo + Nab-paclitaxel in Study WO29522 (IMpassion130)

Adverse Drug Reaction (MedDRA) System Organ Class (SOC)	Tecentriq (intravenous formulation) + Nab-paclitaxel N = 460 n (%)		Placebo + Nab-paclitaxel N = 430 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Blood and Lymphatic System Disorders				
Neutropenia ^b	154 (33.5)	64 (13.9)	111 (25.8)	50 (11.6)
Anemia	130 (28.3)	16 (3.5)	116 (27.0)	12 (2.8)
Leukopenia ^c	67 (14.6)	16 (3.5)	42 (9.8)	11 (2.6)
Lymphopenia ^d	20 (4.3)	9 (2.0)	10 (2.3)	4 (0.9)
Thrombocytopenia ^e	12 (2.6)	3 (0.7)	6 (1.4)	2 (0.5)
Endocrine Disorders				
Hypothyroidism ^f	84 (18.3)	0	19 (4.4)	0
Hyperthyroidism	22 (4.8)	1 (0.2)	5 (1.2)	0
Adrenal Insufficiency ^g	5 (1.1)	1 (0.2)	0	0
Gastrointestinal Disorders				
Nausea	215 (46.7)	5 (1.1)	165 (38.4)	8 (1.9)
Diarrhea	151 (32.8)	8 (1.7)	149 (34.7)	9 (2.1)
Constipation	117 (25.4)	3 (0.7)	108 (25.1)	1 (0.2)
Vomiting	92 (20.0)	5 (1.1)	75 (17.4)	5 (1.2)
Abdominal pain	53 (11.5)	2 (0.4)	53 (12.3)	1 (0.2)
Stomatitis	49 (10.7)	1 (0.2)	21 (4.9)	1 (0.2)
Oropharyngeal Pain ^h	33 (7.2)	0	15 (3.5)	0
Dysphagia	10 (2.2)	1 (0.2)	5 (1.2)	0
Colitis ⁱ	7 (1.5)	2 (0.4)	3 (0.7)	1 (0.2)
General Disorders and Administration				
Fatigue	216 (47.0)	18 (3.9)	194 (45.1)	15 (3.5)
Pyrexia	93 (20.2)	3 (0.7)	46 (10.7)	0
Peripheral edema	73 (15.9)	1 (0.2)	68 (15.8)	6 (1.4)
Asthenia	60 (13.0)	3 (0.7)	51 (11.9)	5 (1.2)
Chills	42 (9.1)	1 (0.2)	23 (5.3)	0
Influenza-like illness	29 (6.3)	0	12 (2.8)	0
Hepatobiliary Disorders				
ALT increased	54 (11.7)	10 (2.2)	38 (8.8)	5 (1.2)
AST increased	50 (10.9)	9 (2.0)	42 (9.8)	9 (2.1)
Hepatitis ^j	11 (2.4)	7 (1.5)	7 (1.6)	1 (0.2)
Immune System Disorders				
Hypersensitivity	8 (1.7)	0	2 (0.5)	0
Infections and Infestations				
Urinary tract infection ^k	73 (15.9)	5 (1.1)	51 (11.9)	3 (0.7)
Lung infection ^l	52 (11.3)	14 (3.0)	21 (4.9)	4 (0.9)
Cellulitis	13 (2.8)	3 (0.7)	10 (2.3)	2 (0.5)
Injury, Poisoning and Procedural Complications				
Infusion-related reaction	6 (1.3)	0	5 (1.2)	0
Investigations				
Blood alkaline phosphatase increased	18 (3.9)	3 (0.7)	13 (3.0)	2 (0.5)

Adverse Drug Reaction (MedDRA) System Organ Class (SOC)	Tecentriq (intravenous formulation) + Nab-paclitaxel N = 460 n (%)		Placebo + Nab-paclitaxel N = 430 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4
Metabolism and Nutrition Disorders				
Decreased appetite	92 (20.0)	3 (0.7)	80 (18.6)	3 (0.7)
Hypokalemia ^m	31 (6.7)	11 (2.4)	11 (2.6)	4 (0.9)
Hypomagnesemia	26 (5.7)	0	11 (2.6)	0
Hyperglycemia	21 (4.6)	3 (0.7)	17 (4)	4 (0.9)
Hyponatremia ⁿ	12 (2.6)	4 (0.9)	16 (3.7)	6 (1.4)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain ^o	113 (24.6)	6 (1.3)	98 (22.8)	7 (1.6)
Arthralgia	89 (19.3)	1 (0.2)	70 (16.3)	1 (0.2)
Back pain	74 (16.1)	6 (1.3)	58 (13.5)	2 (0.5)
Nervous System Disorder				
Peripheral neuropathy ^p	198 (43.0)	43 (9.3)	171 (39.8)	22 (5.1)
Headache	116 (25.2)	3 (0.7)	93 (21.6)	4 (0.9)
Dizziness	69 (15.0)	0	43 (10.0)	0
Dysgeusia	52 (11.3)	0	44 (10.2)	0
Photophobia	5 (1.1)	0	2 (0.5)	0
Renal and Urinary Disorders				
Blood Creatinine Increased	8 (1.7)	1 (0.2)	5 (1.2)	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	126 (27.4)	0	80 (18.6)	0
Nasopharyngitis ^q	80 (17.4)	0	50 (11.6)	0
Dyspnea	75 (16.3)	3 (0.7)	62 (14.4)	3 (0.7)
Dysphonia	22 (4.8)	1 (0.2)	11 (2.6)	0
Pneumonitis ^r	18 (3.9)	2 (0.4)	1 (0.2)	0
Pulmonary Embolism	6 (1.3)	4 (0.9)	6 (1.4)	6 (1.4)
Skin and Subcutaneous Tissue Disorders				
Alopecia ^s	263 (57.2)	2 (0.4)	247 (57.4)	1 (0.2)
Rash ^t	165 (35.9)	5 (1.1)	112 (26.0)	2 (0.5)
Pruritus	73 (15.9)	0	45 (10.5)	0
Dry Skin	42 (9.1)	0	25 (5.8)	0
Vascular Disorders				
Hypertension ^u	27 (5.9)	6 (1.3)	23 (5.3)	9 (2.1)
Hypotension	11 (2.4)	0	7 (1.6)	2 (0.5)

^a ADRs known to be associated with atezolizumab monotherapy and combination therapy

^b Includes reports of neutropenia, neutrophil count decreased, febrile neutropenia and neutropenic sepsis

^c Includes reports of white blood cell count decreased and leukopenia

^d Includes reports of lymphocyte count decreased and lymphopenia

^e Includes reports of platelet count decreased and thrombocytopenia

^f Includes reports of autoimmune thyroiditis, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, goitre, hypothyroidism, thyroid function test abnormal, thyroiditis, thyroxine decreased, thyroxine free increased, and tri-iodothyronine free decreased

^g Includes reports of adrenal insufficiency, addison's disease, adrenocortical insufficiency acute, cortisol decreased

^h Includes reports of oropharyngeal pain, oropharyngeal discomfort and throat irritation

ⁱ Includes reports of colitis and colitis ulcerative

Adverse Drug Reaction (MedDRA) System Organ Class (SOC)	Tecentriq (intravenous formulation) + Nab-paclitaxel N = 460 n (%)		Placebo + Nab-paclitaxel N = 430 n (%)	
	All Grades	Grades 3 – 4	All Grades	Grades 3 – 4

^j Includes ascites, autoimmune hepatitis, hepatitis, hepatotoxicity, hepatitis toxic, immune-mediated hepatitis, hepatic encephalopathy, hepatic failure, liver disorder (*1 fatal case of autoimmune hepatitis)

^k Includes reports of cystitis, pyelonephritis, pyelonephritis acute and urinary tract infection

^l Includes reports of bronchitis, lower respiratory tract infection, infective exacerbation of chronic obstructive airways disease, and pneumonia (*1 fatal case of pneumonia)

^m Includes reports of blood potassium decreased and hypokalaemia

ⁿ Includes reports of blood sodium decreased and hyponatremia

^o Includes reports of musculoskeletal pain, myalgia and bone pain

^p Includes reports of herpes zoster, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy and toxic neuropathy

^q Includes reports of nasopharyngitis, nasal congestion, and rhinorrhea

^r Includes reports of pneumonitis and lung opacity

^s Includes reports of alopecia and madarosis

^t Includes reports of acne, blister, dermatitis, dermatitis acneiform, dermatitis allergic, drug eruption, eczema, erythema, erythema of eyelid, folliculitis, furuncle, genital blister, lip blister, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin toxicity, skin ulcer, and toxic epidermal necrolysis

^u Includes reports of hypertension and blood pressure increased

8.3 Less Common Clinical Trial Adverse Reactions

SUBCUTANEOUS FORMULATION (Tecentriq SC)

Study BP40657 (IMscin001)

Listing 1 Less Common Adverse Drug Reactions Occurring in (<1%) Patients with locally advanced or metastatic Non-Small Cell Lung Cancer Treated with Tecentriq SC in Study BP40657 (IMscin001)

Blood and lymphatic system disorders: leukopenia, neutropenia

Endocrine disorders: thyroiditis

Gastrointestinal disorders: dysphagia

General disorders and administration site conditions: chills

Hepatobiliary disorders: immune-mediated hepatitis

Immune system disorders: hypersensitivity

Infections and infestations: pneumonia aspiration, infective exacerbation of bronchiectasis, rash pustular, sepsis, tracheobronchitis

Investigations: blood thyroid stimulating hormone increased, blood bilirubin increased, blood creatinine increased, blood sodium decreased, blood thyroid stimulating hormone decreased, neutrophil count decreased, white blood cell count decreased

Musculoskeletal and connective tissue disorders: bone pain

Nervous system disorders: peripheral sensory neuropathy, polyneuropathy, dysgeusia, neuropathy peripheral, syncope

Renal and urinary disorders: hypertensive nephropathy

Respiratory, thoracic and mediastinal disorders: dysphonia, hypoxia, pneumonitis

Skin and subcutaneous tissue disorders: rash maculo-papular, alopecia, dermatitis, dermatitis allergic, psoriasis, rash pruritic, skin toxicity, toxic epidermal necrolysis

Vascular disorders: hypertension

INTRAVENOUS FORMULATION (Tecentriq)

Information in this section reports data from a separate Product Monograph for Tecentriq (intravenous formulation).

Extensive-Stage Small Cell Lung Cancer (ES-SCLC)

Study GO30081 (IMpower133) - First-Line Combination Therapy

Listing 2 Less Common Adverse Drug Reactions Occurring in (<1%) Patients with First-Line Extensive-Stage Small Cell Lung Cancer (ES-SCLC) Treated with Tecentriq (intravenous formulation) in Study IMpower133

Renal and urinary disorders: tubulointerstitial nephritis

Endocrine disorders: diabetes mellitus, temperature regulation disorder

Nervous system disorders: Guillan Barré Syndrome

Musculoskeletal and connective tissue disorders: myopathy, rhabdomyolysis

Non-Small Cell Lung Cancer (NSCLC)

Study GO29527 (IMpower010) – Adjuvant Treatment of Early-stage NSCLC

Listing 3 Less Common Adverse Drug Reactions Occurring in (<1%) Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with Tecentriq (intravenous formulation) in Study GO29527 (IMpower010)

Cardiac disorders: Myocarditis

Endocrine disorders: Hypophysitis

Gastrointestinal Disorders: Dysphagia, colitis, pancreatitis

Hepatobiliary disorders: Hepatitis

Immune system disorders: Hypersensitivity, sarcoidosis

Metabolism and nutrition disorders: Diabetes mellitus, hyponatraemia

Musculoskeletal and connective tissue disorders: Myositis

Nervous System Disorders: Guillain Barré Syndrome, dysgeusia, meningoencephalitis

Skin and Subcutaneous Tissue Disorders: Severe cutaneous adverse reactions

Renal and Urinary Disorders: Nephritis

Respiratory, Thoracic, and Mediastinal Disorders: Nasal congestion, hypoxia

Study GO29431 (IMpower110) – First Line Monotherapy

Listing 4 Less Common Adverse Drug Reactions Occurring in (<1%) Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) Treated with Tecentriq (intravenous formulation) in Study GO29431 (IMpower110)

Cardiac disorders: Myocarditis

Endocrine disorders: Adrenal insufficiency

Hepatobiliary disorders: Hepatitis
Immune system disorders: Hypersensitivity
Metabolism and nutrition disorders: Diabetes mellitus
Musculoskeletal and connective tissue disorders: Myositis
Skin and Subcutaneous Tissue Disorders: Dermatitis exfoliative, Erythema multiforme
Renal and urinary disorders: Nephritis
Vascular disorders: Hypotension

Study GO29436 (IMpower150) (First-Line Combination Therapy)

Listing 5 **Less Common Adverse Drug Reactions Occurring in (< 1%) Patients with NSCLC Treated with Tecentriq (intravenous formulation) in Combination with bevacizumab, Paclitaxel and Carboplatin in the Pivotal Study GO29436 (IMpower150)**

Metabolism & Nutrition Disorders: Dehydration: Hypovolemia.
Psychiatric Disorders: Delirium, Hallucination. Insomnia: Sleep Disorder.
Renal & Urinary Disorders: Urinary Obstruction: Urinary Tract Obstruction.

Metastatic Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Study GO29537 (IMpower130) – First-Line Combination Therapy

Listing 6 **Less Common Adverse Drug Reactions Occurring in (< 1%) Patients with NSCLC Treated with Tecentriq (intravenous formulation) in Combination with nab-Paclitaxel and Carboplatin in the Pivotal Study GO29537 (IMpower130)**

Liver Function Test Abnormalities: Blood Bilirubin Increased
Altered Mentation: Delirium, Hallucination.
Urinary Obstruction: Urinary Tract Obstruction.
Skin and Subcutaneous Tissue Disorders: Erythema Multiforme, Toxic Skin Eruption

Study GO28915 (OAK) – Second Line Monotherapy

Listing 7 **Less Common Adverse Drug Reactions Occurring in (< 1%) Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with Tecentriq (intravenous formulation) in the Pivotal Study GO28915 (OAK)**

Endocrine Disorders: Adrenal insufficiency, type 2 diabetes mellitus and type 1 diabetes mellitus.
Gastrointestinal Disorders: Colitis, pancreatitis.
Hepatobiliary Disorders: Hepatitis
Injury, Poisoning and Procedural Complications: Infusion related reaction
Nervous System Disorders: Guillain-Barré syndrome, Meningitis Noninfective, Noninfective encephalitis.
Skin and Subcutaneous Tissue Disorders: Dermatitis bullous, erythema multiforme

Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

Listing 8 Less Common Adverse Drug Reactions Occurring in (< 1%) Patients with Hepatocellular Carcinoma Treated with Tecentriq (intravenous formulation) plus Bevacizumab in Study Y040245 (IMbrave150)

Blood and Lymphatic System Disorders: haemolytic anaemia

Cardiac Disorders: acute coronary syndrome, acute myocardial infarction, aortic valve stenosis, atrial fibrillation, cardiac arrest, conduction disorder, myocardial infarction

Congenital, Familial and Genetic Disorders: hydrocele

Ear and Labyrinth Disorders: hypoacusis

Endocrine Disorders: adrenal insufficiency

Eye Disorders: blindness

Gastrointestinal disorders: dental caries, duodenal ulcer, gastric mucosal lesion, gastric ulcer perforation, gastric varices haemorrhage, gastrointestinal necrosis, haematemesis, hiatus hernia, ileus, large intestinal haemorrhage, melaena, mesenteric vein thrombosis, oesophageal haemorrhage, oesophageal stenosis, varices oesophageal

General Disorders and Administration Site Conditions: multiple organ dysfunction syndrome

Hepatobiliary Disorders: autoimmune hepatitis, bile duct stone, hepatic cirrhosis, hepatitis, hepatobiliary disease, hepatorenal failure, immune-mediated hepatitis, jaundice, liver injury

Immune System Disorders: anaphylactic reaction, cytokine release syndrome, hypersensitivity

Infections and infestations: burkholderia pseudomallei infection, cellulitis, empyema, escherichia sepsis, gastroenteritis, haemophilus infection, herpes simplex encephalitis, neutropenic sepsis, peritonitis, post procedural infection, septic shock, skin infection, tooth infection

Injury, Poisoning and Procedural Complications: acetabulum fracture, femur fracture, head injury, hip fracture

Investigations: granulocyte count decreased, liver function test abnormal

Metabolism and Nutrition Disorders: hyperammonaemia, hypoproteinaemia, lactic acidosis, metabolic acidosis, tumour lysis syndrome, type 2 diabetes mellitus

Musculoskeletal and Connective Tissue Disorders: autoimmune arthritis, groin pain, hypercreatinaemia, pathological fracture, tendonitis

Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps): chronic myeloid leukaemia, oesophageal squamous cell carcinoma, oropharyngeal neoplasm, tumour haemorrhage

Nervous System Disorders: cerebral infarction, cerebrovascular accident, subarachnoid haemorrhage, subdural hygroma, syncope, VIth nerve disorder, VIth nerve paralysis

Psychiatric Disorders: delirium

Renal and Urinary Disorders: acute kidney injury, ketonuria, nephritis, nephrotic syndrome

Reproductive System and Breast Disorders: pelvic pain

Respiratory, Thoracic and Mediastinal Disorders: asthma, chronic obstructive pulmonary disease, laryngeal pain, pharyngeal inflammation, pneumonitis, pneumothorax, pulmonary haemorrhage, respiratory distress

Skin and Subcutaneous Tissue Disorders: psoriasis, toxic skin eruption

Vascular Disorders: bleeding varicose vein

Locally Advanced or Metastatic Triple Negative Breast Cancer (TNBC)

Study WO29522 (IMpassion130) – First-Line Combination Therapy

Listing 9 Less Common Adverse Drug Reactions Occurring in (< 1%) Patients with Triple-Negative Breast Cancer (TNBC) Treated with Tecentriq (intravenous formulation) + Nab-paclitaxel in Study WO29522 (IMpassion130) (MedDRA PTs)

Endocrine Disorders: diabetes mellitus, diabetic ketoacidosis, hypophysitis

Gastrointestinal Disorders: amylase abnormal, amylase increased

Hepatobiliary Disorders: autoimmune cholangitis, gamma-glutamyltransferase increased, blood bilirubin increased, transaminases increased, hepatic function abnormal, hepatic pain, liver function test increased

Musculoskeletal and Connective Tissue Disorders: myositis, myopathy

Nervous System Disorders: syncope

Renal and Urinary Disorders: autoimmune nephritis, proteinuria

Respiratory, Thoracic, and Mediastinal Disorders: hypoxia

Skin and Subcutaneous Tissue Disorders: dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, psoriasis

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

SUBCUTANEOUS FORMULATION (Tecentriq SC)

Study BP40657 (IMscin001)

The information provided in Table 12 summarizes grade 3-4 laboratory abnormalities that occurred in ≥ 1% of patients treated with Tecentriq SC and Tecentriq (intravenous formulation) in Study BP40657.

Table 12 Grade 3-4 Laboratory Abnormalities in ≥1% of Patients Treated with Tecentriq SC and Tecentriq (intravenous formulation) in BP40657

Laboratory Test	Grade 3-4 (%)	
	Tecentriq SC	Tecentriq (intravenous formulation)
Albumin, low	3.0	0.9
Alkaline Phosphatase, high	1.3	0.0
Bilirubin, high	1.7	0.9
Calcium, high	2.6	1.7
Calcium, low	1.7	0.0
Creatinine, high	3.0	2.6
Hemoglobin, high	2.1	0.9
Hemoglobin, low	5.6	3.4
International Normalized Ratio, high	2.1	0.0
Lymphocytes Abs, low	13.3	17.9
Neutrophils, Total, Abs, low	9.0	7.7
Platelet, low	2.6	0.0
Potassium, high	1.3	1.7
Potassium, low	1.7	4.3

AST, high	2.1	1.7
ALT, high	2.6	0.9
Sodium, low	3.4	4.3
Total leukocyte count, low	1.3	1.7

INTRAVENOUS FORMULATION (Tecentriq)

Information in this section reports data from a separate Product Monograph for Tecentriq (intravenous formulation).

