Tecentriq®

Atezolizumab

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Anti-neoplastic agent, humanized immunoglobulin G1 (IgG1) monoclonal antibody.

ATC code: L01FF05

1.2 Type of Dosage Form

- Intravenous (IV) formulation: Concentrate for solution for infusion
- Subcutaneous (SC) formulation: Solution for injection

1.3 Route of Administration

Intravenous (IV) infusion

Subcutaneous (SC) injection

1.4 Sterile / Radioactive Statement

Sterile product

1.5 Qualitative and Quantitative Composition

Active ingredient: atezolizumab

Tecentriq IV

Tecentriq solution for intravenous (IV) infusion is supplied as a single-use vial containing preservative-free, colorless to slightly yellow solution, at an active ingredient concentration of 60 mg/ml, as follows:

- 14 mL vial containing a total of 840 mg atezolizumab
- 20 mL vial containing a total of 1,200 mg atezolizumab

Excipients: as registered locally

Tecentriq SC

Tecentriq solution for subcutaneous (SC) injection is supplied as sterile ready-to-use single-dose vials containing preservative-free, colorless to slightly yellow solution, at an active ingredient concentration of 125 mg/mL, as follows:

- 15 mL containing a total 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.

Excipients: As registered locally.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Tecentriq IV and Tecentriq SC

Urothelial carcinoma

Tecentriq as monotherapy is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC)

- after prior chemotherapy, or
- who are considered cisplatin ineligible and whose tumours have a PD-L1 expression ≥ 5%

Early-stage non-small cell lung cancer

Tecentriq as monotherapy is indicated as adjuvant treatment following resection and platinum-based chemotherapy for patients with stage II to IIIA (7th edition of the UICC/AJCC-staging system) NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells (TC).

Metastatic non-small cell lung cancer

Tecentriq, in combination with Avastin (bevacizumab), paclitaxel and carboplatin, is indicated for the first-line treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumor aberrations.
Patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for NSCLC harboring these aberrations prior to receiving Tecentriq.

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

Tecentriq as monotherapy is indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have a PD-L1 expression* ≥ 50% tumor cells (TC) or ≥ 10% tumor-infiltrating immune cells (IC) and who do not have EGFR or ALK genomic tumor aberrations

** apply for any PD-L1 IHC assays*

Tecentriq as monotherapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.

Small cell lung cancer

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

Triple-negative breast cancer

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

Hepatocellular carcinoma

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

2.2 Dosage and Administration

General

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

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

It is important to check the product labels to ensure that the correct formulation (Tecentriq IV or Tecentriq SC) is being administered to the patient as prescribed. Patients currently receiving Tecentriq IV may transition to Tecentriq SC.

Tecentriq IV

Tecentriq IV formulation is not intended for subcutaneous administration.

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

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

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

The recommended dose of Tecentriq in monotherapy or combination therapy is

- 840 mg administered by IV infusion every 2 weeks, or
- 1200 mg administered by IV infusion every 3 weeks, or
- 1680 mg administered by IV infusion every 4 weeks.

Tecentriq SC

Tecentriq SC formulation is not intended for intravenous administration.

Tecentriq SC must be administered as a subcutaneous injection only (see section 4.2 Special Instructions for Use, Handling and Disposal). Prior to administration, remove Tecentriq SC from refrigeration and allow the solution to reach room temperature.

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.

The recommended dose of Tecentriq in monotherapy or combination therapy is 1875 mg administered by SC injection every 3 weeks.

Tecentriq monotherapy

1L cisplatin – ineligible mUC, early-stage NSCLC, 1L metastatic NSCLC

Patients should be selected for treatment based on the tumor expression of PD-L1 confirmed by a validated test (see section 3.1.2 Clinical/ Efficacy Studies)

Tecentriq combination therapy

For the use of Tecentriq in combination therapy, please also refer to the full prescribing information for the combination product. Tecentriq should be administered prior to the combination therapy if given on the same day.

1L non-squamous metastatic NSCLC

<u>Tecentriq in combination with Avastin (bevacizumab), paclitaxel, and carboplatin</u>

During the induction phase, Tecentriq is administered according to its dosing schedule by intravenous (IV) infusion or SC injection, and Avastin (bevacizumab), paclitaxel, and carboplatin are administered every 3 weeks for four or six cycles.

The induction phase is followed by a maintenance phase without chemotherapy in which Tecentriq is administered according to its dosing schedule by IV infusion or SC injection, and Avastin (bevacizumab) is administered every 3 weeks.

<u>Tecentriq in combination with nab-paclitaxel and carboplatin</u>

During the induction phase, Tecentriq is administered according to its dosing schedules by IV infusion or SC injection, and nab-paclitaxel and carboplatin are administered every 3 weeks for four or six cycles. For each 21-day cycle, nab-paclitaxel and carboplatin are administered on day 1. In addition, nab-paclitaxel is administered on days 8 and 15.

1L ES-SCLC

Tecentriq in combination with carboplatin and etoposide

During the induction phase, Tecentriq is administered according to its dosing schedules by IV infusion or SC injection, and carboplatin and etoposide are administered by IV infusion every three weeks for four cycles. Carboplatin and etoposide are administered on day 1 of each cycle, and etoposide is also administered on days 2 and 3.