Extensive-Stage Small Cell Lung Cancer (ES-SCLC)

Study GO30081 (IMpower133) - First-Line Combination Therapy

The information provided in Table 13 summarizes grade 3-4 laboratory abnormalities that occurred in ≥ 1% of patients treated with Tecentriq (intravenous formulation) in pivotal study GO30081 (IMpower133).

Table 13 Grade 3-4 Laboratory Abnormalities in ≥1% of Patients with First-Line Extensive-Stage Small Cell Lung Cancer (ES-SCLC) Treated with Tecentriq (intravenous formulation) in Pivotal Study GO30081 (IMpower133)

Laboratory Test	Grade 3 – 4 (%)
Neutropenia	45
Leukopenia	23
Thrombocytopenia	20
Anemia	17
Hyponatremia	15
Lymphopenia	14
Increased creatinine	4
Hypokalemia	3
Hypomagnesemia	3
Increased SGPT/ALT	3
Hypocalcemia	3
Hypophosphatemia	3
Hypermagnesemia	2
Hypercalcemia	2
Increased bilirubin	2
Increased hemoglobin	2
Hypoalbuminemia	1
Increased alkaline phosphatase	1
Hyperkalemia	1
Increased SGOT/AST	1
Hypernatremia	1

Non-Small Cell Lung Cancer (NSCLC)

Study GO29527 (IMpower010) – Adjuvant Treatment of Early-Stage NSCLC

The information provided in Table 14 summarizes grade 3 – 4 laboratory abnormalities that occurred in $\geq 1\%$ of patients treated with Tecentriq (intravenous formulation) in pivotal study GO29527 (IMpower010).

Table 14 Grade 3 – 4 Laboratory Abnormalities in $\geq 1\%$ of Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with Tecentriq (intravenous formulation) vs. Best Supportive Care in Study GO29527 (IMpower010)

Laboratory Test	Tecentriq (intravenous formulation) (n=495)	Best Supportive Care (n=495)
	Grade 3–4 (%)	Grade 3 – 4 (%)
Increased Glucose	16 (3.3)	17 (3.6)
Increased Potassium	18 (3.7)	13 (2.7)
Increased SGOT/AST	12 (2.5)	0 (0.0)
Increased SGPT/ALT	16 (3.3)	2 (0.4)
Decreased Calcium	7 (1.5)	3 (0.6)
Decreased Leukocytes	7 (1.5)	0 (0.0)
Decreased Lymphocytes	6 (1.7)	2 (0.5)
Decreased Neutrophils	7 (1.9)	2 (0.5)
Decreased Phosphate	7 (0.8)	7 (1.5)
Decreased Potassium	6 (1.2)	1 (0.2)
Decreased Sodium	13 (2.7)	7 (1.5)

Study GO29431 (IMpower110) – First Line Monotherapy

The information provided in Table 15 summarizes grade 3-4 laboratory abnormalities that occurred in $\geq 1\%$ of patients treated with Tecentriq (intravenous formulation) in study GO29431 (IMpower110).

Table 15 Grade 3 – 4 Laboratory Abnormalities in $\geq 1\%$ of Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) Treated with Tecentriq (intravenous formulation) vs. Platinum Agent in Combination with Pemetrexed or Gemcitabine in Study GO29431 (IMpower110)

Laboratory Test	Tecentriq (intravenous formulation) (n=286)	Platinum Agent in Combination with Pemetrexed or Gemcitabine (n=263)
	Grade 3 – 4 (%)	Grade 3 – 4 (%)
Lymphopenia	9	17
Hyponatremia	9	7

Hypermagnesemia	5	2
Hypophosphatemia	4	2
Hypercalcemia	4	0
Hyperkalemia	4	3
Increased Bilirubin	3	0
Increased AST	3	1
Increased ALT	3	1
Increased Alkaline Phosphatase	3	1
Hypocalcemia	1	3
Anemia	2	20
Neutropenia	1	27
Thrombocytopenia	1	13
Hypokalemia	1	2
Increased Creatinine	1	2
Hypoalbuminemia	0	2
Hypomagnesemia	0	1
Leukopenia	0	15

Study GO29436 (IMpower150) - First-Line Combination Therapy

The information provided in Table 16 summarizes grade 3-4 laboratory abnormalities that occurred in ≥ 1% of patients treated with Tecentriq (intravenous formulation) in pivotal study GO29436 (IMpower150).

Table 16 **Grade 3 – 4 Laboratory Abnormalities in ≥ 1% Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with Tecentriq (intravenous formulation) in Combination with Bevacizumab, Paclitaxel and Carboplatin, in Pivotal Study GO29436 (IMpower150)**

Laboratory Test	Arm B: TECENTRIQ (intravenous formulation) + bevacizumab + paclitaxel + carboplatin (n=393)	Arm C: bevacizumab + paclitaxel + carboplatin (n=394)
	Grade 3 – 4 (%)	Grade 3 – 4 (%)
Neutropenia	31	26
Lymphopenia	17	13
Thrombocytopenia	11	9
Anemia	10	9
Hyperkalemia	7	4
Increased ALT,	6	1
Hypophosphatemia	4	4
Increased AST,	4	1
Hypocalcemia	3	3

Laboratory Test	Arm B: TECENTRIQ (intravenous formulation) + bevacizumab + paclitaxel + carboplatin (n=393)	Arm C: bevacizumab + paclitaxel + carboplatin (n=394)
	Grade 3 – 4 (%)	Grade 3 – 4 (%)
Hypoalbuminemia	3	2
Hypomagnesemia	2	1
Increased Alkaline Phosphatase,	2	1
Hypoglycemia	2	0
Increased Creatinine,	1	2
Increased Bilirubin	1	0

Metastatic Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Study GO29537 (IMpower130) – First-Line Combination Therapy

The information provided in Table 17 summarizes grade 3 – 4 laboratory abnormalities that occurred in $\geq 1\%$ of patients treated with Tecentriq (intravenous formulation) in combination with nab-paclitaxel and carboplatin in pivotal study GO29537 (IMpower130).

Table 17 **Grade 3 – 4 Laboratory Abnormalities in $\geq 1\%$ Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with Tecentriq (intravenous formulation) in combination with nab-Paclitaxel and Carboplatin in Pivotal Study GO29537 (IMpower130)**

Laboratory Test	Grade 3 – 4 (%)
Neutropenia	50
Leukopenia	36
Anemia	33
Lymphopenia	24
Thrombocytopenia	19
Hyponatremia	9
Hypokalemia	6
Hypophosphotamia	6
Hypomagnesemia	3
Increased creatinine	3
Increased SGPT/ALT	3
Increased alkaline phosphatase	3
Hypocalcemia	3
Hypermagnesemia	3
Increased SGOT/AST	2
Hyperkalemia	2
Increased International Normalized Ratio	2
Decreased albumin	1

Laboratory Test	Grade 3 – 4 (%)
Increased hemoglobin	1

Unresectable or Metastatic Hepatocellular Carcinoma

Study YO40245 (IMbrave150) - First-Line Combination Therapy

The following Table 18 summarizes grade 3 – 4 laboratory abnormalities in $\geq 1\%$ adult patients with unresectable or metastatic hepatocellular carcinoma treated with Tecentriq (intravenous formulation) in combination with bevacizumab in pivotal study YO40245.

Table 18 Grade 3 – 4 Laboratory Abnormalities in $\geq 1\%$ Patients with Unresectable or Metastatic Hepatocellular Carcinoma Treated with Tecentriq (intravenous formulation) in combination with Bevacizumab in Pivotal Study YO40245 (IMbrave150)

Laboratory Abnormality	Grades 3 – 4 (%)
Chemistry	
Increased AST	16
Decreased Sodium	13
Increased Glucose	9
Increased ALT	8
Decreased Phosphorus	5
Increased Alkaline Phosphatase	4
Increased Potassium	2
Decreased Albumin	2
Decreased Potassium	2
Decreased Glucose	1
Hematology	
Decreased Lymphocytes	14
Increased Bilirubin	8
Decreased Platelet	7
Decreased Leukocyte	3
Decreased Hemoglobin	3
Decreased Neutrophil	2

Study GO28915 (OAK) - Second Line Monotherapy

The information provided in Table 19 summarizes grade 3 – 4 laboratory abnormalities that occurred in $\geq 1\%$ of patients treated with Tecentriq (intravenous formulation) in pivotal study GO28915 (OAK).

Table 19 Grade 3 – 4 Laboratory Abnormalities in ≥ 1% Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with Tecentriq (intravenous formulation) in Pivotal Study GO28915 (OAK)

Laboratory Test	Grade 3 – 4 (%)
Lymphopenia	14
Anemia	3
Hyponatremia	7
Increased alkaline phosphatase	2
Hypophosphatemia	5
Hypoalbuminemia	4
Hypokalemia	2
Increased ALT	3
Increased AST	3
Increased creatinine	2
Increased bilirubin	2
Hyperkalemia	2
Thrombocytopenia	2
Hypercalcemia	2
Leukopenia	2
Hypoglycemia	1
INR increased	2
Neutropenia	2
Hypomagnesemia	1

Locally Advanced or Metastatic Triple-Negative Breast Cancer (TNBC)

Study WO29522 (IMpassion130) – First-Line Combination Therapy

The information provided in Table 20 summarizes grade 3 – 4 laboratory shifts from baseline (defined as shifts from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post baseline) that occurred in ≥ 1% of patients treated with Tecentriq (intravenous formulation) in pivotal study WO29522.

Table 20 Grade 3 – 4 Laboratory Shifts from Baseline in ≥ 1% Patients with (TNBC) Treated with Tecentriq (intravenous formulation) in Pivotal Study WO29522 (IMpassion130)

Laboratory Test	Grade 3 – 4 (%)
Decreased neutrophils	19.6
Decreased lymphocytes	18.9
Decreased leukocytes	15.7
Increased ALT	6.5
Increased AST	5.9
Decreased sodium	5.7
Decreased potassium	5.2
Decreased phosphorus	4.3
Decreased hemoglobin	4.1
Increased alkaline phosphatase	3.7
Increased bilirubin	2.2
Increased lymphocytes	2.0

Laboratory Test	Grade 3 – 4 (%)
Increased magnesium	1.9
Decreased calcium	1.5
Decreased platelets	1.5
Increased potassium	1.1
Decreased albumin	1.1
Increased creatinine	1.1

Additional Information on Selected Adverse Reactions

General

- **Monotherapy**

Clinically significant adverse drug reactions were observed for TECENTRIQ (intravenous formulation) monotherapy and reflect exposure to Tecentriq (intravenous formulation) in 3178 patients in three randomized, active-controlled studies (POPLAR, OAK, IMmotion150) and four open-label, single arm studies (PCD4989g, IMvigor210, IMvigor211, BIRCH, FIR) which provided 983 patients with metastatic urothelial carcinoma, 1636 patients with metastatic NSCLC, 175 patients with renal cell carcinoma (RCC) and 384 patients with other tumour types. Cases of dry skin were also observed in a Tecentriq (intravenous formulation) monotherapy study.

- **Combination Therapy**

Details for the significant adverse reactions for TECENTRIQ (intravenous formulation) when given in combination are presented if clinically relevant differences were noted in comparison to Tecentriq (intravenous formulation) monotherapy. See 7 WARNINGS AND PRECAUTIONS. Cases of dysphonia, alopecia and peripheral edema were also observed in Tecentriq combination studies.

Immune-Mediated Adverse Reactions

- **Haemophagocytic Lymphohistiocytosis**

Haemophagocytic lymphohistiocytosis (HLH) occurred in <0.1% (1/3178, Grade 5) of patients who received Tecentriq (intravenous formulation) monotherapy. The time to onset was 1.6 months. The duration was 1.4 months. HLH led to discontinuation of Tecentriq in this 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 (intravenous formulation) monotherapy, including Grade 1 – 2 in 1.9% (59/3178), Grade 3-4 in 0.8% (27/3178), and Grade 5 in 1 (<0.1%) patient. The median time to onset was 3.4 months (range: 0.1 to 24.8 months). The median duration was 1.4 months (range: 0 to 21.2+ months; + denotes a censored value). Pneumonitis resolved in 59 patients. Pneumonitis led to discontinuation of Tecentriq (intravenous formulation) in 12 (0.4%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.6% (51/3178) of patients receiving Tecentriq (intravenous formulation).

In IMpower010, pneumonitis occurred in 3.8% (19/495) of patients who received Tecentriq (intravenous formulation) monotherapy, including Grade 3-4 in 0.8% (4/495), and Grade 5 in 1 (0.2%)

patient. Pneumonitis led to discontinuation of Tecentriq (intravenous formulation) in 11 (2.2%) patients.

- ***Immune-Mediated Hepatitis***

Hepatitis occurred in 2.0% (62/3178) of patients who received Tecentriq (intravenous formulation) monotherapy. Grade 3 – 4 hepatitis occurred in 0.8% (25/3178) of patients. The median time to onset was 1.5 months (range 0.2 to 18.8 months). The median duration was 2.1 months (range: 0 to 22.0+ months; + denotes a censored value). Hepatitis led to discontinuation in 6 (0.2%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.6% (18/3178) of patients.

- ***Immune-Mediated Colitis***

Colitis occurred in 1.1% (34/3178) of patients who received Tecentriq (intravenous formulation) monotherapy. Grade 3 – 4 colitis occurred in 0.6% (18/3178) of patients. The median time to onset was 4.7 months (range: 0.5 to 17.2 months). The median duration was 1.2 months (range 0.1 to 17.8+ months; + denotes a censored value). Colitis led to discontinuation of Tecentriq (intravenous formulation) in 8 (0.3%) patients. Colitis requiring the use of corticosteroids occurred in 0.6% (19/3178) of patients receiving Tecentriq (intravenous formulation).

Diarrhea occurred in 19.7% (626/3178) patients, including Grade 3 – 4 diarrhea in 1.1% (36/3178) of patients who received Tecentriq (intravenous formulation).

- ***Immune-Mediated Endocrinopathies***

Hypophysitis

Across clinical trials, hypophysitis occurred in <0.1% (2/3178) of all patients who received Tecentriq (intravenous formulation) 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 (intravenous formulation) was discontinued.

Hypophysitis occurred in 0.8% (3/393) of patients who received Tecentriq (intravenous formulation) 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.

Hypothyroidism

Hypothyroidism occurred in 5.2% (164/3178) of patients who received Tecentriq (intravenous formulation) monotherapy. The median time to onset was 4.9 months (range: 0 to 31.3 months). Hypothyroidism requiring the use of corticosteroids occurred in 0.6% (18/3178) of patients receiving Tecentriq (intravenous formulation).

In IMpower010, hypothyroidism occurred in 17.4% (86/495) of patients who received Tecentriq (intravenous formulation) monotherapy. Hypothyroidism led to discontinuation of Tecentriq (intravenous formulation) in 8 (1.6%) patients. Hypothyroidism requiring the use of corticosteroids occurred in 1.4% (7/495) of patients receiving Tecentriq (intravenous formulation).

Hypothyroidism occurred in 14.2% (56/393) of patients who received Tecentriq (intravenous formulation) with bevacizumab, paclitaxel, and carboplatin. One patient had Grade 3 and 49 patients had Grade 1 – 2 hypothyroidism. The median time to onset was 4.9 months (range: 15 days to 31.3 months). Thyroid stimulating hormone (TSH) was elevated and above the patient's baseline in 28.5% (101/355) of patients with a follow-up measurement.

Hyperthyroidism

Hyperthyroidism occurred in 0.9% (30/3178) of patients who received Tecentriq (intravenous formulation) monotherapy. Grade 1 – 2 hyperthyroidism occurred in 0.9% (29/3178) of patients. The median time to onset was 2.1 months (range: 0.7 to 15.7 months). The median duration was 2.6 months (range: 0+ to 17.1+ months; + denotes a censored value).

In IMpower010, hyperthyroidism occurred in 6.5% (32/495) of patients who received Tecentriq (intravenous formulation) monotherapy. Hyperthyroidism led to discontinuation of Tecentriq (intravenous formulation) in 4 (0.8%) patients.

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

Adrenal Insufficiency

Adrenal insufficiency occurred in 0.3% (11/3178) of patients who received Tecentriq (intravenous formulation) monotherapy, including Grades 1 – 2 in 0.3% (9/3178) of patients. The median time to onset was 5.5 months (range: 0.1 to 19.0 months). The median duration was 16.8 months (range: 0 to 16.8 months). Adrenal insufficiency led to discontinuation of Tecentriq (intravenous formulation) in 1 (<0.1%) patient. Adrenal insufficiency requiring the use of corticosteroids occurred in 0.3% (9/3178) of patients receiving Tecentriq (intravenous formulation).

In IMpower010, adrenal insufficiency occurred in 1.2% (6/495) of patients who received Tecentriq (intravenous formulation) monotherapy, including Grades 3–4 in 0.4% (2/495) of patients. Adrenal insufficiency led to discontinuation of Tecentriq (intravenous formulation) in 3 (0.6%) patients.

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

Diabetes Mellitus

Diabetes mellitus occurred in 0.3% (11/3178) of patients who received Tecentriq (intravenous formulation) monotherapy, including Grade 1 – 2 in 0.2% (5/3178) and Grade 3 – 4 in 0.2% (6/3178) of patients. The median time to onset was 3.6 months (range: 0.1 to 9.9 months). The median duration

was 2.4 months (range: 0.1 to 15.2+ months; + denotes a censored value). Diabetes mellitus resolved in 8 patients.

- ***Immune-Mediated Meningoencephalitis***

Meningoencephalitis occurred in 0.4% (13/3178) of patients who received Tecentriq (intravenous formulation) monotherapy, including Grade 1 – 2 in 0.2% (7/3178) of patients and Grade 3-4 in 0.2% (6/3178) of patients. The median time to onset was 0.5 months (range: 0 to 12.5 months). The median duration was 0.7 months (range: 0.2 to 14.5+ months; + denotes a censored value).

Meningoencephalitis requiring the use of corticosteroids occurred in 0.2% (6/3178) of patients receiving Tecentriq (intravenous formulation) and led to discontinuation of Tecentriq (intravenous formulation) 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 (intravenous formulation) monotherapy. Guillain-Barré syndrome Grade 3 occurred in 0.1% (4/3178) patients and demyelinating polyneuropathy Grade 2 occurred in 1 (<0.1%) patient. The median time to onset was 7.0 months (range: 0.6 to 8.1 months). The median duration was 8.0 months (0.6 to 8.3+ months; +denotes a censored value). Guillain-Barré syndrome led to the discontinuation of Tecentriq (intravenous formulation) in 1 (<0.1%) patient. Guillain-Barré syndrome requiring the use of corticosteroids occurred in <0.1% (2/3178) of patients.

Myasthenia gravis occurred in <0.1% (1/3178) of patients who received Tecentriq (intravenous formulation) for metastatic urothelial carcinoma and NSCLC. The time to onset was 1.2 months and the duration was 12.7 months.

Immune-Mediated Facial Paresis

Facial paresis occurred in <0.1% (1/3178) of patients who received Tecentriq (intravenous formulation) 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 discontinuation of Tecentriq (intravenous formulation).

- ***Immune-Mediated Pancreatitis***

Pancreatitis, including amylase increased and lipase increased, occurred in 0.6% (18/3178) of patients who received Tecentriq (intravenous formulation) monotherapy, including Grade 1 – 2 in 0.2% (5/3178) and Grade 3 – 4 in 0.4% (13/3178) of patients. The median time to onset was 5.0 months (range: 0.3 to 16.9 months). The median duration was 0.8 months (range: 0.1 to 12.0+ months; + denotes a censored value). Pancreatitis led to discontinuation of Tecentriq (intravenous formulation) in 3 (<0.1%) patients. Pancreatitis requiring the use of corticosteroids occurred in 0.1% (4/3178) patients receiving Tecentriq (intravenous formulation). Pancreatitis resolved in 14 patients.