1L TNBC

Tecentriq in combination with nab-paclitaxel

Tecentriq is administered according to its dosing schedules by IV infusion or SC injection, and 100 mg/m^2 nab-paclitaxel is administered on days 1, 8 and 15 during each 28-day cycle.

Patients should be selected for treatment based on the tumor expression of PD-L1 confirmed by a validated test (see section 3.1.2 Clinical / Efficacy Studies).

HCC

Tecentriq in combination with Avastin (bevacizumab)

Tecentriq is administered according to its dosing schedules by IV infusion or SC injection, and Avastin (bevacizumab) 15 mg/kg is administered every 3 weeks.

Duration of treatment

Patients are treated with Tecentriq until loss of clinical benefit (see section 3.1.2 Clinical / Efficacy Studies) or unacceptable toxicity.

1L TNBC

Patients are treated with Tecentriq until disease progression or unacceptable toxicity. (see section 3.1.2 Clinical / Efficacy Studies)

Early-stage NSCLC

Patients are treated with Tecentriq for 1 year unless there is disease recurrence or unacceptable toxicity (see section 3.1.2 Clinical / Efficacy Studies).

Delayed or missed doses

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

Dose modifications

No dose reductions of Tecentriq are recommended.

Dose modifications for immune-mediated adverse reactions

Recommendations for specific adverse drug reactions (*see sections 2.4.1 Warnings and Precautions, General and 2.6.1 Undesirable Effects, Clinical Trials)* are presented in Table 1.

Table 1: Recommended dose modifications for specific adverse drug reactions

Adverse Reaction	Severity	Treatment 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 If AST/ALT is >1 to ≤3x ULN at baseline and increases to >5x to ≤10x ULN If AST/ALT is >3x to ≤5x ULN at baseline and increases to >8x to ≤10x ULN	Withhold[1]
	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

Adverse Reaction	Severity	Treatment Modification
Immune-mediated adrenal insufficiency	Symptomatic	Withhold[1]
Immune-mediated hypophysitis	Grade 2 or 3	Withhold[1]
	Grade 4	Permanently discontinue
Immune-mediated type 1 diabetes	For ≥ Grade 3 hyperglycemia (fasting glucose >250 mg/dL)	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 ≥ 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 - 3.0 x ULN)	Withhold[1]
	Grade 3 or 4 (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 infusion/injection or withhold treatment/pause the injection. Premedication with antipyretic and antihistamines may be considered for subsequent dose
	Grade 3 or 4	Permanently discontinue
Haemophagocytic lymphohistiocytosis	Suspected haemophagocytic lymphohistiocytosis[4]	Permanently discontinue
	Grade 3	Withhold[1]

Adverse Reaction	Severity	Treatment Modification
Rash/Severe cutaneous adverse reactions	or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[4]	
	Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[4]	Permanently discontinue

[1] Treatment with corticosteroid therapy (1-2 mg/kg/day prednisone or equivalent) should be initiated. Treatment with Tecentriq may be resumed in patients with complete or partial resolution (Grade 0 to 1) within 12 weeks, and after corticosteroids have been reduced to ≤10 mg/day oral prednisone or equivalent.

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

[3] 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 should be withheld for Grades 2 or 3 immune-mediated adverse reactions and corticosteroid therapy (1-2 mg/kg/day prednisone or equivalent) should be initiated. If symptoms improve to ≤ Grade 1, taper corticosteroids as clinically indicated. Treatment with Tecentriq may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day.

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

2.2.1 Special Dosage Instructions

Pediatric use

The safety and efficacy of Tecentriq in children and adolescents below 18 years of age have not been established (See section 2.5.4 Pediatric Use, and 3.2.5 Pharmacokinetics in Special Populations)

Geriatric use

Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq is required in patients ≥ 65 years of age (see sections 2.5.5 Geriatric Use, and 3.2.5 Pharmacokinetics in Special Populations).

Renal impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with renal impairment (see section 3.2.5 Pharmacokinetics in Special Populations).

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 on patients with moderate or severe hepatic impairment (see section 3.2.5 Pharmacokinetics in Special Populations).

2.3 Contraindications

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

2.4 Warnings and Precautions

2.4.1 General

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Haemophagocytic lymphohistiocytosis

Haemophagocytic lymphohistiocytosis (HLH), including fatal cases, has been reported in patients receiving Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials and 2.6.2 Postmarketing Experience). 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 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated myocarditis

Myocarditis, including fatal cases, has been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, 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 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated pericardial disorders

Pericardial disorders, including pericarditis, pericardial effusion and cardiac tamponade, some leading to fatal outcomes, have been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials and 2.6.2 Postmarketing Experience). Patients should be monitored for clinical signs and symptoms of pericardial disorders. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated endocrinopathies

Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, and type 1 diabetes mellitus, including diabetic ketoacidosis, have been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable Effects, Clinical Trials). Patients should be monitored for clinical signs and symptoms of endocrinopathies. Monitor thyroid function prior to and periodically during treatment with Tecentriq. Consider appropriate

management of patients with abnormal thyroid function tests at baseline. Patients with abnormal thyroid function tests who are asymptomatic may receive Tecentriq. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated colitis

Cases of diarrhea or colitis have been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable Effects, Clinical Trials). Patients should be monitored for signs and symptoms of colitis. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated pancreatitis

Pancreatitis, including increases in serum amylase and lipase levels, has been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable Effects, Clinical Trials). Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Infusion-related reactions

Infusion-related reactions (IRRs) have been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials). Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated hepatitis

Cases of hepatitis, some leading to fatal outcomes, have been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable Effects, Clinical Trials). 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. Consider appropriate management of patients with abnormal liver function tests (LFTs) at baseline. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated myositis

Case of myositis, including fatal cases, have been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical trials). Patients should be monitored for the signs and symptoms of myositis. Patients with possible myositis should be monitored for signs of myocarditis. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated meningoencephalitis

Meningoencephalitis has been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable Effects, Clinical Trials). Patients should be monitored for clinical signs and symptoms of meningitis or encephalitis. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated neuropathies

Myasthenic syndrome / myasthenia gravis or Guillain-Barré syndrome, which may be life threatening, and facial paresis were observed in patients receiving Tecentriq (see section 2.6.1 Undesirable Effects, Clinical Trials). Patients should be monitored for symptoms of motor and sensory neuropathy. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated myelitis

Myelitis has been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials and 2.6.2 Postmarketing Experience). Patients should be closely monitored for signs and symptoms that are suggestive of myelitis. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated nephritis

Nephritis has been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials). Patients should be monitored for changes in renal function. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated pneumonitis

Cases of pneumonitis, including fatal cases, have been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable Effects, Clinical Trials). Patients should be monitored for signs and symptoms of pneumonitis. Refer to section 2.2. Dosage and Administration for recommended dose modifications.

Immune-mediated severe cutaneous adverse reactions

Immune-mediated severe cutaneous adverse reactions (SCARs), including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients receiving Tecentriq. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, Tecentriq should be withheld for Grade 3 skin reactions until recovery to Grade ≤ 1 or permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered (see Section 2.2).

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

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

Special populations

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

Embryo-fetal toxicity

Based on the mechanism of action, the use of Tecentriq may cause fetal harm. Animal studies have demonstrated that inhibition of the PD-L1 / PD-1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death.

Pregnant women should be advised of the potential risk to the fetus. Women of childbearing potential should be advised to use highly effective contraception during treatment with Tecentriq and for 5 months after the last dose (see sections 2.5.1 Females and Males of Reproductive Potential, and 3.3.4 Reproductive Toxicity).

2.4.2 Ability to Drive and Use Machines

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

2.5 Use in Special Populations

2.5.1 Females and Males of Reproductive Potential

Fertility

Based on animal studies, Tecentriq may impair fertility in females of reproductive potential while receiving treatment (see section 3.3.3 Impairment of Fertility)

Contraception

Female patients of childbearing potential should use highly effective contraception and take active measures to avoid pregnancy while undergoing Tecentriq treatment and for at least 5 months after the last dose (see sections 2.4.1 Warnings and Precautions, General, and 3.3.4-Reproductive Toxicity).

2.5.2 Pregnancy

There are no clinical studies of Tecentriq in pregnant women. Tecentriq is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus (see section 3.3.4 Reproductive Toxicity).

Labor and Delivery

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

2.5.3 Lactation

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

2.5.4 Pediatric Use

Tecentriq is not approved for use in the patients under the age of 18 years. The safety and efficacy of Tecentriq in this population has not been established. Tecentriq did not

demonstrate clinical benefit in pediatric patients in a clinical trial. (see section 3.2.5 Pharmacokinetics in Special Populations)

2.5.5 Geriatric Use

No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients (see sections 2.2.1 Special Dosage Instructions, and 3.2.5 Pharmacokinetics in Special Populations).

2.5.6 Renal Impairment

See sections 2.2.1 Special Dosage Instructions, and 3.2.5 Pharmacokinetics in Special Populations.

2.5.7 Hepatic Impairment

See sections 2.2.1 Special Dosage Instructions, and 3.2.5 Pharmacokinetics in Special Populations.

2.6 Undesirable Effects

2.6.1 Clinical Trials

The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000).

Tecentriq monotherapy

The safety of Tecentriq monotherapy is based on pooled data on 3178 patients withmultiple tumor types, with supporting data from the estimated cumulative exposure on >13000 patients across all clinical trials. Table 2 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of Tecentriq IV and SC.