Pancreatitis, including amylase increased and lipase increased, occurred in 1.3% (5/393) of patients who received Tecentriq (intravenous formulation) with bevacizumab, paclitaxel, and carboplatin and one of these patients was treated with corticosteroids. The median time to onset of pancreatitis was 4.4 months (range: 20 days to 9.4 months). The median duration of pancreatitis was 12 days (range: 3 days+ to 12+ months).

- ***Immune-Mediated Myelitis***

Myelitis occurred in <0.1% (1/3178, Grade 3) of patients who received Tecentriq (intravenous formulation) monotherapy. The time to onset was 0.76 months. The event required the use of corticosteroids but did not lead to discontinuation of Tecentriq (intravenous formulation).

- ***Immune-Mediated Myositis***

Myositis, including rhabdomyolysis, occurred in 0.4% (13/3178) of patients who received Tecentriq (intravenous formulation) for various cancers, including Grade 1 – 2 in 0.3% (8/3178) and Grade 3 – 4 in 0.2% (5/3178) of patients. The median time to onset was 5.1 months (range: 0.7 to 11.0 months). The median duration was 5.0 months (range: 0.7 to 22.6+ months, + denotes a censored value). Myositis requiring the use of corticosteroids occurred in 0.2% (7/3178) of patients receiving Tecentriq (intravenous formulation).

- ***Immune-Mediated Nephritis***

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

- ***Immune-Mediated Skin Reactions***

Severe cutaneous adverse reactions (SCARs) (including reports of erythema multiforme, dermatitis bullous, toxic skin eruption, toxic epidermal necrolysis (TEN), exfoliative rash, and dermatitis exfoliative generalized) occurred in 0.7% (22/3178) of patients who received Tecentriq (intravenous formulation) monotherapy. Grade 3 – 4 severe cutaneous adverse reactions occurred in <0.1% (3/3178) of patients. One (<0.1%) fatal case of TEN was observed. 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 (intravenous formulation) in 3 (<0.1%) patients. SCARs requiring the use of systemic corticosteroids occurred in 0.2% (6/3178) of patients receiving Tecentriq (intravenous formulation) monotherapy.

Cases of severe cutaneous adverse reactions (including reports of erythema multiforme, dermatitis bullous, toxic skin eruption, exfoliative rash, dermatitis exfoliative generalized, TEN, and cutaneous vasculitis) were observed in 0.6% (27/4371) of patients in Tecentriq combination therapy studies. Grade 3 – 4 severe cutaneous adverse reactions occurred in 0.2% (8/4317) of patients. No fatal cases were observed. The median time to onset was 2.0 months (range 0.2 to 18.3 months). The median duration of the first event was 1.1 months (range 0.1 to 9.9 months). SCARs led to discontinuation of Tecentriq in 5 (0.1%) patients. SCARs requiring the use of systemic corticosteroids occurred in 0.3% (11/4371) of patients receiving Tecentriq in combination therapy. Cases of Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in studies outside the pivotal study dataset.

- ***Immune-Mediated Pericardial Disorders***

Pericardial disorders occurred in 1.4% (45/3178) of patients who received Tecentriq (intravenous formulation) monotherapy, including Grade 1 – 2 in 0.7% (21/3178) and Grade 3 – 4 in 0.7% (22/3178). Two (<0.1%) fatal cases (cardiac tamponade and pericarditis constrictive) were observed. 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).

- ***Infection***

In 3178 patients who received Tecentriq (intravenous formulation) monotherapy, infection occurred in

1351 (42.5%) patients. Grade 1 – 2 infection occurred in 984 (31.0%) patients and Grade 3 or 4 infection occurred in 336 (10.6%) patients, while 31 (1.0%) patients died due to infection. Pneumonia was the most common type of Grade 3 or higher infection, occurring in 108 (3.4%) patients.

- **Infusion-Related Reactions**

Infusion-related reactions occurred in 1.1% (34/3178) of patients who received Tecentriq (intravenous formulation) monotherapy. Grade 1 – 2 infusion-related reactions occurred in 0.9% (29/3178) of patients and Grade 3 – 4 in 0.2% (5/3178) of patients.

8.5 Post-Market Adverse Reactions

INTRAVENOUS FORMULATION (Tecentriq)

Information in this section reports data from a separate Product Monograph for Tecentriq (intravenous formulation).

The following adverse drug reactions have been identified from post marketing surveillance with Tecentriq (intravenous formulation). Adverse drug reactions from post marketing surveillance are listed by MedDRA system organ class. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: haemophagocytic lymphohistiocytosis

Cardiac Disorders: pericardial disorders ^a

Nervous System Disorders: facial paresis, myelitis

^aIncludes reports of pericarditis, pericardial effusion, cardiac tamponade and pericarditis constrictive

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

No formal drug-behavioral interaction studies have been conducted with atezolizumab.

9.4 Drug-Drug Interactions

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 microenvironment.

Atezolizumab is an Fc-engineered humanized 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. In syngeneic mouse tumour models, blocking PD-L1 activity resulted in decreased tumour growth.

10.2 Pharmacodynamics

The time course of pharmacodynamic response of atezolizumab is unknown. There were no clinically significant exposure-efficacy and -safety relationship of atezolizumab in the non- and extensive stage-small cell lung cancer, hepatocellular carcinoma, or triple negative breast cancer populations over the tested doses of 1875 mg Q3W SC, 840 mg Q2W IV or 1200 mg Q3W IV. The exposure-efficacy and -safety relationship of atezolizumab was flat in various solid tumors over a dose range of 1-20 mg/kg IV Q3W.

Cardiac Electrophysiology

The effect of subcutaneous atezolizumab following dose of 1875 mg q3w on the QTc interval has not been studied. Intravenous atezolizumab demonstrated no clinically meaningful impact of atezolizumab PK on QTcF in patients with metastatic solid tumors.

10.3 Pharmacokinetics

SUBCUTANEOUS FORMULATION (Tecentriq SC)

Non-inferiority of the exposure of subcutaneous atezolizumab compared to intravenous atezolizumab was demonstrated (See 14 CLINICAL PHARMACOLOGY). A subcutaneous and intravenous atezolizumab population pharmacokinetic (PopPK) model (two-compartment disposition model with first order absorption and elimination) was developed from Parts 1 and 2 of IMscin001 study. Based on the PopPK modeling, steady state is achieved after 6 to 9 weeks (2 to 3 cycles) and the average systemic accumulation ratio following 1875 mg Q3W of Tecentriq SC is 2.2.

Table 21: Summary of Atezolizumab Pharmacokinetic Parameters for Tecentriq SC 1875 mg q3w Regimen in patients with locally advanced or metastatic NSCLC

	C_{trough} (µg/mL)	C_{max} (µg/mL)	T_{max} (days)	AUC (µg/mL•day)	t_{1/2}^c (days)	CL^c (L/day)	V_{ss}^c (L)
Cycle 1	97.2 (42%)	189 (36%)	4.5 days (2.2-9.0)	5896 (47%) ^a	27	0.2	6.91
Steady	205 (58%)	376 (43%)	3.8 (2-5)	6163 (47%) ^b			

State							
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Parameters are presented as geometric mean values (% geometric mean coefficient of variation – geoCV) or median (min to max) for T_{max} based on population pharmacokinetics analysis.

AUC: area under the curve from time zero to infinity^a or zero to 21 days^b; C_{max} : maximum concentration; C_{trough} : minimum concentration; $t_{1/2}$: terminal half-life; T_{max} : time to reach C_{max} ; V_{ss} : volume of distribution at steady-state; CL: clearance at steady-state

^c $T_{1/2}$, CL and V_d (reported under Distribution and Elimination) were considered the same for the SC and IV formulations in the PopPK model.

Absorption

Based on PopPK analysis, the absolute bioavailability was 72% with an inter-individual variability of 83% and the first-order absorption rate (K_a) is 0.3 (1/day). The atezolizumab geometric mean maximum serum concentration (C_{max}) was 189 $\mu\text{g/mL}$. The median time to maximum serum concentration (T_{max}) at Cycle 1 was 4.5 days (median; 2.2-9.0 days min-max) and 3.8 days (median; 2.0-5.0 days min-max) at steady state through PopPK.

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.

Elimination

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.

Special Populations and Conditions

- **Pediatrics:** Tecentriq SC is not approved for use in pediatric patients below 18 years of age. No dedicated studies of Tecentriq SC have been conducted in pediatric patients.
- **Geriatrics:** No dedicated studies of atezolizumab have been conducted in elderly patients. The effect of age on the pharmacokinetics of atezolizumab was assessed in a population pharmacokinetic analysis. Age was not identified as a significant covariate influencing 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 subcutaneous and intravenous atezolizumab among patients < 65 years patients between 65-75 years and patients > 75 years (see 4 DOSAGE AND ADMINISTRATION).
- **Hepatic Impairment:** No dedicated studies of atezolizumab have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of atezolizumab between patients with mild hepatic impairment (bilirubin \leq ULN and AST > ULN or bilirubin > 1.0 to 1.5 x ULN and any AST), or moderate hepatic impairment (bilirubin > 1.5 to 3x ULN and any AST). No data are available in patients with severe (bilirubin > 3.0 x ULN and any AST) hepatic impairment. Hepatic impairment was defined by the National Cancer Institute (NCI) criteria of hepatic dysfunction (see 4 DOSAGE AND ADMINISTRATION).
- **Renal Impairment:** No dedicated studies of atezolizumab have been conducted in patients with renal impairment. In the population pharmacokinetic analysis, no clinically important differences in the clearance atezolizumab were found in patients receiving subcutaneous and

intravenous atezolizumab with mild (eGFR 60 to 89 mL/min/1.73 m²) or moderate (eGFR 30 to 59 mL/min/1.73 m²) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m²) renal function. Only a few patients had severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²). The impact of severe renal impairment on the clearance of atezolizumab is unknown (see 4 DOSAGE AND ADMINISTRATION).

INTRAVENOUS FORMULATION (Tecentriq)

For pharmacokinetic information on the IV formulation, please refer to the separate Product Monograph for Tecentriq.

11 STORAGE, STABILITY AND DISPOSAL

Store Tecentriq SC (atezolizumab) vials at 2-8°C.

Keep Tecentriq SC in outer carton in order to protect from light.

Do not freeze. Do not shake.

Storage of the syringe

- Since Tecentriq SC does not contain any antimicrobial preservative, it should be used immediately once transferred from the vial to the syringe. If not used immediately, in-use storage times and conditions prior to use are the responsibility 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 and in the refrigerator [2°C to 8°C] for up to 30 days if prepared under controlled and validated aseptic conditions.

Incompatibilities

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

12 SPECIAL HANDLING INSTRUCTIONS

Tecentriq SC should not be used after the expiry date (EXP) shown on the pack.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: atezolizumab

Chemical name: Non-glycosylated IgG1 kappa immunoglobulin monoclonal antibody which consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each).

Molecular formula and molecular mass: $C_{6434}H_{9878}O_{1996}N_{1702}S_{42}$. Atezolizumab has a calculated molecular mass of 144,356 Da.

Physicochemical properties: colourless to slightly yellow solution

Pharmaceutical standard: Professed

Product Characteristics:

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

Viral Inactivation

Not applicable.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

SUBCUTANEOUS FORMULATION

Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Study BP40657 (IMscin001)

Study Demographics and Trial Design

Table 22 Summary of patient demographics for Study BP40657 (IMscin001) in Locally Advanced or Metastatic Non-Small Cell Lung Cancer Patients

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (range)	Sex
BP40657	Phase Ib/III, two-part, randomized, multicentre, open-label, active controlled, Part 2: 2 arm	Part 2: Atezo IV: 1200 mg Q3W Atezo SC: 1875 mg Q3W Until disease progression, loss of clinical benefit, unacceptable toxicity, or withdrawal of consent	Part 2: 371 Atezo IV: 124 Atezo SC: 247	64 years (27 to 85)	M: 257 (69%) F: 114 (31%)

Atezo = Atezolizumab; IV Intravenous; Q3W = every three weeks; SC = subcutaneous

A phase Ib/III, open-label, multi-center, international, randomized study, BP40657 (IMscin001), was conducted to evaluate the pharmacokinetics, efficacy and safety of atezolizumab subcutaneous compared with atezolizumab intravenous 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. In Part 1, the study consisted of three single-arm cohorts and determined the dose of atezolizumab SC that yields comparable exposure to atezolizumab IV on the basis of serum C_{trough} at Cycle 1 (predose Cycle 2). Part 2 of 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 subcutaneous compared with atezolizumab intravenous (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. The efficacy analysis was considered to be exploratory.

In Part 2 (Phase III), a total of 371 patients were enrolled and randomized to receive either 1875 mg of atezolizumab subcutaneous Q3W or 1200 mg of atezolizumab intravenous Q3W. No dose reduction was allowed. The median time taken to administer atezolizumab via the subcutaneous route was approximately 7 minutes (range 3 to 14 minutes).

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 randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization.

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.

Study Results

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 corresponding GMR for Cycle 1 model-predicted for AUC from 0 to 21 days (AUC_{0-21d}) was 0.87 (90% CI: 0.83–0.92).

Table 23 Atezolizumab exposure (geometric mean with range and CV%) following subcutaneous or intravenous administration of atezolizumab

Co-primary Endpoints	Atezolizumab within Tecentriq SC (N=205 ^a /247 ^b)	Atezolizumab within Tecentriq (intravenous formulation) (N=97 ^a /122 ^b)	% Ratio of Geometric Means	Confidence Interval
Cycle 1 observed serum C _{trough} (µg/mL)	89.4 (127%)	85.4 (34%)	1.05	(0.88-1.24)

Cycle 1 model-predicted AUC _{0-21d} ^c (µg/mL•day)	2907 (36%)	3328 (19%)	0.87	(0.83-0.92)
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- a) Cycle 1 observed serum C_{trough}
b) Cycle 1 model-predicted AUC_{0-21d}
c) Model predicted exposure based on population pharmacokinetics analysis

Descriptive results of the exploratory analysis of the secondary efficacy endpoint investigator-assessed PFS were: Tecentriq SC: median duration of PFS = 2.8 months (95% CI: 2.1 – 3.1; 168 events out of 247 patients (68%)); Tecentriq (intravenous formulation): median duration of PFS = 2.9 months (95% CI: 1.7 – 4.2; 84 events out of 124 patients (68%). Descriptive results of the exploratory analysis of the secondary efficacy endpoint investigator-assessed ORR (RECIST v1.1) were: Tecentriq SC: ORR = 12% (29/245; 95% CI: 8.1 – 17); Tecentriq (intravenous formulation): ORR = 9.7% (12/124; 95% CI: 5.1 – 16).

INTRAVENOUS FORMULATION (Tecentriq)

Information in this section reports data from a separate Product Monograph for Tecentriq (intravenous formulation).

Extensive-Stage Small Cell Lung Cancer (ES-SCLC)

Study GO30081 (IMpower133) – First-Line Combination Therapy

Study Demographics and Trial Design

Table 24: Summary of patient demographics for Study GO30081 (IMpower133) in Extensive-Stage Small Cell Lung Cancer (ES-SCLC) Patients

Study Number	Study Design	Dosage, route of administration and duration	Study subjects (n)	Median age (range)	Sex
GO30081	Multicenter, double-blind, placebo-controlled, randomized study	Induction (4 cycles): atezolizumab 1200 mg IV or placebo q3w (day 1) carboplatin AUC 5mg/mL/min q3w (day 1) etoposide 100 mg/m ² IV q3w (days 1, 2, 3) Maintenance: atezolizumab 1200 mg IV or placebo q3w (day 1) Duration: atezolizumab: progressive disease or loss of clinical benefit carboplatin + etoposide: until completion of 4 cycles, progressive disease, unacceptable toxicity, or death, whichever occurs first	403	64 years (26 – 90)	M: 261 (65) F: 142 (35)

IV = Intravenous; Q3W = every three weeks

A Phase I/III, randomized, multicentre, double-blind, placebo controlled study, GO30081 (IMpower133), was conducted to evaluate the efficacy and safety of Tecentriq (intravenous formulation) in combination with carboplatin and etoposide in patients with chemotherapy-naïve ES-SCLC. The study enrolled patients with ES-SCLC who had received no prior chemotherapy for extensive stage disease and ECOG performance status 0 or 1. This study excluded patients who had active or untreated CNS metastases (patients with a history of treated asymptomatic CNS metastases were included); history of autoimmune disease; administration of live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunosuppressive medications within 1 week prior to randomization. Thoracic radiation with curative intent was not permitted.

Randomization was stratified by sex, ECOG performance status, and presence of brain metastases. A total of 403 patients were randomized (1:1) to receive one of the treatment regimens described in Table 25. Administration of Tecentriq (intravenous formulation) was permitted beyond RECIST-defined disease progression. Prophylactic cranial irradiation (PCI) was permitted during the maintenance phase in accordance with local standards of care.

Table 25 Intravenous Treatment Regimen in Study GO30081 (IMpower133)

Treatment regimen	Induction (Four 21-Day Cycles)	Maintenance (21-Day Cycles)
A	Tecentriq (intravenous formulation) (1200 mg) ^a + carboplatin (AUC 5) ^b + etoposide (100 mg/m ²) ^{b,c}	Tecentriq (intravenous formulation) (1200 mg) ^a
B	placebo + carboplatin (AUC 5) ^b + etoposide (100 mg/m ²) ^{b,c}	Placebo

^a Tecentriq (intravenous formulation) is administered until loss of clinical benefit as assessed by investigator; administer Tecentriq (intravenous formulation) prior to chemotherapy when given on the same day.

^b AUC5 was calculated using Calvert formula; 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.

Tumour assessments performed by the investigator according to RECIST v.1.1 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.

The co-primary efficacy endpoints were OS and PFS as assessed by the investigator according to RECIST v1.1. Additional study endpoints included ORR and DOR as assessed by the investigator per RECIST v1.1. One interim efficacy analysis of OS was planned for when approximately 240 OS events had been observed. The primary analysis of PFS was conducted at the same time as the interim OS analysis.

The demographic and baseline disease characteristics of the primary analysis population were 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 were current or previous smokers (97%). Baseline ECOG performance status was 0 (35%) or 1 (65%) and 9% of patients had brain metastases.

Study Results

At the time of the primary analysis, patients had a median survival follow up time of 13.9 months (range: 0.0 to 21.4 months). The key results are summarized in Table 26. Kaplan-Meier curves for OS and PFS are presented in Figure 1 and Figure 2, respectively.