Table 2: Summary of adverse reactions occurring in patients treated with Tecentriq IV or SC monotherapy in clinical trials

ADR (MedDRA)	Tecentriq (n= 3178)			
System Organ Class	All grades (%)	Grade 3-4 (%)	Grade 5 (%)	Frequency (All grades)
Blood and Lymphatic System Disorders				
Thrombocytopenia[n]	116 (3.7%)	27 (0.8%)	0 (0%)	Common
Haemophagocytic lymphohistiocytosis[ff]	1 (<0.1%)	0 (0%)	1 (<0.1%)	Rare

ADR (MedDRA)	Tecentriq (n= 3178)			
System Organ Class	All grades (%)	Grade 3-4 (%)	Grade 5 (%)	Frequency (All grades)
Cardiac Disorders				
Myocarditis[a]	-	-	-	Rare
Pericardial disorders[ee,ff]	45 (1.4%)	22 (0.7%)	2 (<0.1%)	Common
Endocrine Disorders				
Hypothyroidism [b]	164 (5.2%)	6 (0.2%)	0 (0%)	Common
Hyperthyroidism [c]	30 (0.9%)	1 (<0.1%)	0 (0%)	Uncommon
Adrenal insufficiency [d]	11 (0.3%)	2 (<0.1%)	0 (0%)	Uncommon
Hypophysitis[y]	2 (<0.1%)	0 (0%)	0 (0%)	Rare
Diabetes mellitus [e]	10 (0.3%)	6 (0.2%)	0 (0%)	Uncommon
Gastrointestinal Disorders				
Diarrhea[o]	626 (19.7%)	36 (1.1%)	0 (0%)	Very common
Dysphagia	82 (2.6%)	16 (0.5%)	0 (0%)	Common
Colitis [f]	34 (1.1%)	18 (0.6%)	0 (0%)	Common
Nausea	747 (23.5%)	35 (1.1%)	0 (0%)	Very common
Vomiting	477 (15.0%)	26 (0.8%)	0 (0%)	Very common
Abdominal pain	268 (8.4%)	34 (1.1%)	0 (0%)	Common
Pancreatitis [g]	18 (0.6%)	13 (0.4%) (%)	0 (0%)	Uncommon
Oropharyngeal pain [q]	131 (4.1%)	0 (0%)	0 (0%)	Common
Dry mouth	154 (4.8%)	0 (0%)	0 (0%)	Common
General Disorders and Administration Site Conditions				
Chills	207 (6.5%)	2 (<0.1%)	0 (0%)	Common
Fatigue	1142 (35.9%)	109 (3.4%)	0 (0%)	Very common
Asthenia	461 (14.5%)	63 (2.0%)	0 (0%)	Very common
Influenza-like illness	188 (5.9%)	1 (<0.1%)	0 (0%)	Common

ADR (MedDRA)	Tecentriq (n= 3178)			
System Organ Class	All grades (%)	Grade 3-4 (%)	Grade 5 (%)	Frequency (All grades)
Pyrexia	638 (20.1%)	17 (0.5%)	0 (0%)	Very common
Infusion-related reaction[h]	34 (1.1%)	5 (0.2%)	0 (0%)	Common
Injection site reaction [gg]	11 (4.5%)	0 (0%)	0 (0%)	Common
Hepatobiliary Disorders				
ALT increased	167 (5.3%)	46 (1.4%)	0 (0%)	Common
AST increased	180 (5.7%)	46 (1.4%)	0 (0%)	Common
Hepatitis [i]	62 (0.2%)	25 (0.8%)	2 (<0.1%)	Common
Immune System Disorders				
Hypersensitivity	36 (1.1%)	3 (<0.1%)	0 (0%)	Common
Infections and Infestations				
Urinary tract infection [p]	368 (11.6%)	86 (2.7%)	0 (0%)	Very Common
Metabolism and Nutrition Disorders				
Decreased appetite	810 (25.5%)	35 (1.1%)	0 (0%)	Very common
Hypokalemia[v]	142 (4.5%)	33 (1.0%)	0 (0%)	Common
Hyponatremia[w]	171 (5.4%)	98 (3.1%)	0 (0%)	Common
Hyperglycemia	103 (3.2%)	32 (1.0%)	0 (0%)	Common
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	441 (13.9%)	23 (0.7%)	0 (0%)	Very common
Back pain	487 (15.3%)	52 (1.6%)	0 (0%)	Very Common
Musculoskeletal pain [r]	489 (15.4%)	36 (1.1%)	0 (0%)	Very Common
Myositis [t, u]	13 (0.4%)	5 (0.2%)	0	Uncommon
Nervous System Disorders				
Headache	352 (11.1%)	10 (0.3%)	0 (0%)	Very Common
Guillain-Barré syndrome [j]	5 (0.2%)	4 (0.1%)	0 (0%)	Uncommon

ADR (MedDRA)	Tecentriq (n= 3178)			
System Organ Class	All grades (%)	Grade 3-4 (%)	Grade 5 (%)	Frequency (All grades)
Meningo encephalitis [k]	14 (0.4%)	6 (0.2%)	0 (0%)	Uncommon
Myasthenic syndrome [z]	1 (<0.1%)	0 (0%)	0 (0%)	Rare
Facial paresis[ff]	1 (<0.1%)	0 (0%)	0 (0%)	Rare
Myelitis[ff]	1 (<0.1%)	1 (<0.1%)	0 (0%)	Rare
Renal and Urinary Disorders				
Blood creatinine increased [aa]	171 (5.4%)	14 (0.4%)	0 (0%)	Common
Nephritis [s]	3 (<0.1%)	1 (<0.1%)	0 (0%)	Rare
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	660 (20.8%)	9 (0.3%)	0 (0%)	Very Common
Dyspnea	651 (20.5%)	117 (3.7%)	1 (< 0.1%)	Very common
Hypoxia[x]	75 (2.4%)	36 (1.1%)	0 (0%)	Common
Pneumonitis[l]	87 (2.7%)	27 (0.8%)	1 (< 0.1%)	Common
Nasopharyngitis[bb]	280 (8.8%)	0 (0%)	0 (0%)	Common
Skin and Subcutaneous Tissue Disorders				
Rash[m]	613 (19.3%)	33 (1.0%)	0 (0%)	Very common
Pruritus	401 (12.6%)	7 (0.2%)	0 (0%)	Very common
Dry Skin	187 (5.9%)	1 (<0.1%)	0 (0%)	Common
Psoriatic conditions[cc]	19 (0.6%)	2 (<0.1%)	0 (0%)	Uncommon
Severe cutaneous adverse reactions [dd]	22 (0.7%)	3 (<0.1%)	1 (<0.1%)	Uncommon
Vascular Disorders				
Hypotension	102 (3.2%)	20 (0.6%)	0 (0%)	Common