Table 26 Summary of Efficacy from Study GO30081 (IMpower133)

Key efficacy endpoints	Arm A (Tecentriq (intravenous formulation) + 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 ¹ (95% CI)	0.70 (0.54, 0.91)	
p-value ²	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 ¹ (95% CI)	0.77 (0.62, 0.96)	
p-value ³	0.0170	
6-month PFS (%)	30.9	22.4
12-month PFS (%)	12.6	5.4
Secondary endpoints		
Investigator-assessed ORR (RECIST 1.1)	n = 201	n = 202
No. of responders (%)	121 (60.2%)	130 (64.4%)
95% CI	(53.1, 67.0)	(57.3, 71.0.)
No. of complete response (%)	5 (2.5%)	2 (1.0%)
No. of partial response (%)	116 (57.7%)	128 (63.4%)
Investigator-assessed DOR (RECIST 1.1)	n = 121	n = 130
Median in months	4.2	3.9
95% CI	(4.1, 4.5)	(3.1, 4.2)

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

¹ Based on Cox regression stratified by sex and ECOG performance status

² Based on the stratified log-rank test. Interim Analysis of OS was tested at two-sided alpha of 0.0193 (with 238 observed OS events at the time of analysis) to control the overall two-sided type I error for OS at 0.045 by Lan DeMets function approximating O'Brien-Fleming boundary

³ Based on the stratified log-rank test. Since the null hypothesis for OS was rejected at an overall two-sided significance level of 0.045, PFS was tested at two-sided type I error of 0.05

Figure 1 Kaplan-Meier Plot of Overall Survival in Study GO30081 (IMpower133)

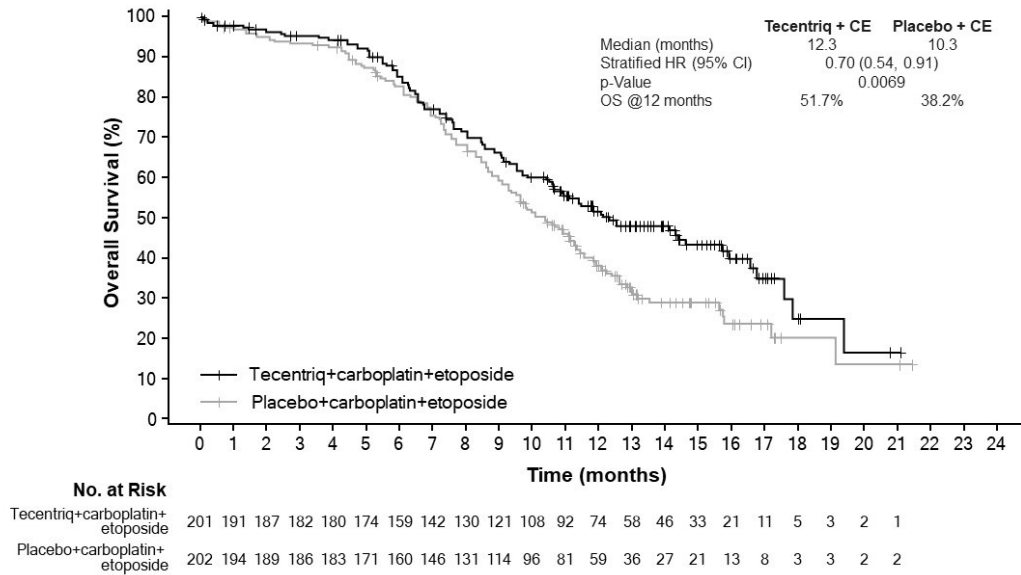
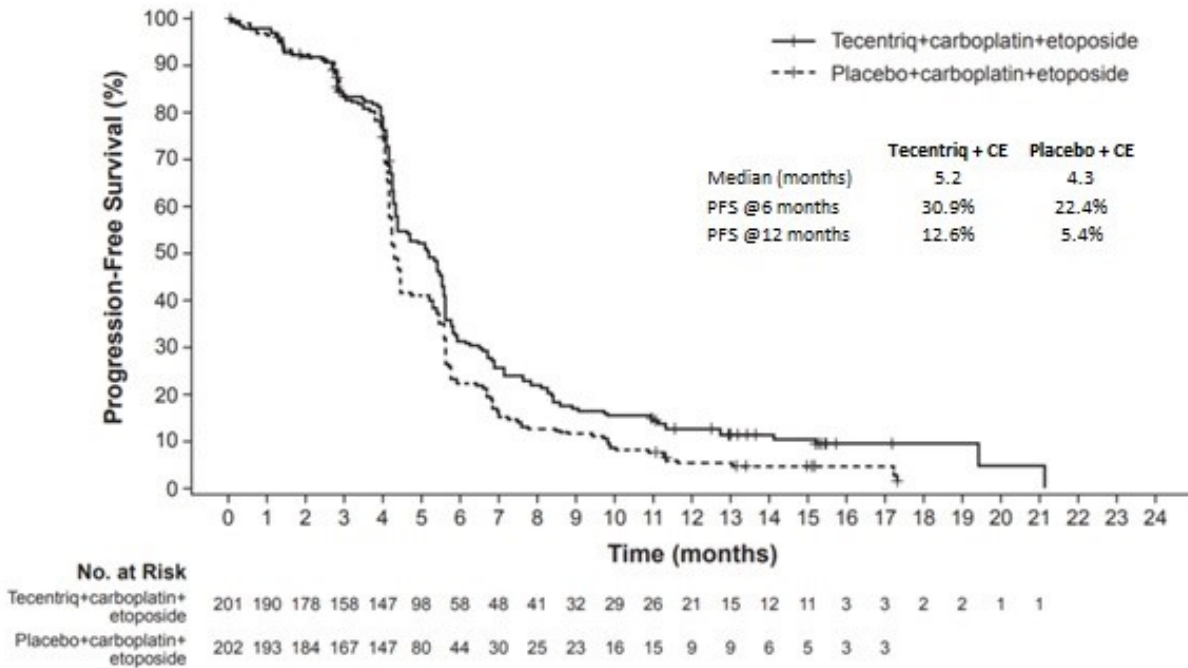


Figure 2 Kaplan-Meier Plot of Progression-Free Survival in Study GO30081 (IMpower133)



Adjuvant Treatment of Non-Small Cell Lung Cancer (NSCLC)

Study GO29527 (IMpower010) – Adjuvant Treatment of Early-Stage NSCLC

Study Demographics and Trial Design

Table 27 Summary of patient demographics for clinical trials in adjuvant treatment of early-stage NSCLC (IMpower010)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
GO29527 (IMpower010)	Phase III, open label, multicentre, randomized study to evaluate the efficacy and safety of Tecentriq (intravenous formulation) for the adjuvant treatment of patients with stage IB (tumors \geq 4 cm) – IIIA NSCLC (per the Union for International Cancer Control / American Joint Committee on Cancer staging system, 7th edition).	Tecentriq (intravenous formulation) 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.	1005 patients	62 years (26 to 84 years)	M: 67% F: 33%

Patients who had complete tumor resection and were eligible to receive cisplatin-based chemotherapy were enrolled. Subsequently, patients whose disease had not progressed following completion of cisplatin-based chemotherapy (up to four cycles) were randomized.

Patients were excluded if they had a history of autoimmune disease; a history of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis; administration of a live, attenuated vaccine within 28 days prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization.

A total of 1005 patients were randomized in a 1:1 ratio to receive Tecentriq (intravenous formulation) (Arm A) or best supportive care (BSC) (Arm B). Randomization was stratified by sex, stage of disease, histology, and PD-L1 expression.

Tumor assessments were conducted at baseline of the randomization 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.

In all randomized ITT patients, the median age was 62 years (range: 26 to 84), and 67% of patients were male. The majority of patients were White (73%), and Asian (24%). 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. PD-L1 expression, defined as the percentage of tumor cells (TC) expressing PD-L1 as measured by the VENTANA PDL1 (SP263) assay, was \geq 50% in 26% of patients, \geq 1% in 53% of patients, $<$ 1% in 44% and

unknown in 2.6%. The percentage of patients with non-squamous histology was 66%. Activating EGFR mutations were detected in 11.6% of patients, ALK mutations in 3.3% of patients.

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 randomization to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC, or death due to any cause, whichever occurred first. DFS was assessed hierarchically in the following analysis populations: patients with Stage II-IIIa NSCLC with PD-L1 expression $\geq 1\%$ TC, all randomized patients with Stage II-IIIa NSCLC, and all randomized ITT patients. DFS in the PD-L1 $\geq 50\%$ TC Stage II-IIIa population and OS in the ITT population were pre-specified key secondary endpoints.

Study Results

At the time of the interim DFS analysis, the study demonstrated a statistically significant improvement in DFS in the Tecentriq (intravenous formulation) arm compared to the BSC arm in the PD-L1 $\geq 1\%$ TC stage II – IIIa patient population (n=476). In the secondary objective analysis of patients with PD-L1 TC $\geq 50\%$ stage II to IIIa (n = 229), a clinically meaningful improvement in DFS in the Tecentriq (intravenous formulation) arm was shown compared to the BSC arm.

The efficacy findings for DFS in the PD-L1 expression $\geq 1\%$ TC, $\geq 50\%$ TC, and 1 – 49% TC Stage II-IIIa patient populations are shown in Table 28. The Kaplan-Meier curves for DFS in $\geq 50\%$ TC Stage II – IIIa patient population are presented in Figure 3. For the interim DFS analysis, the median follow-up time was 32 months.

Table 28 Summary of efficacy from IMpower010 in PD-L1 expression \geq 1% TC, \geq 50% TC, and 1 – 49% TC Stage II - IIIA patient populations

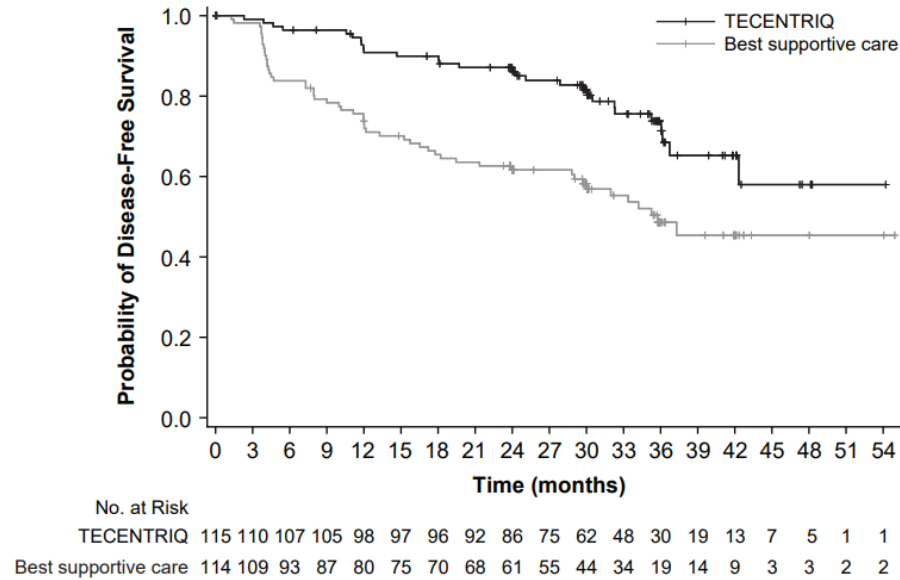
Efficacy endpoints Investigator-assessed DFS	Arm A (Tecentriq intravenous formulation)	Arm B (Best Supportive Care)
Primary Endpoint		
<i>DFS in PD-L1 SP263 \geq1% TC Stage II-III A</i>	n = 248	n = 228
No. of events (%)	88 (35.5)	105 (46.1)
Median duration of DFS (months)	NE	35.3
95% CI	36.1, NE	29.0, NE
Stratified* hazard ratio (95% CI)	0.66 (0.50, 0.88)	
p-value**	0.004	
Secondary Endpoint		
<i>DFS in PD-L1 SP263 \geq50% TC Stage II-III A</i>	n=115	n=114
No. of events (%)	28 (24.3%)	52 (45.6%)
Median duration of DFS (months)	NE	35.7
95% CI	42.3, NE	29.7, NE
Unstratified hazard ratio (95% CI)	0.43 (0.27, 0.68)	
Exploratory Endpoint		
<i>DFS in PD-L1 SP263 1-49% TC Stage II-III A</i>	n=133	n=114
No. of events (%)	60 (45.1%)	53 (46.5%)
Median duration of DFS (months)	32.8	31.4
95% CI	29.4, NE	24.0, NE
Unstratified hazard ratio (95% CI)	0.87 (0.60, 1.26)	

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

*Stratified by stage of disease, sex, and histology

** The p-value (two-sided) for DFS in PD-L1 SP263 \geq 1% TC Stage II-III A was compared with a two-sided significance level of 0.037 at the interim analysis.

Figure 3 Kaplan-Meier Plot of Disease-Free Survival in the PD-L1 expression \geq 50% TC Stage II – IIIA Patient Population



Metastatic Non-Small Cell Lung Cancer (NSCLC)

Study GO29431 (IMpower110) – First Line Monotherapy

Study Demographics and Trial Design

Table 29: Summary of patient demographics for Study GO29431 (IMpower110) in Metastatic Non-Small Cell Lung Cancer Patients

Study Number	Study Design	Dosage, route of administration and duration	Study subjects (n)	Median age (range)	Sex
GO29431	Phase III, multicenter, open-label, randomized, controlled study	Experimental Arm: atezolizumab 1200 mg IV q3w Control Arm: IV, q3w: - carboplatin AUC 6 or AUC 5 - cisplatin 75 mg/m ² - pemetrexed 500 mg/m ² - gemcitabine 1250 mg/m ² or 1000 mg/m ² Duration: atezolizumab: until loss of clinical benefit Induction: cisplatin, carboplatin, pemetrexed and gemcitabine are administered until	WT Population: 205	65 (33 -87)	M: 143 (70%) F: 62 (30%)

		completion of 4 or 6 cycles, or progressive disease, or unacceptable toxicity			
		Maintenance: pemetrexed is administered as maintenance regimen every 21 days until progressive disease or unacceptable toxicity			

Intent to Treat Wild Type Patients are populations excluding patients with a sensitizing EGFR mutation or ALK translocation; IV = Intravenous; Q3W = every three weeks; WT = Wild Type;

A phase III, open label, multi-center, randomized study, GO29431 (IMpower110), was conducted to evaluate the efficacy and safety of Tecentriq (intravenous formulation) in chemotherapy-naïve patients with metastatic NSCLC whose tumours express PD-L1 \geq 1% tumour cells (TCs) (PD-L1 stained \geq 1% of TCs) or \geq 1% immune cells (ICs) (PD-L1 stained tumour-infiltrating ICs covering \geq 1% of the tumour area) by the VENTANA PD-L1 (SP142) Assay.

A total of 572 non-squamous or squamous patients were randomized in a 1:1 ratio to receive Tecentriq (intravenous formulation) (Arm A) or chemotherapy (Arm B). The wild-type population (n=554) was defined as all randomized patients excluding patients with a sensitizing EGFR mutation or ALK translocation. Tecentriq (intravenous formulation) 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 30. Randomization was stratified by sex, ECOG performance status, histology (non-squamous vs. squamous), and PD-L1 tumour expression on TCs and ICs (TCs \geq 1% and any ICs vs. TCs < 1% and ICs \geq 1%). Patients were excluded if they had history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; 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.

Tumour tissues were prospectively tested for PD-L1 expression using the VENTANA PD-L1 (SP142) assay at a central laboratory to define subgroups for pre-specified analyses. The primary endpoint was overall survival (OS). OS was sequentially tested in the following PD-L1 subgroups of patients without EGFR or ALK genomic tumour aberrations: TCs \geq 50% or ICs \geq 10%; TCs \geq 5% or ICs \geq 5%; and TCs \geq 1% or ICs \geq 1%.

Table 30 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/m ²) + pemetrexed ^a (500 mg/m ²) OR carboplatin ^a (AUC 6) + pemetrexed (500 mg/m ²)	Pemetrexed ^{b, d} (500 mg/m ²)
B (Squamous)	Cisplatin ^a (75 mg/m ²) + 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)

The demographics and baseline disease characteristics in the 205 wild-type patients with high PD-L1 expression (PD-L1 \geq 50% TC or \geq 10% IC) who do not have EGFR or ALK genomic tumour aberrations were generally balanced between the treatment arms. The median age was 65 years (range: 33 to 87), and 70% of patients were male. The majority of patients were white (82%) and Asian (17%). Most patients were current or previous smokers (88%) and baseline ECOG performance status in patients was 0 (36%) or 1 (64%). Overall, 76% of patients had non-squamous disease and 24% of patients had squamous disease. The median follow-up in patients with high PD-L1 expression (TCs \geq 50% or ICs \geq 10%) was 16.5 months in the Tecentriq (intravenous formulation) arm and 15.5 months in the chemotherapy arm.

Study Results

OS results for high PD-L1 subgroup (TCs \geq 50% or ICs \geq 10%) are presented in Table 31 and Figure 4. Statistically significant OS benefit was not observed for the TCs \geq 5% or ICs \geq 5% and TCs \geq 1% or ICs \geq 1% subgroups at prespecified analyses.

Table 31 Summary of Efficacy from Study GO29431 (IMpower110) in Patients with High PD-L1 Expression (TCs \geq 50% or ICs \geq 10%) by the VENTANA PD-L1 [SP142] Assay)

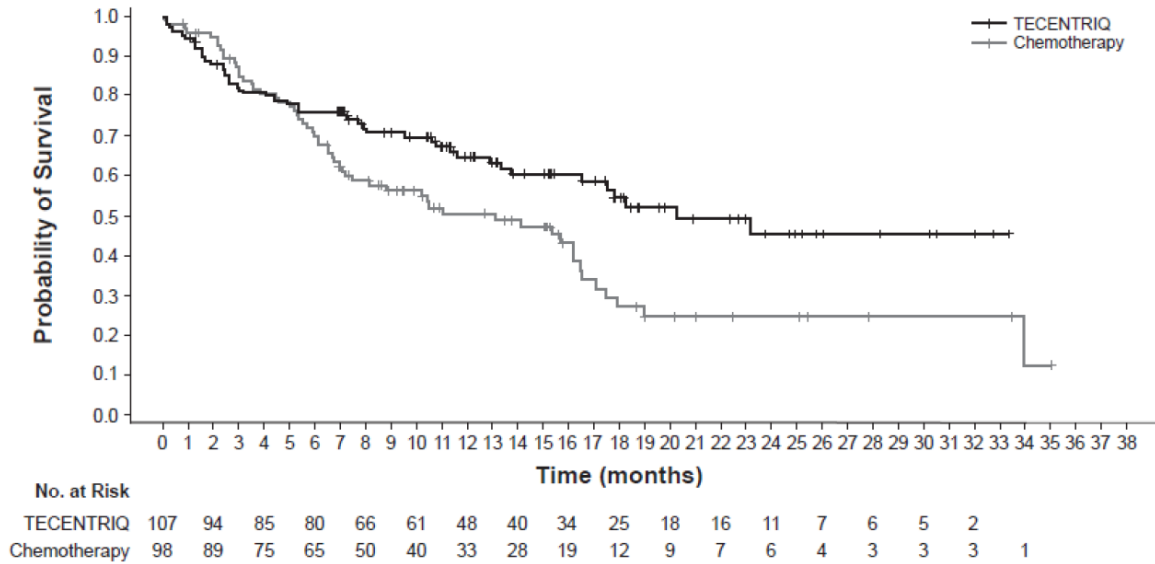
Key Efficacy Endpoints	Arm A (Tecentriq)	Arm B (Chemotherapy)
Primary endpoint		
OS analysis	n=107	n=98
No. of deaths (%)	44 (41.1%)	57 (58.2%)
Median overall survival time (months)	20.2	13.1
95% CI	(16.5, NE)	(7.4, 16.5)
Stratified hazard ratio [‡] (95% CI)	0.59 (0.40, 0.89)	
p-value [‡]	0.0106	

[‡] Stratified by sex and ECOG performance status (0 vs 1)

CI=confidence interval; OS=overall survival; NE=not estimable.

The p-value (two-sided) was compared with the allocated alpha of 0.0413 at the interim analysis.

Figure 4 Kaplan-Meier Plot of Overall Survival in Patients with high PD-L1 Expression (TCs \geq 50% or ICs \geq 10%)



Investigator-assessed PFS showed a HR of 0.63, with median PFS of 8.1 months in the Tecentriq (intravenous formulation) arm and 5 months in the platinum-based chemotherapy arm. The investigator-assessed confirmed ORR was 38% in the Tecentriq (intravenous formulation) arm and 29% in the platinum-based chemotherapy arm.

Metastatic Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

Study GO29436 (IMpower150) - First-Line Combination Therapy

Study Demographics and Trial Design

Table 32: Summary of patient demographics for Study GO29436 (IMpower150) in Metastatic Non-Squamous Non-Small Cell Lung Cancer Patients

Study Number	Study Design	Dosage, route of administration and duration	Study subjects (n)	Median age (range)	Sex
GO29436	Multicentre, open-label, randomized, controlled study	Arm A: atezolizumab + paclitaxel + carboplatin Arm B: atezolizumab + bevacizumab + paclitaxel + carboplatin Arm C: bevacizumab + paclitaxel + carboplatin atezolizumab 1200 mg IV q3w carboplatin AUC 6mg/mL/min q3w paclitaxel 200 mg/m ² IV q3w	1202	63 (31 – 90)	M: 720 (60) F: 482 (40)

		bevacizumab 15 mg/m ² IV q3w Duration: atezolizumab: until loss of clinical benefit bevacizumab: until disease progression, unacceptable toxicity, or death carboplatin + paclitaxel: until completion of 4 or 6 cycles, progressive disease, unacceptable toxicity, or death, whichever occurs first			
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IV = intravenous; q3w = every three weeks A phase III, open-label, multicentre, international randomized study, GO29436 (IMpower150), was conducted to evaluate the efficacy and safety of Tecentriq (intravenous formulation) 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 randomized in a 1:1:1 ratio to receive one of the treatment regimens. For this indication, only the comparison for Arm B versus Arm C has been reviewed and included in this product monograph.

Patients were randomized to one of the following three treatment arms.

- Arm A: Tecentriq (intravenous formulation) 1200 mg, paclitaxel 175 mg/m² or 200 mg/m² and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles
- Arm B: Tecentriq (intravenous formulation) 1200 mg, bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles
- Arm C: bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles

Patients who had not experienced disease progression following the completion or cessation of platinum-based chemotherapy, received:

- Arm A: Tecentriq (intravenous formulation) 1200 mg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity
- Arm B: Tecentriq (intravenous formulation) 1200 mg and bevacizumab 15 mg/kg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity
- Arm C: bevacizumab 15 mg/kg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity

The paclitaxel starting dose for patients of Asian race/ethnicity was 175 mg/m² due to higher overall level of hematologic toxicities in patients from Asian countries compared with those from non-Asian countries.

Randomization was stratified by sex, presence of liver metastases and PD-L1 tumour expression on tumour cells (TC) and tumour infiltrating cells (IC) as follows: TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1.

The PFS and OS results are based on the ITT-WT population, defined as the ITT population excluding EGFR mutations or ALK rearrangements.

Patients were excluded if they had history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; active or untreated brain 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 (82.2%), 12.5% of patients were Asian, and 2.0% of patients were Black or African American. Hispanic or Latino patients represents 9.6% of the enrolled patients. Patients of Asian race/ethnicity received paclitaxel at a dose of 175 mg/m² while the remaining patients received paclitaxel at a dose of 200 mg/m². 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%). Baseline ECOG performance status was 0 (43%) or 1 (57%). PD-L1 was TC3 and any IC in 12%, TC0/1/2 and IC2/3 in 12.8% and TC0/1/2 and IC0/1 in 75.2%.

The median duration of exposure to Tecentriq (intravenous formulation) was 8.3 months in patients receiving Tecentriq with bevacizumab, paclitaxel and carboplatin.

The major efficacy outcome measures were investigator-assessed progression-free survival (PFS) using RECIST v1.1 and overall survival (OS). The primary analysis population excluded patients with EGFR mutations or ALK rearrangements.

Study Results

The results of the primary analysis demonstrated a statistically significant PFS improvement in Arm B as compared to Arm C (HR: 0.62 [95% CI: 0.52, 0.74] median PFS 8.3 vs. 6.8 months). The improvement was maintained at the next PFS update which was conducted at the next OS interim analysis (HR: 0.59 [95% CI: 0.50, 0.70] median PFS 8.3 vs. 6.8 months); the results from this analysis are summarized in Table 33. Kaplan-Meier curves for PFS are presented in Figure 5.

The interim analysis of the co-primary endpoint OS was performed when all patients had a median follow up time of 19.6 months (Arm B) and 19.7 months (Arm C); the results of the analysis demonstrated a statistically significant OS improvement in Arm B as compared to Arm C (HR: 0.78 [95% CI: 0.64, 0.96] median OS 19.2 vs. 14.7 months); the results from this analysis are summarized in Table 33. Kaplan-Meier curves for OS are presented in Figure 6.

Table 33 Primary Efficacy Endpoints in the ITT-WT population in GO29436, (IMpower150), data cut of 22 January 2019

Key Efficacy Endpoints (Primary Analysis Population)	Arm B: TECENTRIQ (intravenous formulation) + bevacizumab + paclitaxel + carboplatin	Arm C: bevacizumab + paclitaxel + carboplatin
Co-Primary Efficacy Endpoints		
Investigator-assessed PFS (RECIST v1.1)	n=359	n=337
No. of events (%)	263 (73.3%)	298 (88.4%)
Median duration of PFS (months)	8.3	6.8
95% CI	(7.7, 9.8)	(6.0, 7.1)
Stratified hazard ratio ¹ (95% CI)	0.59 (0.50, 0.70)	
p-value ²	< 0.0001	
OS	n=359	n=337
No. of deaths (%)	179 (49.9%)	197 (58.5%)
Median time to events (months)	19.2	14.7
95% CI	(17.4, 23.8)	(13.3, 16.9)
Stratified hazard ratio (95% CI)	0.78 (0.64, 0.96)	
p-value ²	0.0164	

¹Stratified 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; OS=overall survival

²Based on the stratified log-rank test. The overall two-sided type I error of 0.05 was controlled by splitting it to 0.012 and 0.038, and allocated to the co-primary endpoints of PFS and OS, respectively. For the testing of OS, the statistically boundary for interim analysis was further accounted for following group sequential design using Lan-Demets approximation to the O'Brien-Fleming boundary

The results for the secondary efficacy endpoint of investigator-assessed overall best response showed higher overall response rate (ORR) in Arm B (55.3%, 95% CI: 50.0, 60.6) compared with Arm C (40.4%, 95% CI: 35.0, 45.9).

The results for the secondary efficacy endpoint of investigator-assessed DOR indicate prolonged DOR among confirmed responders for Arm B compared to Arm C: 11.5 months (95% CI: 8.9, 16.2) vs. 6.4 months (95% CI: 5.7, 7.0) respectively.

Figure 5 Kaplan-Meier Curves for Progression Free Survival (PFS) in the ITT-WT Population in GO29436 (IMpower150)

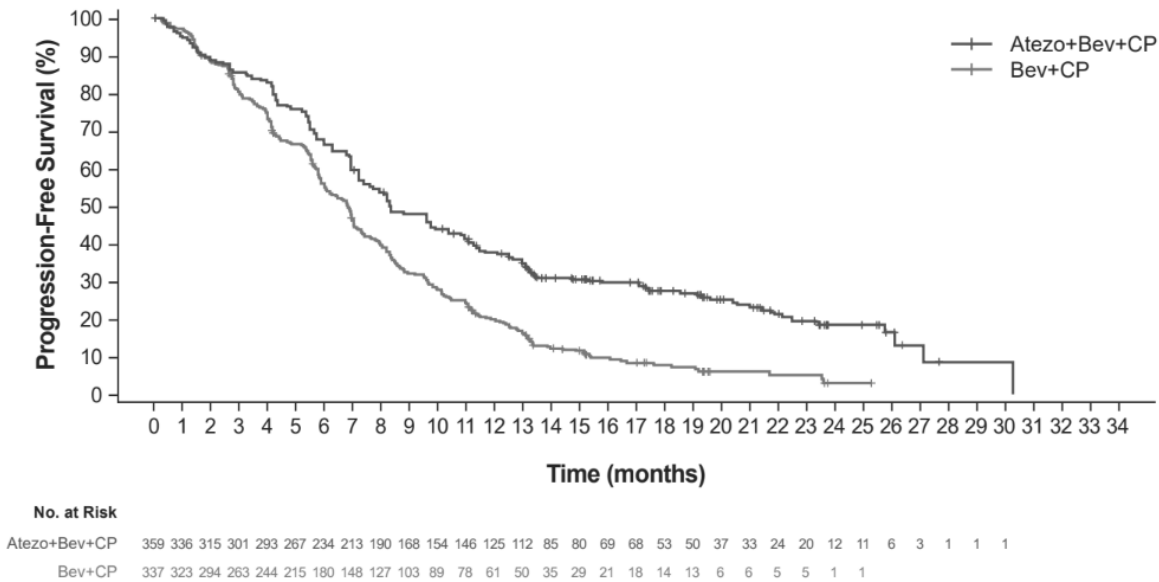
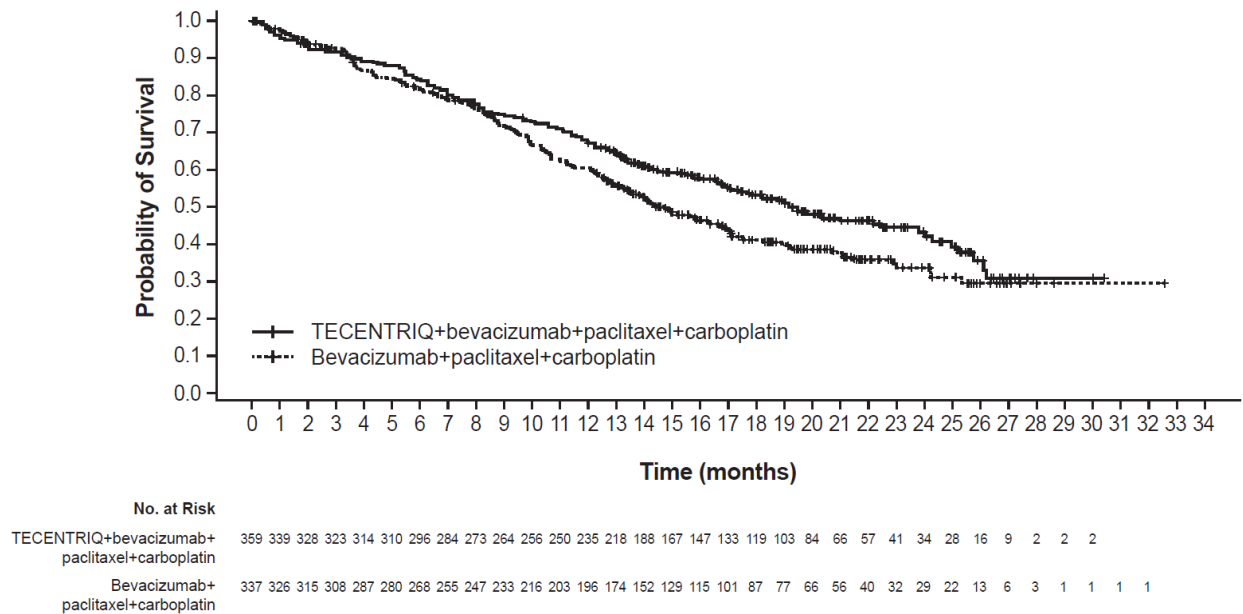


Figure 6 Kaplan-Meier Curves for Overall Survival (OS) the ITT-WT Population in GO29436 (IMpower150)



Study GO29537 (IMpower130) – First-Line Combination Therapy

Study Demographics and Trial Design

Table 34: Summary of patient demographics for Study GO29537 (IMpower130) in Metastatic Non-Squamous Non-Small Cell Lung Cancer Patients

Study Number	Study Design	Dosage, route of administration and duration	Study subjects (n)	Median age (range)	Sex
GO29537	Phase III, multicentre, open-label, randomized, controlled study	<p>Arm A: atezolizumab + carboplatin + nab-paclitaxel</p> <p>Arm B: carboplatin + nab-paclitaxel</p> <p>atezolizumab 1200 mg IV q3w</p> <p>carboplatin AUC 6mg/mL/min IV q3w</p> <p>nab-paclitaxel 100 mg/m² IV Day 1, 8, and 15 of each 21-day cycle</p> <p>Duration:</p> <p>atezolizumab + carboplatin + nab-paclitaxel: until loss of clinical benefit</p> <p>carboplatin + nab-paclitaxel: until completion of 4 or 6 cycles, progressive disease, or unacceptable toxicity</p>	723	64 years (18-86)	<p>M: 415 (57%)</p> <p>F: 308 (43%)</p>

IV = Intravenous; q3w = every three weeks

A Phase III, open-label, randomized study, GO29537 (IMpower130) was conducted to evaluate the efficacy and safety of Tecentriq (intravenous formulation) 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 randomized in a 2:1 ratio to receive one of the treatment regimens described in Table 35. Randomization was stratified by sex, presence of liver metastases and PD-L1 tumour expression on tumour cells (TC) and tumour infiltrating cells (IC). Patients in treatment regimen B (Nab-paclitaxel (100mg/m²)^b + Carboplatin (AUC 6)^c) were able to crossover and receive Tecentriq (intravenous formulation) monotherapy following disease progression.

Table 35 Intravenous treatment regimens in GO29537 (IMpower130)

Treatment Regimen	Induction (Four or Six 21-Day Cycles)	Maintenance (21-Day Cycles)
A	Tecentriq (intravenous formulation) (1200mg) ^a + nab-paclitaxel (100mg/m ²) ^{b,c} + carboplatin (AUC 6) ^c	Tecentriq (intravenous formulation) (1200mg) ^a
B	Nab-paclitaxel (100mg/m ²) ^b + Carboplatin (AUC 6) ^c	Best supportive care or pemetrexed

^a Tecentriq is administered until loss of clinical benefit as assessed by investigator

^b Nab-paclitaxel is administered on days 1, 8, and 15 of each cycle

^c Nab-paclitaxel and carboplatin is administered until completion of 4-6 cycles, or progressive disease or unacceptable toxicity whichever occurs first

Patients were excluded if they had history of autoimmune disease, administration of live, attenuated vaccine within 28 days prior to randomization, administration of immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization, 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%).

Study Results

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 (intravenous formulation)+ nab-paclitaxel + carboplatin compared to the control. The key results are summarized in Table 36 and Kaplan-Meier curves for OS and PFS are presented in Figure 7 and

Figure 9, respectively.

All PD-L1 subgroups, regardless of expression, derived benefit in terms of OS and PFS; the results are summarized in Figure 8 and Figure 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 (intravenous formulation), 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 (intravenous formulation), nab-paclitaxel and carboplatin arm. These included, approximately 59% of patients in the nab-paclitaxel and carboplatin arm received any cancer immunotherapy after disease progression, which includes Tecentriq (intravenous formulation) as crossover (41% of all patients), compared to 7.3% in the Tecentriq (intravenous formulation), nab-paclitaxel and carboplatin arm.

Table 36 Summary of efficacy from GO29537 (IMpower130) in the Primary Analysis Population

Key efficacy endpoints	Tecentriq (INTRAVENOUS FORMULATION) + 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	56
Investigator-assessed PFS (RECIST v1.1)	n = 451	n = 228
No. of events (%)	347 (76.9)	198 (86.8)
Median duration of PFS (months)	7.0	5.5
95% CI	(6.2, 7.3)	(4.4, 5.9)
Stratified hazard ratio [†] (95% CI)	0.64 (0.54, 0.77)	
p-value	< 0.0001	

Key efficacy endpoints	Tecentriq (INTRAVENOUS FORMULATION) + nab-paclitaxel + carboplatin	nab-paclitaxel + carboplatin
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 Plot for Overall Survival GO29537 (IMpower130)

p-value (log-rank)
Atezo+CnP (Randomized) (N=451): 0.0331
Median + 95% CI
CnP (Randomized) (N=228): 13.9 (12.0, 18.7)
Atezo+CnP (Randomized) (N=451): 18.6 (16.0, 21.2)
Hazard Ratio + 95% CI
Atezo+CnP (Randomized) (N=451): 0.79 (0.64, 0.98)

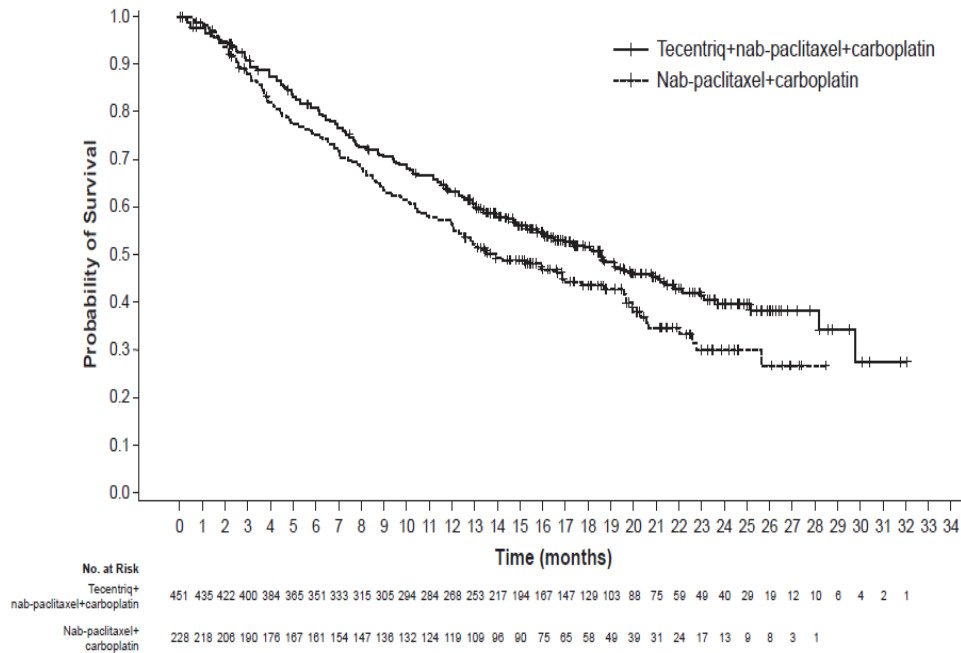


Figure 8 Forest Plot of Overall Survival by PD-L1 expression GO29537 (IMpower130)

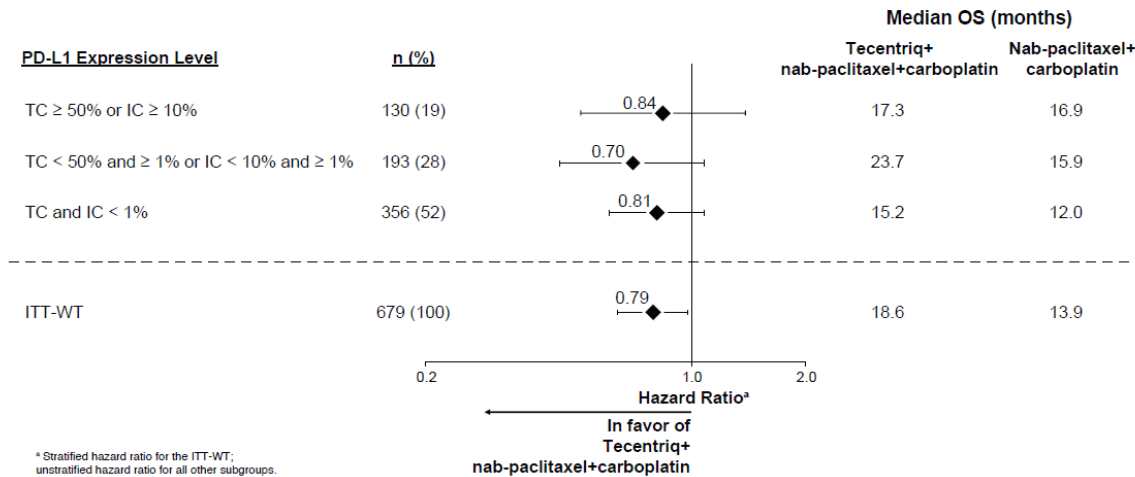


Figure 9 Kaplan-Meier Plot for Progression Free Survival (PFS) GO29537 (IMpower130)

p-value (log-rank)
 Atezo+CnP (Randomized) (N=451): <.0001
 Median + 95% CI
 CnP (Randomized) (N=228): 5.5 (4.4, 5.9)
 Atezo+CnP (Randomized) (N=451): 7.0 (6.2, 7.3)
 Hazard Ratio + 95% CI
 Atezo+CnP (Randomized) (N=451): 0.64 (0.54, 0.77)