a. Reported in studies outside the pooled dataset. The frequency is based on the program-wide exposure.
b. Includes reports of hypothyroidism, blood thyroid-stimulating hormone increased, blood thyroid-stimulating hormone decreased, thyroiditis, autoimmune hypothyroidism, euthyroid sick syndrome, myxedema, thyroid function test abnormal, thyroiditis acute, thyroxine decreased,
c. Includes reports of hyperthyroidism, , Basedow's disease, endocrine ophthalmopathy, exophthalmos,
d. Includes reports of adrenal insufficiency, primary adrenal insufficiency
e. Includes reports of diabetes mellitus, type 1 diabetes mellitus and ketoacidosis
f. Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic, colitis ulcerative
g. Includes reports of pancreatitis,autoimmune pancreatitis, pancreatitis acute, lipase increased and amylase increased
h. includes infusion related reaction and cytokine release syndrome
i. Includes reports of ascites, autoimmune hepatitis,hepatocellular injury, hepatitis, hepatitis acute, hepatotoxicity, liver disorder, drug-induced liver injury, hepatic failure, hepatic steatosis, hepatic lesion, esophageal varices hemorrhage, varices esophageal
j. Includes reports of Guillain-Barré syndrome and demyelinating polyneuropathy
k. Includes reports of encephalitis, meningitis, photophobia
l. Includes reports of pneumonitis, lung infiltration, bronchiolitis, interstitial lung disease, radiation pneumonitis
m. Includes reports of rash, rash maculo-papular, erythema, rash pruritic, dermatitis acneiform, eczema, dermatitis, rash erythematous, skin ulcer, rash papular, folliculitis, rash macular, skin exfoliation, rash pustular, furuncle, acne, drug eruption, palmar-plantar erythrodysaesthesia syndrome, seborrhoeic dermatitis, dermatitis allergic, erythema of eyelid, skin toxicity, eyelid rash, fixed eruption, rash papulosquamous, rash vesicular, blister, lip blister, pemphigoid, oral blood blister, scrotal dermatitis (cases of scrotal dermatitis have been reported in studies outside the pooled dataset)
n. Includes reports of thrombocytopenia and platelet count decreased
o. Includes reports of diarrhoea, frequent bowel movements, and gastrointestinal hypermotility
p. Includes reports of urinary tract infection, cystitis, pyelonephritis, escherichia urinary tract infection, pyelonephritis acute, urinary tract infection bacterial, kidney infection, urinary tract infection fungal, urinary tract infection pseudomonal
q. Includes reports of oropharyngeal pain, throat irritation, oropharyngeal discomfort
r. Includes reports of musculoskeletal pain, myalgia, bone pain
s. Includes reports of nephritis and Henoch-Schonlein Purpura nephritis
t. Includes reports of myositis, rhabdomyolysis, polymyalgia rheumatica, dermatomyositis, muscle abscess, myoglobin urine present
u. Fatal cases have been reported in studies outside the pooled dataset
v. Includes reports of hypokalaemia and blood potassium decreased
w. Includes reports of hyponatraemia and blood sodium decreased
x. Includes reports of hypoxia, oxygen saturation decreased, PO_2 decreased
y. Includes reports of hypophysitis and temperature regulation disorder
z. Includes report of myasthenia gravis
aa. Includes reports of blood creatinine increased and hypercreatininaemia
bb. Includes reports of nasopharyngitis, nasal congestion and rhinorrhea
cc. Includes reports of dermatitis psoriasiform and psoriasis.
dd. Includes reports of dermatitis bullous, exfoliative rash, erythema multiforme, dermatitis exfoliative generalised, toxic skin eruption, toxic epidermal necrolysis.
ee. Includes reports of pericarditis, pericardial effusion, cardiac tamponade and pericarditis constrictive
ff. Reported from postmarketing experience outside the pooled dataset. The frequency is based on the program-wide exposure.
gg. Reported in a study outside the pooled dataset (subcuntaneous administration related). The frequency is based on exposure to Tecentriw SC in IMscin001 and includes reports of injection site reaction, injection site pain, injection site erythema, and injection site rash

Tecentriq combination therapy

Additional ADRs identified in clinical trials (not reported in monotherapy trials) associated with the use of Tecentriq in combination therapy across multiple indications are summarized in Table 3. ADRs with a clinically relevant difference when compared to monotherapy (refer to Table 2) are also presented.