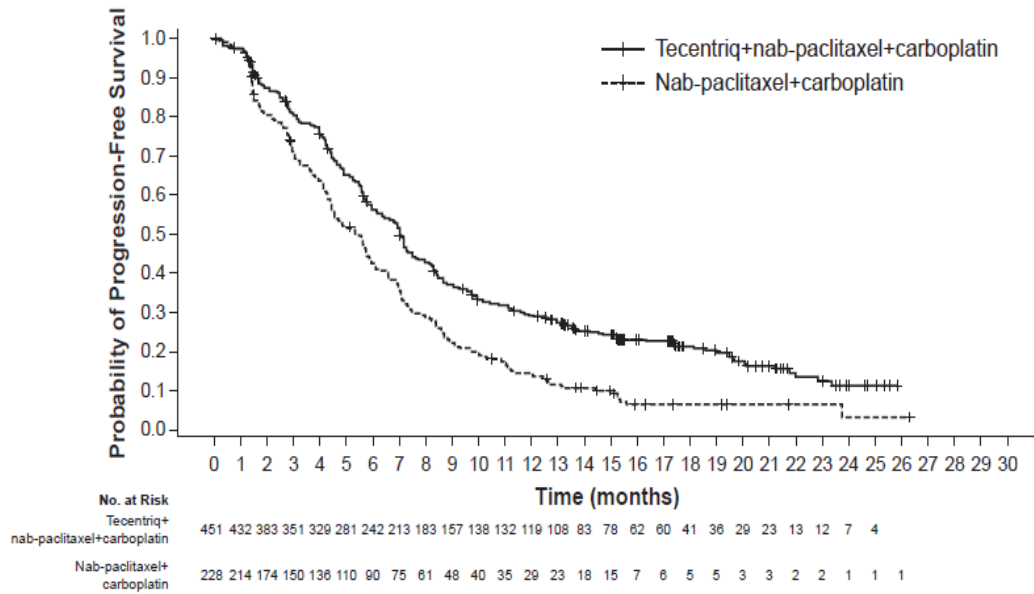
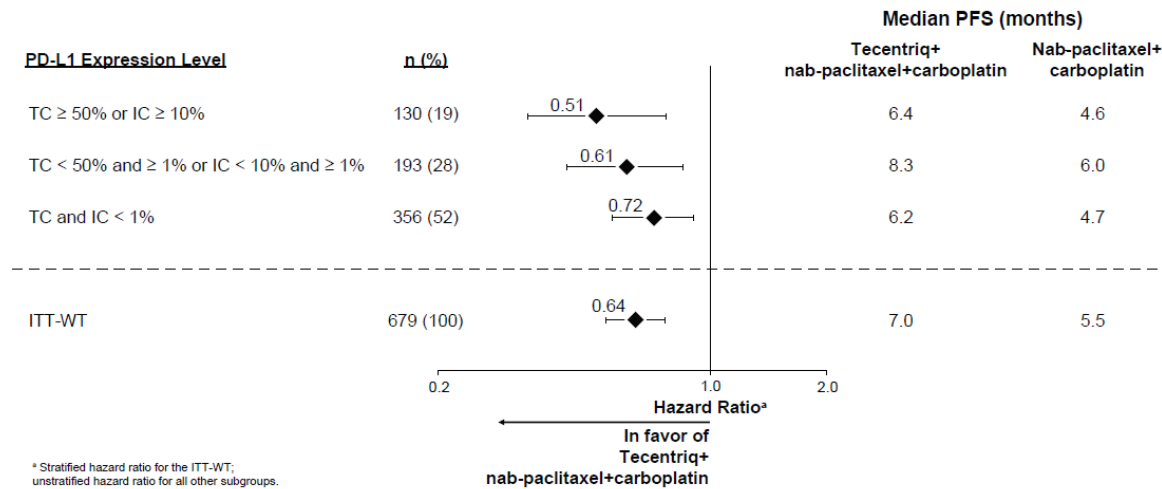


Figure 10 Forest Plot of Progression Free Survival (PFS) by PD-L1 expression GO29537 (IMpower130)



Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Study GO28915 (OAK) – Second Line Monotherapy

Study Demographics and Trial Design

Table 37: Summary of patient demographics for Study GO28915 (OAK) in Locally Advanced or Metastatic Non-Small Cell Lung Cancer Patients

Study Number	Study Design	Dosage, route of administration and duration	Study subjects (n)	Median age (range)	Sex

GO28915	Phase III, multicentre, open-label, randomized, controlled	atezolizumab 1200 mg IV q3w docetaxel 75 mg/m ² IV q3w Duration: Atezolizumab arm: Until loss of clinical benefit or unacceptable toxicity Docetaxel arm: Until disease progression or unacceptable toxicity	Total randomized: 1225		
			Primary Population:		
			First 850 randomized intent-to-treat patients	64 (33-85)	M: 520 (61%) F: 330 (39%)

IV = Intravenous; Q3W = every three weeks

A phase III, open-label, multi-center, international, randomized study, GO28915 (OAK), was conducted to evaluate the efficacy and safety of Tecentriq (intravenous formulation) 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 randomized 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 randomized (1:1) to receive either Tecentriq (intravenous formulation) or docetaxel. This study excluded patients who had a history of autoimmune disease, active or corticosteroid-dependent brain metastases, HIV, Hepatitis B or Hepatitis C infection, 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 using the VENTANA PD-L1 (SP142) Assay and the results were used to define the PD-L1 expression subgroups for the analyses described below.

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-fourths of patients had non-squamous disease (74%), 10% had known EGFR mutation, 0.2% had known ALK rearrangements, 10% had brain 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 (intravenous formulation) was administered as a fixed dose of 1200 mg by IV infusion every 3 weeks. No dose reduction was allowed. Patients were treated until unacceptable toxicity or disease progression. However, treatment with Tecentriq (intravenous formulation) was permitted until loss of clinical benefit (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Duration of Treatment).

Docetaxel was administered at 75 mg/m² by IV infusion on day 1 of each 21-day cycle until unacceptable toxicity or 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 (intravenous formulation) arm.

The primary efficacy endpoint was Overall Survival (OS) in the primary analysis population (first 850 randomized patients). Key secondary efficacy endpoints were Investigator-assessed PFS, Investigator-assessed ORR, and Investigator-assessed DOR.

Study Results

The key results of this study with a median survival follow-up of 21 months are summarized in Table 38.

Table 38 Summary of Efficacy from Pivotal Study GO28915 (OAK)

Efficacy Endpoints	Tecentriq (intravenous formulation)	Docetaxel
Primary Efficacy Endpoint		
Overall Survival (OS)		
All Patients*	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)
^a Stratified hazard ratio (95% CI)	0.73 (0.62, 0.87)	
p-value**	0.0003	
12-month OS (%)	218 (55%)	151 (41%)
18-month OS (%)	157 (40%)	98 (27%)
Secondary Endpoints		
Investigator-assessed PFS (RECIST v1.1)		
All Patients	n=425	n=425
No. of deaths (%)	380 (89%)	375 (88%)
Median time to events (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 Patients	n=425	n=425
No. of responders (%)	58 (14%)	57 (13%)
95% CI	(10.5, 17.3)	(10.3, 17.0)
Complete Response	6 (1%)	1 (<1%)
Partial Response	52 (12%)	56 (13%)
Investigator-assessed DOR (RECIST v1.1)		
All Patients	n=58	n=57
Median in months	16.3	6.2
95% CI	(10.0, NE)	(4.9, 7.6)

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

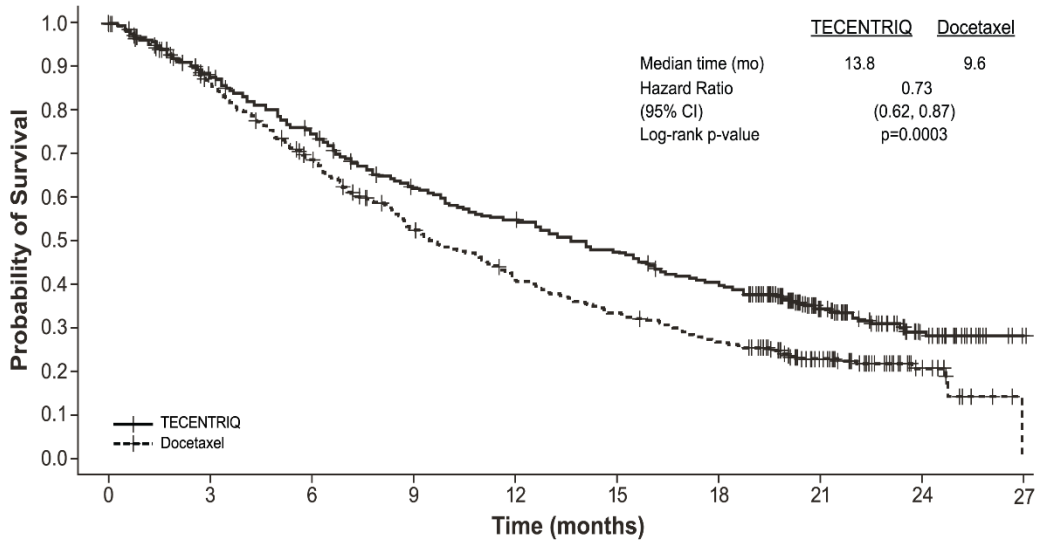
*All patients refer to the primary analysis population consisting of the first 850 randomized patients

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

** Based on the stratified log-rank test

Kaplan-Meier curves for OS in the intention-to-treat (ITT) population are presented in Figure 11.

Figure 11 Kaplan-Meier Plot for Overall Survival in the Primary Analysis Population (All Patients, GO28915)

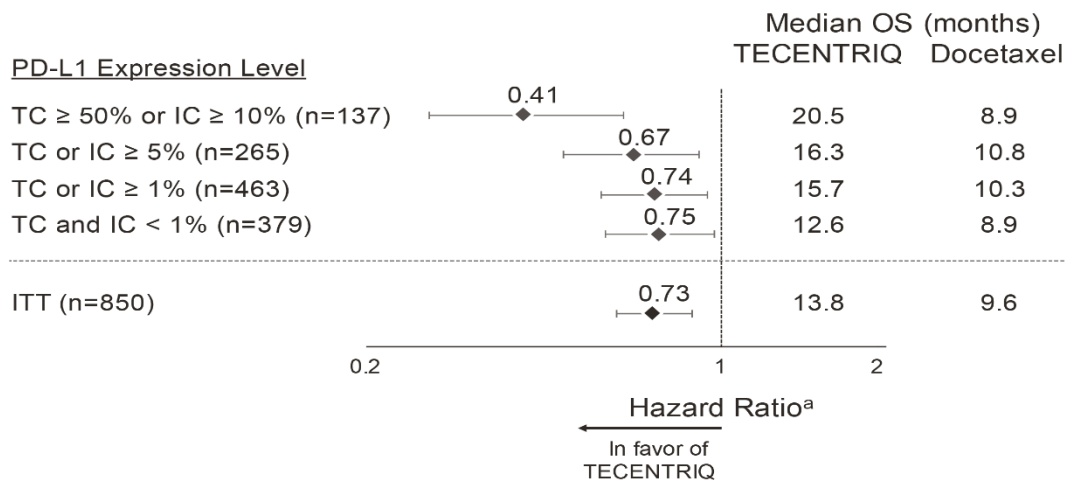


No. Patients at Risk																												
TECENTRIQ	425	407	382	363	342	326	305	279	260	248	234	223	218	205	198	188	175	163	157	141	116	74	54	41	28	15	4	1
Docetaxel	425	390	365	336	311	286	263	236	219	195	179	168	151	140	132	123	116	104	98	90	70	51	37	28	16	6	3	

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

Figure 12 summarizes the results of OS in the ITT and PD-L1 subgroups, demonstrating OS benefit with Tecentriq (intravenous formulation) in all subgroups, including those with PD-L1 expression <1% in TC and IC.

Figure 12 Forest Plot of Overall Survival by PD-L1 Expression in the Primary Analysis Population GO28915 (OAK)



^aStratified HR for ITT and TC or IC ≥ 1%. Unstratified HR for other subgroups

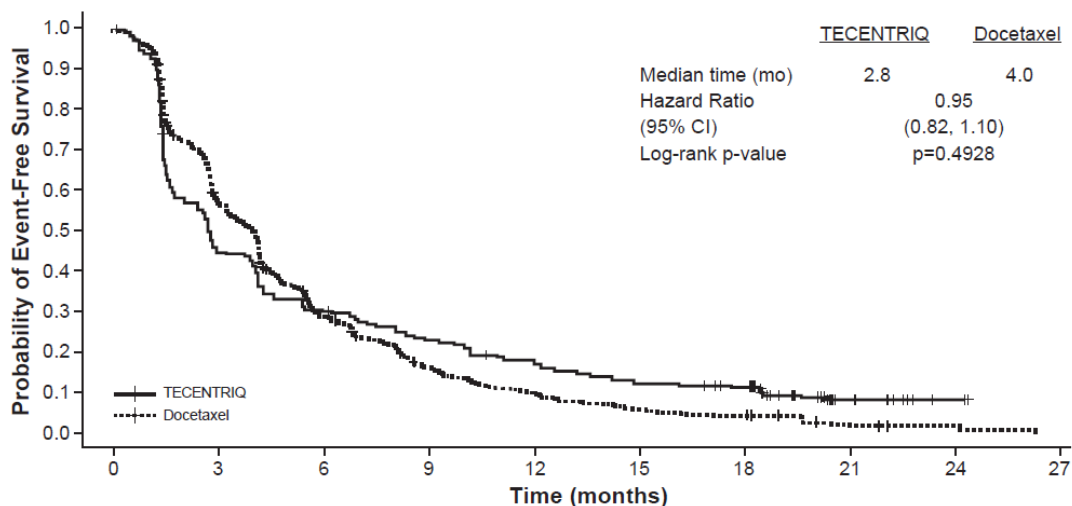
In an exploratory efficacy subgroup analysis based on histology, an improvement in OS was observed with Tecentriq (intravenous formulation) compared to docetaxel in both non-squamous NSCLC patients (hazard ratio [HR] of 0.73, 95% CI: 0.60, 0.89; median OS of 15.6 vs. 11.2 months for Tecentriq (intravenous formulation) 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 (intravenous formulation) and docetaxel, respectively).

Tumour specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define the PD-L1 expression subgroups for pre-specified analyses. Of the 850 patients constituting the primary analysis population, 16% were classified as having the highest PD-L1 expression, defined as PD-L1 expression on ≥ 50% of TC or ≥ 10% of IC, and 45% were classified as having the lowest (absence of discernable staining or presence of < 1 % TC or IC).

The primary efficacy endpoint was OS. In all patients (the primary analysis population consisting of the first 850 randomized patients), the hazard ratio was 0.73 (95% CI: 0.62, 0.87). In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, improved OS for atezolizumab relative to docetaxel was observed across all PD-L1 expression subgroups. In the highest PD-L1 expression subgroup (≥ 50% TC or ≥ 10% IC), numerically more pronounced benefit was observed, with a hazard ratio of 0.41 (95% CI: 0.27, 0.64). In the TC1/2/3 or IC1/2/3 PD-L1 expression subgroup (TC or IC ≥ 1%), OS benefit was demonstrated for atezolizumab vs. docetaxel, with the HR = 0.74 (95% CI: 0.58, 0.93). In the lowest expression subgroup (absence of discernable staining or presence of < 1% TC or IC), OS benefit was also demonstrated for atezolizumab vs. docetaxel, with the HR= 0.75 (95% CI: 0.59, 0.96).

PFS was one of the secondary efficacy endpoints. Delayed crossing of the progression-free survival (PFS) curves on Kaplan-Meier plots was noted. The study was not specifically powered to assess statistical significance of PFS. Per investigator-assessed RECIST v.1.1 in the primary analysis population, the hazard ratio was 0.95 [95% CI: 0.82, 1.10]. See Figure 13.

Figure 13 Kaplan-Meier Plot for Progression-Free Survival in the Primary Analysis Population (All Patients, GO28915)



No. Patients at Risk

TECENTRIQ	425	395	243	190	181	139	128	119	111	99	92	80	75	64	59	53	51	49	45	29	22	12	9	7	2		
Docetaxel	425	385	283	223	198	142	110	91	81	60	50	41	38	29	27	23	19	17	16	13	11	5	4	2	2	1	1

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

GO28753 (POPLAR)

Study Demographics and Trial Design

Table 39: Summary of patient demographics in Study GO28753 in Non-Small Cell Lung Cancer patients

Study Number	Study Design	Dosage, route of administration and duration	Study subjects (n)	Median age (range)	Sex
GO28752	Phase II, multicentre, open-label, randomized, controlled study	atezolizumab 1200 mg IV q3w until loss of clinical benefit or docetaxel 75 mg/m ² IV q3w until disease progression or unacceptable toxicity	287	62 years (36 – 84)	M: 169 (59%) F: 118 (41%)

IV = Intravenous; q3w = every three weeks

A phase II, multi-center, international, randomized, open-label, controlled study GO28753 (POPLAR), was conducted in patients with locally advanced or metastatic NSCLC. The primary efficacy outcome was overall survival. A total of 287 patients were randomized 1:1 to receive either Tecentriq (intravenous formulation) or docetaxel. Randomization was stratified by PD-L1 expression status in IC, by the number of prior chemotherapy regimens and by histology.

Study Results

At the time of the primary analysis with 173 events (deaths), OS was observed for patients assigned to atezolizumab in the all-comer (ITT) population compared with docetaxel (HR = 0.73; 95% CI: [0.53, 0.99]; p= 0.0404; median OS 9.7 months in the docetaxel arm versus 12.6 months in the atezolizumab

arm. Results of an updated post-hoc 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 (intravenous formulation), 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 (intravenous formulation) vs. docetaxel, respectively.

Unresectable or Metastatic Hepatocellular Carcinoma

Study YO40245 (IMbrave150) - First-Line Combination Therapy

Study Demographics and Trial Design

Table 40: Summary of patient demographics for Study YO40245 (IMbrave150) in Unresectable or Metastatic Hepatocellular Carcinoma Patients

Study Number	Study Design	Dosage, route of administration and duration	Study subjects (n)	Median age (range)	Sex
YO40245	Phase III, multicenter, randomized, open-label study	Atezo: IV, 1200 mg Q3W Bev: IV, 15 mg/kg Q3W or Sorafenib: 400 mg PO, BID, continuously Duration: Patients received treatment until unacceptable toxicity or loss of clinical benefit as determined by the Investigator after an integrated assessment of radiographic and biochemical data, and clinical status	501	65 years (26-88)	M: 414 (83%) F: 87 (17%)

Atezo = Atezolizumab; Bev = Bevacizumab; BID = twice per day; IV = Intravenous; PO = dosed by mouth; Q3W = every three weeks

A global phase III, randomized, multi-centre, open-label study, YO40245 (IMbrave150), was conducted to evaluate the efficacy and safety of Tecentriq (intravenous formulation) in combination with bevacizumab, compared to sorafenib, as first-line systemic treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC). A total of 501 patients were randomized (2:1) to receive either Tecentriq (intravenous formulation) 1200 mg and 15 mg/kg of bevacizumab every 3 weeks administered via IV infusion (n = 336), or sorafenib 400 mg orally twice per day (n = 165). Randomization was stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion, extrahepatic spread (presence vs. absence), baseline alpha-fetoprotein (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 (intravenous formulation) 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 or 1 and who had not received prior systemic treatment for HCC. Patients who were Child-Pugh B were excluded from the study and no information on the safety and efficacy of Tecentriq (intravenous formulation) plus bevacizumab is available from YO40245 in these patients. 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.

Other exclusions included patients with moderate or severe ascites; a history of abdominal or tracheoesophageal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess within 6 months prior to initiation of study treatment; an intra-abdominal inflammatory process within 6 months prior to initiation of study treatment; a history of hepatic encephalopathy; a history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; untreated or corticosteroid-dependent brain metastases.

The demographic and baseline disease characteristics of the study population were generally 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 \geq 400 ng/mL. Baseline ECOG performance status was 0 (62%) or 1 (38%). The primary risk factors for the development of HCC were Hepatitis B virus infection in 48% of patients, Hepatitis C virus infection in 22% of patients, and non-viral disease in 31% of patients. HCC was categorized as Barcelona Clinic Liver Cancer (BCLC) stage C in 82% of patients, stage B in 16% of patients, and stage A in 3% of patients.

Study Results

The primary efficacy endpoints were overall survival (OS) and independent review facility (IRF)-assessed progression free survival (PFS) according to RECIST v1.1. Tumour assessments were performed every 6 weeks for the first 54 weeks following Cycle 1, Day 1, and then every 9 weeks thereafter. The key efficacy results from the primary analysis are summarized in Table 41. The Kaplan-Meier curves for OS and PFS are presented in Figure 14 and Figure 15, respectively.