Table 3: Summary of adverse reactions occurring in patients treated with Tecentriq combination therapy in clinical trials

ADR (MedDRA)	Tecentriq + Combination Treatments (n = 4371)			
System Organ Class	All Grades (%)	Grade 3-4 (%)	Grade 5 (%)	Frequency (All Grades)
Blood and Lymphatic System Disorders				
Anemia[*]	1608 (36.8%)	631 (14.4%)	0 (0%)	Very Common
Lymphopenia[*, k]	145 (3.3%)	63 (1.4%)	0 (0%)	Common
Neutropenia[*,a]	1565 (35.8%)	1070 (24.5%)	6 (0.1%)	Very Common
Thrombocytopenia[*,‡, b]	1211 (27.7%)	479 (11.0%)	1 (<0.1%)	Very Common
Leukopenia[*, i]	571 (13.1%)	245 (5.6%)	0 (0%)	Very Common
Endocrine Disorders				
Hypothyroidism[*,‡,c]	586 (13.4)	9 (0.2%)	0 (0%)	Very Common
Hyperthyroidism[‡]	193 (4.4%)	7 (0.2%)	0 (0%)	Common
Adrenal insufficiency[‡,d]	40 (0.9%)	8 (0.2%)	1 (<0.1%)	Uncommon
Hypophysitis[‡,e]	13 (0.3%)	5 (0.1%)	0 (0%)	Uncommon
Gastrointestinal Disorders				
Constipation[*]	1123 (25.7%)	24 (0.5%)	0 (0%)	Very Common
Stomatitis[*]	351 (8.0%)	23 (0.5%)	0 (0%)	Common
General Disorders and Administration Site Condition				
Oedema Peripheral[*]	451 (10.3%)	11 (0.3%)	0 (0%)	Very Common
Infections and Infestations				
Lung infection[*,h]	564 (12.9%)	226 (5.2%)	26 (0.6%)	Very Common
Investigations				
Blood alkaline phosphatase increased	200 (4.6%)	26 (0.6%)	0 (0%)	Common
Metabolism and Nutrition Disorders				
Hypomagnesemia[*, j]	403 (9.2%)	22 (0.5%)	0 (0%)	Common
Nervous System Disorders				
Dizziness[*]	408 (9.3%)	9 (0.2%)	0 (0%)	Common

ADR (MedDRA)	Tecentriq + Combination Treatments (n = 4371)			
System Organ Class	All Grades (%)	Grade 3-4 (%)	Grade 5 (%)	Frequency (All Grades)
Dysgeusia*	269 (6.2%)	0 (0.0%)	0 (0%)	Common
Peripheral neuropathy*,f	1007 (23.0%)	107 (2.4%)	0 (0%)	Very Common
Syncope*	68 (1.6%)	36 (0.8%)	0 (0%)	Common
Renal and Urinary Disorders				
Nephritis‡,l	23 (0.5%)	15 (0.3%)	0 (0%)	Uncommon
Proteinuria*,g	359 (8.2%)	61 (1.4%)	0 (0%)	Common
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia*	236 (5.4%)	4 (<0.1%)	0 (0%)	Common
Nasopharyngitis°	442 (10.1%)	1 (< 0.1%)	0 (0%)	Very Common
Skin and Subcutaneous Tissue Disorders				
Alopecia[n]	1152 (26.4%)	3 (< 0.1%)	0 (0%)	Very Common
Severe cutaneous adverse reactions [p]	27 (0.6 %)	8 (0.2 %)	0 (0%)	Uncommon
Vascular Disorders				
Hypertension*,m	611 (14.0%)	258 (5.9%)	0 (0%)	Very Common

* ADR occurring at a frequency difference of ≥5% (All grades) or ≥2% (Grades 3-4) compared to the control arm.
‡ Observed rate in the combination represents a clinically relevant difference in comparison to Tecentriq monotherapy
a. Includes reports of neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis and granulocytopenia
b. Includes reports of thrombocytopenia and platelet count decreased
c. Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, blood thyroid stimulating hormone decreased, autoimmune thyroiditis, goitre, thyroiditis, thyroxine free decreased, tri−iodothyronine free decreased, thyroid disorder, thyroxine free increased, thyroxine increased, tri−iodothyronine decreased, tri-iodothyronine free increased, blood thyroid stimulating hormone abnormal, euthyroid sick syndrome, myxoedema coma, thyroid function test abnormal, thyroxine decreased, tri-iodothyronine abnormal, silent thyroiditis and thyroiditis chronic
d. Includes reports of adrenal insufficiency, cortisol decreased, adrenocortical insufficiency acute, secondary adrenocortical insufficiency, adrenocorticotropic hormone stimulation test abnormal, Addison's disease, adrenalitis and adrenocorticotropic hormone deficiency
e. Includes reports of hypophysitis and temperature regulation disorder
f. Includes reports of neuropathy peripheral, peripheral sensory neuropathy, polyneuropathy, herpes zoster, peripheral motor neuropathy, autoimmune neuropathy, neuralgic amyotrophy, peripheral sensorimotor neuropathy, axonal neuropathy, lumbosacral plexopathy, neuropathic arthropathy, toxic neuropathy and peripheral nerve infection
g. Includes reports of proteinuria, protein urine present, haemoglobinuria, nephrotic syndrome, urine abnormality and albuminuria
h. Includes reports of pneumonia, bronchitis, lower respiratory tract infection, tracheobronchitis, infective exacerbation of chronic obstructive airways disease, infectious pleural effusion, paracancerous pneumonia, atypical pneumonia, lung abscess, pleural infection and pyopneumothorax
i. Includes reports of white blood cell count decreased and leukopenia
j. Includes reports of hypomagnesaemia and blood magnesium decreased
k. Includes reports of lymphopenia and lymphocyte count decreased

l. Includes reports of nephritis, tubulointerstitial nephritis, autoimmune nephritis, nephritis allergic, glomerulonephritis, nephrotic syndrome and mesangioproliferative glomerulonephritis
m. Includes reports of hypertension, blood pressure increased, hypertensive crisis, blood pressure systolic increased, diastolic hypertension, blood pressure inadequately controlled and retinopathy hypertensive
n. Includes reports of alopecia, madarosis, alopecia areata, alopecia totalis and hypotrichosis
o. Includes reports of nasopharyngitis, nasal congestion and rhinorrhea
p. Includes reports of dermatitis bullous, exfoliative rash, erythema multiforme, dermatitis exfoliative generalised, toxic skin eruption, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), and cutaneous vasculitis (cases of SJS and DRESS have been reported in studies outside the pooled dataset).

Additional information for selected adverse reactions

The data below reflect information for significant adverse reactions for Tecentriq monotherapy. Details for the significant adverse reactions for Tecentriq when given in combination are presented if clinically relevant differences were noted in comparison to Tecentriq monotherapy. See section 2.4.1 Warnings and Precautions, General, for management of the following:

Haemophagocytic lymphohistiocytosis

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

Immune-mediated pericardial disorders

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

Immune-mediated endocrinopathies

Thyroid Disorders

Hypothyroidism occurred in 5.2% (164/3178) of patients who received Tecentriq monotherapy. The median time to onset was 4.9 months (range 0 to 31.3 months). Hypothyroidism occurred in 24.3% (134/552) of patients who received Tecentriq with bevacizumab

Hyperthyroidism occurred in 0.9% (30/3178) of patients who received Tecentriq monotherapy. The median time to onset was 2.1 months (range 0.7 to 15.7 months). The median duration was 2.6 months (range: 0+ to 17.1+ months; + denotes a censored value). Hyperthyroidism occurred in 6.3% (35/552) of patients who received Tecentriq with bevacizumab.

Adrenal Insufficiency

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

Hypophysitis

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

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

Diabetes Mellitus

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

Immune-mediated colitis

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

Immune-mediated pancreatitis

Pancreatitis, including increased amylase and lipase levels, occurred in 0.6% (18/3178) of patients who received Tecentriq monotherapy. The median time to onset was 5.0 months (range: 0.3 to 16.9 months). The median duration was 0.8 months (range 0.1 to 12.0+ months; +denotes a censored value) Pancreatitis led to discontinuation of Tecentriq in 3 (<0.1%) patients. Pancreatitis requiring the use of corticosteroids occurred in 0.1% (4/3174) of patients receiving Tecentriq.

Immune-mediated hepatitis

Hepatitis occurred in 2.0 (62/3178) of patients who received Tecentriq monotherapy.Of the 62 patients, two events were fatal. The median time to onset was1.5 months; (range: 0.2 to 18.8 months). The median duration was2.1 months (range: 0 to 22.2+ months; + denotes a censored). Hepatitis led to discontinuation of Tecentriq in 6 (0.2%)patients. Hepatitis

requiring the use of corticosteroids occurred in 0.6% (18/3178) of patients receiving Tecentriq

Immune-mediated myositis

Myositis occurred in 0.4% (13/3178) of patients who received Tecentriq monotherapy. The median time to onset was 5.1 months (range: 0.7 to 11.0 months). The median duration was 5.0 months (range 0.7 to 22.6+ months, + denotes a censored value). Myositis led to discontinuation of Tecentriq in 1 (<0.1%) patient. Myositis requiring the use of corticosteroids occurred in 0.2% (7/3178) of patients receiving Tecentriq.

Immune-mediated meningoencephalitis

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

Immune-mediated neuropathies

Guillain-Barré syndrome and demyelinating polyneuropathy

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

Immune-mediated facial paresis

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

Immune-mediated myelitis

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

Immune-mediated nephritis

Nephritis, occurred in <0.1% (3/3178) of patients who received Tecentriq monotherapy. The median time to onset was 13.1 months (range: 9.0 to 17.5 months). The median duration was 2.8 months (range 0.5 to 9.5+ months; + denotes a censored value).

Nephritis led to discontinuation of Tecentriq in 2 (<0.1%) patients. One patient required the use of corticosteroids.

Immune-mediated pneumonitis

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

Immune-mediated severe cutaneous adverse reactions

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

2.6.2 Postmarketing Experience

The following adverse drug reactions have been identified from post marketing surveillance with TECENTRIQ (see Table 4). Adverse drug reactions from post marketing surveillance are listed by MedDRA system organ class.