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

The IRF-assessed overall response rate (ORR) was 29.8% (95% CI: 24.8, 35.0) in the Tecentriq + bevacizumab arm and 11.3% (95% CI: 6.9, 17.3) in the sorafenib arm.

The IRF-assessed median duration of response (DOR) among confirmed responders was 18.1 months (95% CI: 14.6, NE) in the Tecentriq + bevacizumab arm compared to 14.9 months (95% CI: 4.9, 17.0) in the sorafenib arm.

Table 41 Summary of Efficacy - YO40245 (IMbrave150 – Primary Analysis)

	Tecentriq (intravenous formulation) in combination with Bevacizumab (N= 336)	Sorafenib (N=165)
Overall Survival		

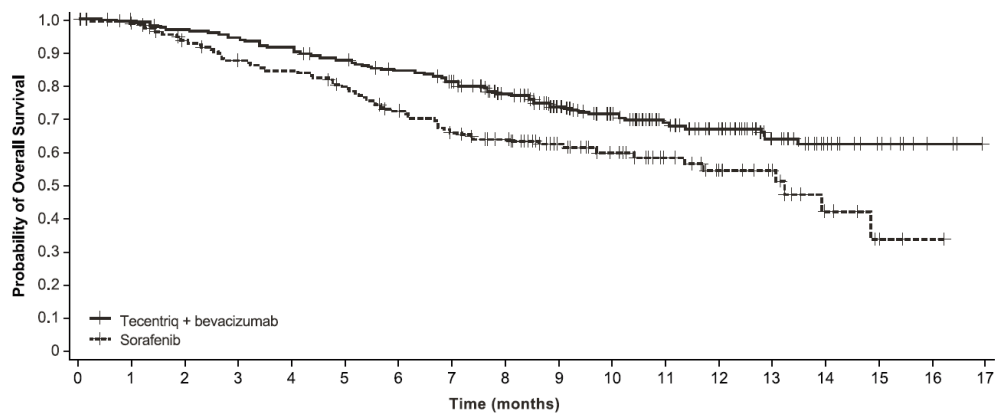
Number of deaths (%)	96 (28.6%)	65 (39.4%)
Median time to event (months) 95% CI	NE (NE, NE)	13.2 (10.4, NE)
Stratified hazard ratio [‡] (95% CI)	0.58 (0.42, 0.79)	
p-value ¹	0.0006	
IRF-assessed PFS, RECIST 1.1		
Number of events (%)	197 (58.6%)	109 (66.1%)
Median duration of PFS (months) (95% CI)	6.8 (5.8, 8.3)	4.3 (4.0, 5.6)
Stratified hazard ratio [‡] 95% CI	0.59 (0.47, 0.76)	
p-value ¹	<0.0001	
IRF-assessed ORR, RECIST 1.1		
	n=326	n=159
Number of confirmed responders (%)	89 (27.3%)	19 (11.9%)
95% CI	(22.5, 32.5)	(7.4, 18.0)
Number of complete responses (%)	18 (5.5%)	0
Number of partial responses (%)	71 (21.8%)	19 (11.9%)
IRF-assessed ORR, HCC mRECIST		
	n=325	n=158
Number of responders (%) (95% CI)	108 (33.2%) (28.1, 38.6)	21 (13.3%) (8.4, 19.6)
Number of complete responses (%)	33 (10.2%)	3 (1.9%)
Number of partial responses (%)	75 (23.1%)	18 (11.4%)

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

1. Based on two-sided stratified log-rank test. OS two-sided significance level 0.004, based on 161/312 OS events =52% of OS information using the OBF like method. PFS two-sided significance level 0.002.

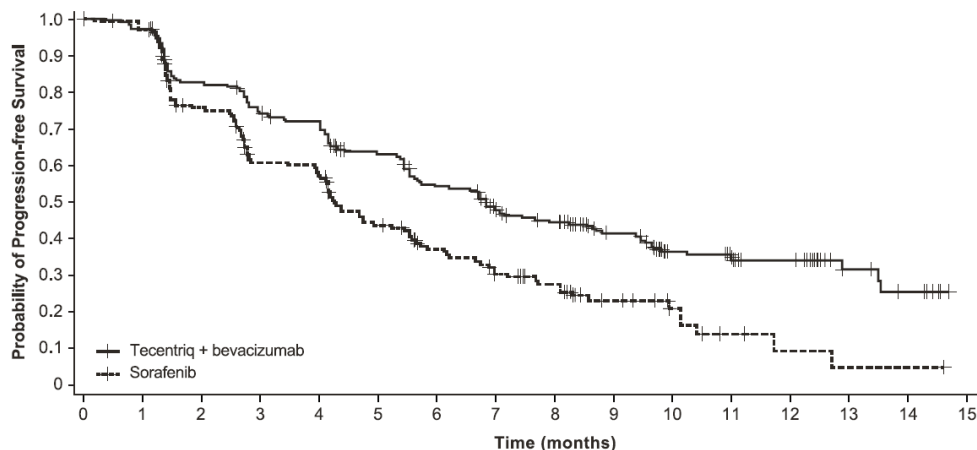
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1; HCC mRECIST = Modified RECIST Assessment for Hepatocellular Carcinoma ; CI=confidence interval; ORR=objective response rate; OS=overall survival; NE=not estimable; N/A=not applicable

Figure 14 Kaplan-Meier Plot for Overall Survival YO40245 (IMbrave150 – Primary Analysis)



No. of Patients at Risk		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Tecentriq + bevacizumab		336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib		165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE

Figure 15 Kaplan-Meier Plot for Progression-Free Survival per RECIST v1.1 YO40245 (IMbrave150)



No. of Patients at Risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
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

Locally Advanced or Metastatic Triple-Negative Breast Cancer (TNBC)

Study WO29522 (IMpassion130) - First-Line Therapy in Combination with Nab-Paclitaxel

Table 42: Summary of patient demographics for Study WO29522 (IMpassion130) in Locally Advanced or Metastatic Triple-Negative Breast Cancer Patients

Study Number	Study Design	Dosage, route of administration and duration	Study subjects (n)	Median age (range)	Sex
WO29522	Phase III, randomized, placebo-controlled, double-blinded, two-arm	atezolizumab or placebo: IV, 840mg q2w nab-paclitaxel: IV, 100 mg/m ² weekly for three consecutive weeks followed by a 1-week rest period Duration: Until disease progression or unacceptable toxicity nab-paclitaxel: target of at least 6 cycles in the absence of disease progression or unacceptable toxicity	902	55 years (20 – 86)	F: 898 (99.6%) M: 4 (0.4%)

IV = Intravenous; q2w = every two weeks

Study Demographics and Trial Design

Designed as a phase III, double-blind, two-arm, randomized, placebo-controlled study, WO29522 (IMpassion130), was conducted to evaluate the efficacy and safety of Tecentriq (intravenous formulation) in combination with nab-paclitaxel compared to placebo plus 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 IC in <1% of the tumour area vs. ≥1% of the tumour area) by the VENTANA PD-L1 (SP142) Assay. Patients were randomized to receive Tecentriq (intravenous formulation) (840 mg) or placebo IV

infusions on Days 1 and 15 of every 28-day cycle, plus nab-paclitaxel (100 mg/m²) 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. Tumour assessments were performed every 8 weeks (\pm 1 week) for the first 12 months after Cycle 1, day 1 and every 12 weeks (\pm 1 week) thereafter.

Patients were excluded if they had a history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; untreated or corticosteroid-dependent brain metastases.

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 on IC covering \geq 1% of the tumor area, 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.

The co-primary efficacy endpoints were OS and PFS as assessed by the investigator according to RECIST V1.1, both in the ITT population and the PD-L1-positive patient population. Secondary endpoints included ORR and DOR as assessed by the investigator per RECIST v1.1. Two interim and one final analyses of OS were planned. OS in the PD-L1-positive patient population was formally tested only if the OS results in the ITT population were statistically significant.

Study Results

PFS, ORR and DOR results for patients with PD-L1 expression of \geq 1% on IC with a median survival follow up of 13 months are summarized in Table 43 and Figure 16.

A final OS analysis was performed in patients with PD-L1 expression of \geq 1% on IC with a median survival follow-up of 19.12 months. OS results are presented in Table 43 and Figure 17.

Table 43 Summary of Efficacy in Patients with PD-L1 Expression of $\geq 1\%$ on IC (IMpassion130)

Efficacy endpoint	Tecentriq (intravenous formulation) + nab-paclitaxel	Placebo + nab-paclitaxel
Primary endpoint		
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
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	
OS²	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)	
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%)
Investigator-assessed DOR*	n=109	n=78
Median in months	8.5	5.5
95% CI	(7.3, 9.7)	(3.7, 7.1)

* The results were similar to those obtained using independent review committee assessment of these endpoints

¹ Based on the stratified log-rank test at significance level 0.005 as per the pre-specified type I error control rate

² OS comparisons between treatment arms in patients with PD-L1 expression of $\geq 1\%$ on IC 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, NE=not estimable

Figure 16 Kaplan-Meier Plot for Progression Free Survival in Patients with PD-L1 Expression of $\geq 1\%$ on IC (IMpassion130)

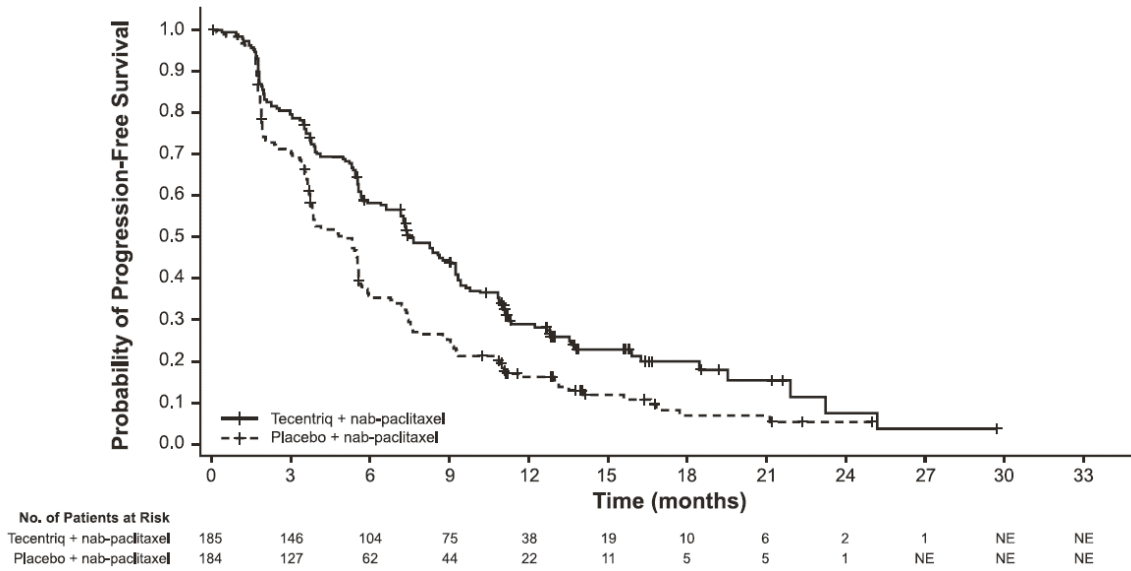
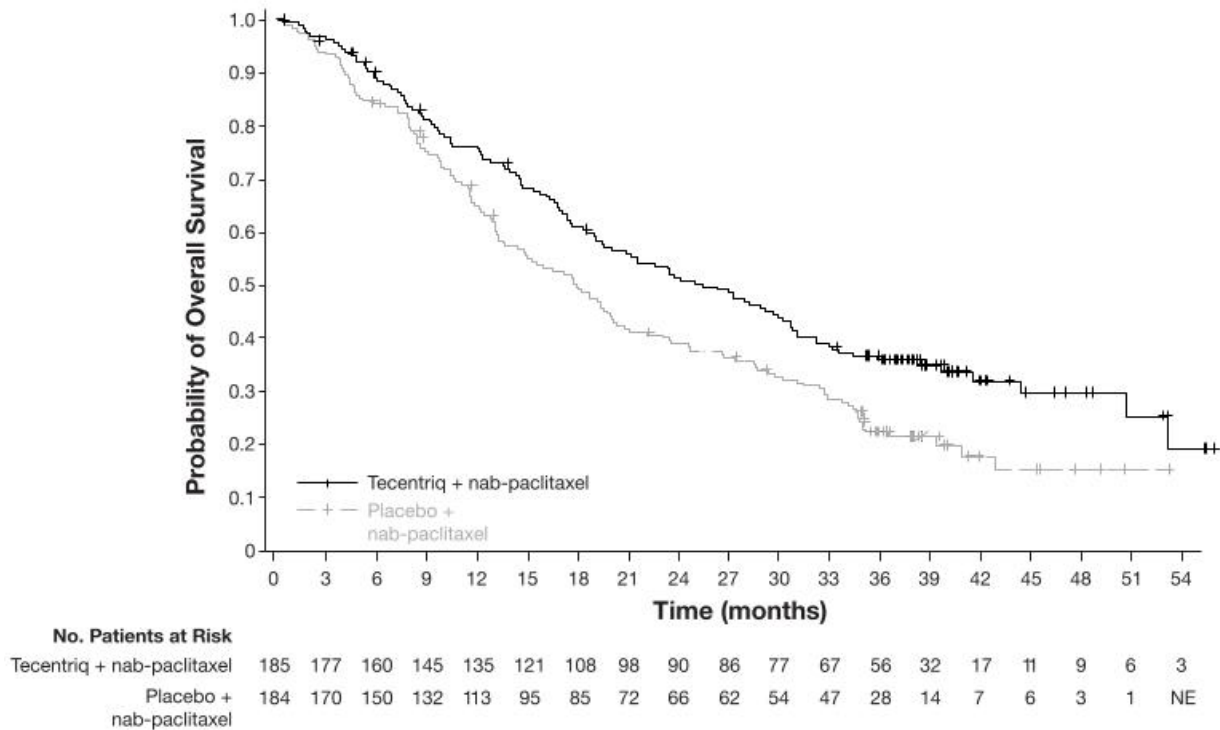


Figure 17 Kaplan-Meier Plot for Overall Survival in Patients with PD-L1 Expression of $\geq 1\%$ on IC (IMpassion130)



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

Study MO39196 (IMpassion131) was a phase III, double-blind, randomized (2:1), placebo-controlled study that evaluated Tecentriq (intravenous formulation) in combination with paclitaxel compared to placebo plus paclitaxel in patients with unresectable locally advanced or metastatic TNBC who had not received prior chemotherapy for metastatic disease. Tecentriq (intravenous formulation) (840 mg) was administered by IV infusion on Days 1 and 15 of every 28-day cycle, plus paclitaxel (90 mg/m²) intravenously on Days 1, 8 and 15 of every 28-day cycle. Among the 651 randomized patients, 292 were PD-L1-positive, which was defined as PD-L1 expression on IC covering ≥ 1% of the tumor area. For the PD-L1-positive patients, results of the final OS analysis with a total of 123 deaths and a median survival follow-up of 15.4 months showed a median OS of 22.1 month in the Tecentriq (intravenous formulation) arm compared to 28.3 months in the placebo arm (HR of 1.11, 95% CI: 0.76, 1.64).

14.2 Comparative Bioavailability Studies

Not applicable.

14.3 Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response to atezolizumab.

In IMscin001, the incidence of treatment-emergent anti-drug antibodies (ADAs) in patients treated with Tecentriq SC and atezolizumab IV was 19.5% [43/221] and 13.9% [15/108], respectively. The incidence of neutralizing antibodies to atezolizumab (NABs) in patients treated with Tecentriq SC and atezolizumab IV was 9.7% [21/217] and 8.3% [9/108], respectively. ADA status did not appear to have a clinically relevant impact on atezolizumab pharmacokinetics, efficacy or safety. The incidence of treatment-emergent anti-rHuPH20 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.

Across multiple phase II and III studies with intravenous atezolizumab, 13.1% to 54.1% of patients developed ADAs and 4.3% to 27.5% of patients developed NABs. In general, patients who developed ADAs and NABs had worse baseline prognostic factors, which can confound the interpretation of ADA subgroup analyses of PK, efficacy, and safety. A decrease in atezolizumab exposure was observed in ADA-positive patients compared to ADA-negative patients, but this effect on exposure is not expected to be clinically meaningful. Exploratory OS meta-analyses showed that while there appears to be some attenuation in efficacy in the ADA-positive subgroup compared to the ADA-negative subgroup, the ADA-positive subgroup derives meaningful OS benefit from atezolizumab treatment compared to control.

Across pooled datasets for patients treated with atezolizumab monotherapy (N=3460) and with combination therapies (N=2285), the following rates of adverse events (AEs) have been observed for the ADA-positive population compared to the ADA-negative population, respectively: Grade 3-4 AEs 45.9% vs. 39.1%, Serious Adverse Events (SAEs) 39.4% vs. 33.0%, AEs leading to treatment withdrawal 8.4% vs 7.7% (for monotherapy); Grade 3-4 AEs 63.9% vs. 60.9%, SAEs 43.9% vs. 35.6%, AEs leading to treatment withdrawal 22.8% vs 18.4% (for combination therapy). Available data do not allow conclusions to be drawn on possible patterns of adverse drug reactions or their causal relationship with ADAs.

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 atezolizumab with the incidence of antibodies to other products may be misleading.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Repeat-Dose Toxicity

Repeat-dose toxicity studies were conducted in cynomolgus monkeys and C57BL/6 and CD-1 mice.

Cynomolgus Monkeys:

In an 8-week study, cynomolgus monkeys received 0, 15, or 50 mg/kg atezolizumab by intravenous administration or 15 or 50 mg/kg by subcutaneous injection once per week (9 doses) followed by a 12-week recovery period. In a 26-week study, cynomolgus monkeys received 0, 5, 15 or 50 mg/kg atezolizumab by intravenous administration once per week (27 doses) followed by a 13-week recovery period. All animals survived until scheduled termination.

Atezolizumab-related minimal to mild multi-organ arteritis/periarteritis was observed at dose levels of 15 and 50 mg/kg. The vasculitis is consistent with heightened immune autoreactivity. An additional finding in the 26-week, repeat-dose toxicity study was an atezolizumab-related effect on menstrual cycles. All females in the 50 mg/kg dose group experienced an irregular cycle pattern during the dosing phase. This finding correlated with an absence of fresh corpora lutea in the ovaries (lack of cycling activity) at the time of the terminal phase necropsy. This effect occurred at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose and was reversible. The no observed adverse effect level (NOAEL) was determined to be 5 mg/kg.

C57BL/6 and CD-1 mice:

Female C57BL/6 mice received 0, 10, or 50 mg/kg intravenous administration of atezolizumab weekly for 15 days (3 doses) followed by a 4-week recovery period. Female CD-1 mice received 0 or 50 mg/kg intravenous administration of atezolizumab weekly for 15 days (3 doses) followed by a 4-week recovery period. All animals survived until scheduled termination. Irreversible minimal sciatic neuropathy characterized by vacuolation and lymphocytic infiltration was observed at dose levels of 10 and 50 mg/kg in C57BL/6 mice only. This finding is considered atezolizumab-related and is attributed to a heightened immune response.

For further details on the repeat-dose toxicity studies with atezolizumab, see Table 44.

Impairment of Fertility

No fertility studies have been conducted with Tecentriq SC; however, assessment of the cynomolgus monkey male and female reproductive organs was included in the chronic toxicity study. Atezolizumab had an effect on menstrual cycles in all female monkeys in the 50 mg/kg dose group characterized 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. Based on this observation, atezolizumab may impair fertility in females with reproductive potential. There was no effect on the male reproductive organs.

Table 44 Summary of Toxicology Studies

Study Type	Treatment Duration and Dosing Schedule	Species/ Test System	Gender and No. per group	Doses (mg/kg)	Findings/Conclusions
Non-GLP Repeat Dose Study	Once weekly for 2 weeks (3 total doses); IV	C57BL/6 and CD-1 mice	Female (total of n=32/group); n=8/group for toxicity assessment; n=15/group for immune assessment; n=9/group toxicokinetic assessment	<u>C57BL/6</u> 0 mg/kg 10 mg/kg 50 mg/kg <u>CD-1</u> 0 mg/kg 50 mg/kg	<ul style="list-style-type: none"> Spleen weight and spleen to brain weight ratios from both C57BL/6 and CD-1 animals dosed 50 mg/kg of atezolizumab were greater (approximately 20%) compared to controls animals. There was no histology correlated to these changes. Minimal neuropathy was noted in only C57BL/6 mice on Days 17 and 43 in both dose groups (10 and 50 mg/kg). No clinical observations were noted with this finding. No changes in serum cytokine levels or activation status of peripheral lymphocytes. Atezolizumab serum concentrations dropped rapidly after Day 15 (the third dose) consistent with the detection of anti-atezolizumab antibodies in all animals.
Repeat Dose Study	Once weekly for 8 consecutive weeks (9 total doses)	Cynomolgus monkeys	n=5/sex/group for each main study dose group (IV or SC); n=3/sex/group for cardiovascular safety pharmacology via implanted telemetry (IV)	0 mg/kg (IV/SC) 5 mg/kg (IV) 15 mg/kg (IV) 50 mg/kg (IV) 15 mg/kg (SC) 50 mg/kg (SC)	<ul style="list-style-type: none"> No atezolizumab-related changes in clinical observations, body weight, food consumption, central nervous system, cardiovascular, respiratory safety pharmacology parameters, or clinical pathology endpoints were observed. Atezolizumab administration had no effect on immunologic endpoints, including immunophenotyping via flow cytometry and serum cytokines. Atezolizumab-related minimal to mild arteritis/periarteritis within the interstitium of parenchymal organs (heart, kidney, liver, pancreas, and epididymis), or within the submucosa or muscularis of tubular organs, such as the gastrointestinal and female reproductive tracts, was observed in 1 of 6 animals in the 15 mg/kg SC, and 50 mg/kg IV dose groups and in 2 of 6 animals in the 50 mg/kg SC dose group. These findings were not present following the 12-week recovery periods, indicating either resolution during the recovery period or lack of occurrence in the recovery cohorts. The NOAEL was determined to be 5 mg/kg.

Table 44 Summary of Toxicology Studies

Study Type	Treatment Duration and Dosing Schedule	Species/ Test System	Gender and No. per group	Doses (mg/kg)	Findings/Conclusions
Repeat Dose Study	Once weekly for 26 consecutive weeks (27 total doses)	Cynomolgus monkeys	5/sex/ group	0 mg/kg (IV) 5 mg/kg (IV) 15 mg/kg (IV) 50 mg/kg (IV)	<ul style="list-style-type: none"> • Atezolizumab-related anatomic pathology findings were limited to microscopic, minimal to slight, chronic-active, and multifocal arteritis/periarteritis in multiple organs of two animals at the terminal phase necropsy. One female at 15 mg/kg had arteritis/periarteritis in the heart, stomach, and vagina. Another female at 50 mg/kg had arteritis/periarteritis in the heart, pancreas, kidney, vagina, urinary bladder, stomach, gallbladder, colon, rectum, duodenum, jejunum, ileum, mandibular salivary gland, skin/subcutis, sternum/marrow, femur/marrow, uterus, larynx, and cervix.). These findings were not present following the 13-week recovery periods, indicating either resolution during the recovery period or lack of occurrence in the recovery cohorts. • Atezolizumab-related effect on menstrual cycles was noted in all females in the 50 mg/kg dose group during the dosing phase. This finding was characterized by an irregular cycle pattern with disturbed cycles and correlated with an absence of fresh corpora lutea in the ovaries at the time of the terminal phase necropsy. This effect showed reversibility during the recovery period. • There was no effect of atezolizumab on semen assessments, testicular evaluations, and serum testosterone level measurements in male cynomolgus monkeys. • The NOAEL was determined to be 5 mg/kg.
In vitro cytokine release assay	24 and 48 hrs	In vitro; isolated human peripheral blood mononuclear cells	3 donors	0, 0.25, 2.5, 25, and 250 µg/ml	<ul style="list-style-type: none"> • No apparent atezolizumab-dependent cytokine release was detected following 24- and 48-hour incubations with human PBMCs.

Table 44 Summary of Toxicology Studies

Study Type	Treatment Duration and Dosing Schedule	Species/ Test System	Gender and No. per group	Doses (mg/kg)	Findings/Conclusions
Tissue cross reactivity study	NA	In vitro; human and cynomolgus monkey tissues	3 donors each	0.25 or 1.25 µg/ml	<ul style="list-style-type: none"> • In human tissues, biotin-atezolizumab-specific staining was detected in the placenta, lymph node, tonsil, and thymus. Frequent, moderate, apical cytoplasmic and membranous staining was observed in syncytiotrophoblasts of the placenta. Very rare, minimal to mild, cytoplasmic staining was observed in sinusoidal cells of lymph nodes and tonsil. Rare to frequent, mild to moderate, cytoplasmic staining was observed in thymic cortical and medullary cells. • In cynomolgus monkey tissues, biotin-atezolizumab-specific specific staining was detected only in the lymph node. Rare to frequent, minimal to moderate, cytoplasmic staining was observed in sinusoidal cells of lymph nodes.

NA = not applicable

Carcinogenicity: No carcinogenicity studies have been conducted with atezolizumab.

Genotoxicity: No studies have been performed to establish the mutagenic potential of atezolizumab.

Reproductive and Developmental Toxicology: No reproductive or developmental studies in animals have been conducted with atezolizumab. The PD-L1/PD-1 signaling pathway is well established as essential in maternal / fetal tolerance and embryo-fetal survival during gestation. Blockade of PD-L1 signaling has been shown, in murine models of pregnancy, to disrupt tolerance to the fetus and to result in an increase in fetal loss. Therefore, the potential risks of administering atezolizumab during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to atezolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

Special Toxicology: In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus clone 13.

Juvenile Toxicity: Not applicable.

SUBCUTANEOUS FORMULATION (Tecentriq SC)

No carcinogenicity, genotoxicity, or fertility studies were conducted with Tecentriq SC which contains recombinant human hyaluronidase (rHuPH20) as an excipient.

Hyaluronidase is found in most tissues of the human body. Non-clinical data rHuPH20 reveal no special hazard for humans based on conventional studies of repeated dose toxicity including safety pharmacology endpoints. Reproductive toxicology studies with rHuPH20 at dose levels up to 2,200,000 U/kg, which is >4,400 times higher than the hyaluronidase human dose, revealed decreased fetal body weights and increased late resorptions in mice, and did not show teratogenic potential. No effects were found at a daily dose of 360,000 U/kg, which is > 720 times higher than the hyaluronidase human dose.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

^{Pf}TECENTRIQ® SC

atezolizumab injection, solution for subcutaneous injection, 1875 mg/15 mL vial

Read this carefully before you start taking Tecentriq SC and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Tecentriq SC.

What is Tecentriq SC used for?

Lung Cancer

- Tecentriq SC is used to treat a type of lung cancer called extensive-stage small cell lung cancer (ES-SCLC). Tecentriq SC is used if you have not received any prior chemotherapy for ES-SCLC. Tecentriq SC will be given to you in combination with carboplatin and etoposide.
- Tecentriq SC is used to treat a type of lung cancer called Non-Small Cell Lung Cancer (NSCLC).
 - Tecentriq SC may be used alone as a treatment for your lung cancer:
 - to help prevent your lung cancer from coming back after your tumor(s) has been removed by surgery and you have had chemotherapy,
 - you have stage 2 to stage 3A NSCLC (talk to your healthcare provider about what these stages mean), and
 - your tumour expresses PD-L1 on 50% or more of the tumour cells.
 - Tecentriq SC may be used alone as your first treatment when your lung cancer:
 - has spread or grown, and
 - your tumour expresses high PD-L1, and
 - your tumour does not have an abnormal EGFR or ALK gene
 - Tecentriq SC may be used with bevacizumab and the chemotherapy medicines carboplatin and paclitaxel as your first treatment when your lung cancer:
 - has spread or grown, and
 - is a type of lung cancer called “non-squamous non-small cell lung cancer”, and
 - your tumour does not have an abnormal EGFR or ALK gene
 - Tecentriq SC may be used when your lung cancer:
 - has spread or grown, and
 - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
 - If your tumour has an abnormal EGFR or ALK gene, you should have also tried a therapy for tumours with these abnormal genes, and it did not work or is no longer working.

Breast Cancer

- Tecentriq SC is used to treat a type of breast cancer called Triple-Negative Breast Cancer (TNBC). Tecentriq SC should be used with another drug called nab-paclitaxel when your breast cancer:
 - has spread or cannot be removed by surgery and
 - you have not received any chemotherapy since your cancer has spread and your doctor has tested your cancer and found the presence of a specific protein on your cancer called programmed death-ligand 1 (PD-L1).
- Tecentriq SC should not be used with paclitaxel (a different medicine than nab-paclitaxel) for

the treatment of TNBC when the cancer has spread or cannot be removed by surgery.

Liver Cancer

- Tecentriq SC is used to treat a type of liver cancer called hepatocellular carcinoma (HCC). Tecentriq SC should be used with another drug called bevacizumab when your liver cancer:
 - has spread to other parts of your body or cannot be removed by surgery or cannot be treated locally within the liver, **and**
 - you have not received other medicines to treat your liver cancer.

How does Tecentriq SC work?

Tecentriq SC works by attaching to a specific protein in your body called “PD-L1”. This protein makes the immune system in your body not work as well. By attaching to the protein, Tecentriq SC helps your immune system to fight your cancer.

What are the ingredients in Tecentriq SC?

Medicinal ingredient: atezolizumab

Non-medicinal ingredients: acetic acid, 30%, L-Histidine, L-Methionine, polysorbate 20, recombinant human hyaluronidase PH20 (rHuPH20), sucrose, and water for injection.

Tecentriq SC comes in the following dosage forms:

Supplied as a sterile, ready-to-use solution for subcutaneous injection only. Each single-dose vial contains 1875 mg (in 15 mL) of atezolizumab. Each mL contains 125 mg of atezolizumab.

Do not use Tecentriq SC if:

- you are allergic to atezolizumab or any of the other ingredients in Tecentriq SC

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Tecentriq SC. Talk about any health conditions or problems you may have, including if you:

- have immune system problems such as rheumatoid arthritis, Crohn’s disease, ulcerative colitis, or lupus;
- have had an organ transplant;
- have breathing or lung problems such as inflammation of the lungs (pneumonitis);
- have liver problems;
- have heart problems;
- have kidney problems;
- have muscle weakness and muscle pain;
- have problems with your hormone producing glands including your thyroid, pituitary, adrenal glands, and pancreas;
- have diabetes;
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré Syndrome;
- have or have had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV);
- have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS);
- are taking medicine(s) that affect the immune system such as a steroid;
- have previously experienced severe rash or blistering skin condition
- have been given a live, attenuated vaccine;

- are taking medicine to treat an infection; or
- have any other medical conditions.

Pregnancy

- are pregnant or plan to become pregnant
 - Tecentriq SC can harm your unborn baby. Your healthcare provider should do a pregnancy test before you start treatment with TECENTRIQ SC.
 - If you are able to become pregnant, you should use an effective method of birth control during your treatment with Tecentriq SC and for at least 5 months after your last dose of Tecentriq SC. Talk to your healthcare provider about birth control methods that you can use during this time.
 - Tell your healthcare provider right away if you become pregnant during treatment with Tecentriq SC.

Breast-feeding

- are breastfeeding or plan to breastfeed
 - Tecentriq SC may pass into your breast milk. You should not breast-feed for at least 5 months after the last dose.
 - You and your doctor should decide whether you will breast-feed or take Tecentriq SC. You should not do both.
- **Other warnings you should know about: Children and adolescents:** Tecentriq SC should not be given to children or adolescents. This is because the effects of Tecentriq SC in people younger than 18 years of age are not known.
- **Females of Childbearing Potential:** TECENTRIQ SC may cause fertility problems, which may affect the ability to have children. Talk to your healthcare provider if you have concerns about fertility.
- **Driving and using machines:** It is not known whether Tecentriq SC affects your ability to drive or use tools or machines. However, if you feel tired, do not drive or use tools or machines until you feel better.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Tecentriq SC:

- Your healthcare professional will decide how many treatments you need.
- Tecentriq SC is given as an injection under your skin (subcutaneous injection) by a healthcare professional.
- Injections will be given in the thigh over approximately 7 minutes.
 - Your healthcare professional will make sure each injection is given in a new place (at least 2.5 cm away from any previous injection), and where the skin is not red, bruised, tender or hard. Different places for injection should be used for other medicines.

Usual dose:

- For lung cancer (first-line small cell lung cancer; adjuvant treatment, first-line and second-line non-small cell lung cancer), breast cancer and liver cancer, the recommended dose of Tecentriq SC is 1875 mg given every three weeks.

Overdose:

If you think you, or a person you are caring for, have taken too much Tecentriq SC, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are possible side effects from using Tecentriq SC?

These are not all the possible side effects you may have when taking Tecentriq SC. If you experience any side effects not listed here, tell your healthcare professional.

The following side effects have been reported in clinical trials with Tecentriq SC:

Very common (may affect more than 1 in 10 people):

- feeling very tired with no energy (fatigue);
- lack of energy (asthenia);
- decreased appetite;
- nausea;
- fever;
- chills;
- diarrhea;
- hair loss;
- constipation;
- swelling;
- headache;
- vomiting;
- rash;
- shortness of breath;
- cough;
- lung infection;
- itching of the skin;
- stomach pain;
- joint pain;
- nerve pain;
- back pain;
- muscle pain;
- dizziness;
- urinary tract infection;
- leg swelling caused by the retention of fluid in leg tissues (peripheral edema);
- underactive thyroid gland (hypothyroidism);
- elevated liver enzymes - may be a sign of an inflamed liver (shown in blood tests);
- low neutrophil (a white blood cell) levels in the blood (shown in blood tests); and
- difficulty sleeping (insomnia);
- change in your sense of taste (dysgeusia);
- inflammation of mouth and lips;
- flu-like illness.

Common (may affect up to 1 in 10 people):

- low blood sugar, magnesium, potassium or sodium levels in the blood (shown in blood tests);
- high blood sugar (shown in blood tests);
- sore throat;
- dry skin;
- low blood pressure;
- high blood pressure;
- pain in the bones;
- low platelet count, which may make you more likely to bruise or bleed;
- nasal congestion;
- low oxygen levels which may cause shortness of breath;
- inflammation of the lungs;
- kidney pain;
- abnormal voice;
- coughing up blood;
- overactive thyroid gland (hyperthyroidism);
- difficulty swallowing;
- sensitivity to light;
- acne-like skin problems;
- shingles;
- elevated creatinine levels (shown in blood tests);
- skin infection (cellulitis);
- blood clot in the lungs (pulmonary embolism);
- pain, itching, swelling or redness around site of injection and
- fainting.

In addition to the above mentioned side effects, the following may also occur when Tecentriq SC is given in combination with chemotherapy and/or with bevacizumab. If you are given Tecentriq SC in combination with chemotherapy and/or with bevacizumab, then you should also read the Patient Medication Information for these products as well.

Very common (may affect more than 1 in 10 people):

- bleeding
- low number of red blood cells - which can cause tiredness and shortness of breath;
- low white blood cell count with and without fever – which can increase the risk of infection;
- mouth blisters or sores;
- low levels of magnesium – which can cause weakness and muscle cramping; and numbness and pain in the arms and legs.

Your healthcare professional will test your blood to check you for certain side effects.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Inflammation or problems of the nerves (neuropathy): symptoms may include muscle weakness and numbness, tingling in hands and feet		✓	
COMMON			
Inflammation of the lung (pneumonia, pneumonitis): symptoms may include new or worsening cough, shortness of breath, and chest pain		✓	
Inflammation of the intestines (colitis): symptoms may include diarrhea (watery, loose or soft stools), blood in stools, or dark, tarry, sticky stools, and stomach pain		✓	
Inflammation of the thyroid and adrenal glands (hypothyroidism, hyperthyroidism, or adrenal insufficiency): symptoms may include tiredness, weight loss, weight gain, change in mood, hair loss, constipation, dizziness, and sweating		✓	
Severe reactions associated with injection (events occurring during or within one day of having the injection): symptoms may include fever, chills, shortness of breath, or wheezing, swelling of face or lips, itching or rash, and flushing		✓	
Severe infections: symptoms may include fever, cough, frequent urination, flu-like symptoms, and pain when urinating		✓	
Skin problems which can cause rash, itching, redness, skin blistering, sores, peeling		✓	
Inflammation of the bladder (cystitis): symptoms may include persistent urge to urinate, cloudy or bloody urine, burning feeling when urinating, small amounts of urine frequently		✓	
Problems with the sac that surrounds the heart that can make the heart work poorly (pericardial disorders): shortness of breath or difficulty breathing, chest pain, feeling faint or light headed, swelling in the stomach or legs		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Inflammation of the liver (hepatitis): symptoms may include yellowing of skin or eyes, nausea, vomiting, bleeding or bruising more easily than normal, dark urine, and stomach pain		✓	
Inflammation of the pancreas (pancreatitis): symptoms may include abdominal pain, nausea and vomiting		✓	
Type 1 diabetes mellitus, including acid in the blood produced from diabetes (diabetic ketoacidosis): symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, weight loss, and feeling tired		✓	
Inflammation of the pituitary gland (symptoms may include issues with regulating body temperature)		✓	
Severe skin reactions: very severe blistering skin condition, may appear with ulcers of the skin and digestive tract, and may lead to the loss of a large portion of skin		✓	
RARE			
Inflammation of the brain (encephalitis) or inflammation of the membrane around the spinal cord and brain (meningitis): symptoms may include neck stiffness, headache, fever, chills, vomiting, eye sensitivity to light, confusion and sleepiness		✓	
Inflammation of the eyes: symptoms may include blurry vision, double vision, or other vision problems, and eye pain or redness		✓	
Inflammation of the heart muscles (myocarditis): symptoms may include chest pain, shortness of breath, irregular heartbeat, decreased exercise tolerance, ankle swelling		✓	
Inflammation of the muscles (myositis): symptoms may include muscle weakness and muscle pain that may lead to difficulty moving, breathing, swallowing, and/or dark brown or red colour urine		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Inflammation of the kidneys (nephritis): symptoms may include changes in urine output and colour, pain in pelvis, and swelling of the body		✓	
Inflammation of the pituitary gland (hypophysitis): symptoms may include fatigue and headaches that will not go away, increased thirst, increased urination, and changes in vision		✓	
A condition of muscle weakness of the face or inability to move the muscles of the face caused by nerve damage (immune-mediated facial palsy): symptoms may include weakness and/or drooping of the face, trouble with speaking, blinking, swallowing saliva or eating		✓	
Inflammation of spinal cord (immune-mediated myelitis): symptoms may include pain, muscle weakness, paralysis, muscle spasms, loss of balance, numbness or tingling, bladder and bowel dysfunction		✓	
Certain white blood cells destroy other blood cells and build up in and damage organs (bone marrow, liver, and spleen) (hemophagocytic lymphohistiocytosis): symptoms may include fever, enlargement of your liver or spleen, swollen lymph nodes, skin rash, jaundice (yellow colour of your skin and eyes), coughing, trouble breathing, stomach ache, vomiting, diarrhea, headache, trouble walking, visual problems, and weakness		✓	
Unknown frequency			
Aplastic anemia: Insufficient production of new blood cells		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Tecentriq SC will be stored by your healthcare professionals at the hospital or clinic. The storage details are as follows:

- Keep out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and the vial label after "EXP". The expiry date refers to the last day of that month.
- Store in a refrigerator (2-8°C). Do not freeze.
- Do not shake.
- Keep the vial in the outer carton in order to protect from light.
- Do not throw away any medicines via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help to protect the environment.

If you want more information about Tecentriq SC:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website \(http://hc-sc.gc.ca/index-eng.php\)](http://hc-sc.gc.ca/index-eng.php); the manufacturer's website (www.rochecanada.com), or by calling 1-888-762-4388.

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