Table 4 Adverse Drug Reactions from Postmarketing Surveillance

System Organ Class	**Frequency**
ADR (preferred term, MedDRA)	
Blood and Lymphatic System Disorders	
Haemophagocytic lymphohistiocytosis[a]	Rare
Cardiac Disorders	
Pericardial disorders[a,b]	Common
Nervous System Disorders	
Facial paresis[a]	Rare
Myelitis[a]	Rare

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

2.7 Overdose

There is no information on overdose with Tecentriq.

2.8 Interactions with Other Medicinal Products and Other Forms of Interaction

No formal pharmacokinetic drug-drug interaction studies have been conducted with atezolizumab. Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 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 tumor cells and tumor-infiltrating immune cells, and can contribute to the inhibition of the anti-tumor 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-tumor immune response. Atezolizumab leaves the PD-L2 / PD-1 interaction intact. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

3.1.2 Clinical / Efficacy Studies

UC

IMvigor 211

A phase III, open-label, multi-center, international, randomized study, GO29294 (IMvigor211), was conducted to evaluate the efficacy and safety of Tecentriq compared with chemotherapy (investigator's choice of vinflunine, docetaxel, or paclitaxel) in patients with locally advanced or metastatic urothelial carcinoma who progressed during or following a platinum-containing regimen. This study excluded patients who had a history of autoimmune disease; active or corticosteroid-dependent brain metastases; administration of a live, attenuated vaccine within 28 days prior to enrolment; and administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal product within 2 weeks prior to enrolment. Tumor

assessments were conducted every 9 weeks for the first 54 weeks, and every 12 weeks thereafter. Tumor specimens were evaluated prospectively for PD-L1 expression on tumour-infiltrating immune cells (IC) and the results were used to define the PD-L1 expression subgroups for the analyses described below.

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

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

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

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

The median survival follow up was 17 months. Study IMvigor211 did not meet its primary endpoint. In the subset of patients with tumors having PD-L1 expression ≥5%, Tecentriq did not demonstrate a statistically significant survival benefit compared to chemotherapy with an OS HR of 0.87 (95% CI: 0.63, 1.21; median OS of 11.1 vs. 10.6 months for

Tecentriq and chemotherapy respectively). The stratified log rank p value was 0.41. As a consequence, no formal statistical testing was performed for OS in the PD-L1 expression ≥1% subgroup or in all comers, and results of those analyses are considered exploratory. The key results in the all comer population are summarised in Table 5. The Kaplan Meier curve for OS in the all comer population is presented in Figure 1.

Table 5: Summary of efficacy in all comers (IMvigor211)

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

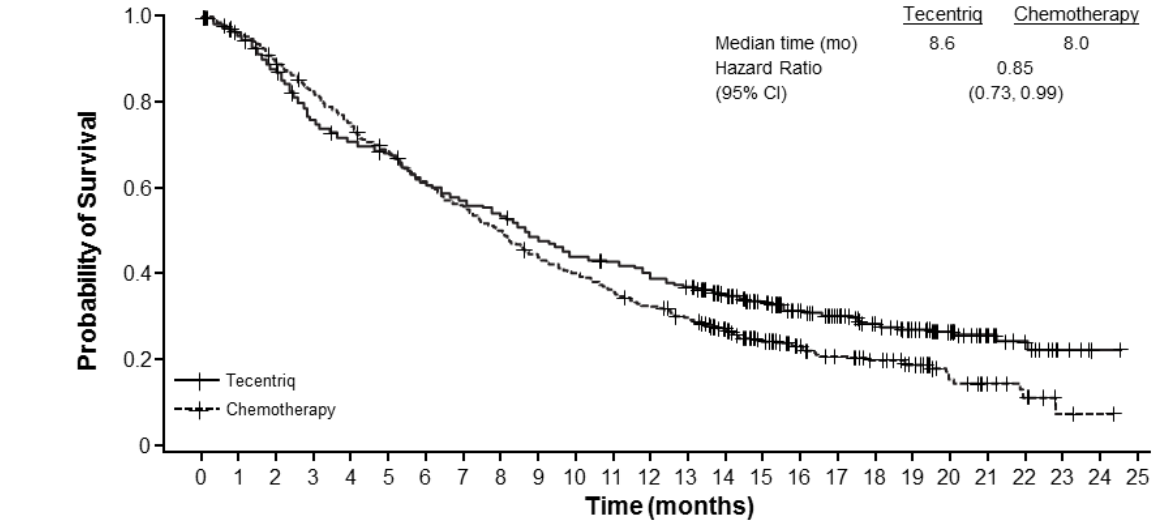
CI=confidence interval; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1.

* Based on Kaplan-Meier estimate

‡ Stratified by chemotherapy (vinflunine vs taxane), PD-L1 status on IC (<5% vs. ≥ 5%), number of prognostic risk factors (0 vs. 1-3), and liver metastases (yes vs. no).

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

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



IMvigor 210

A phase II, multi-center, international, two-cohort, single-arm clinical trial, GO29293 (IMvigor210), was conducted in patients with locally advanced or metastatic urothelial carcinoma (also known as urothelial bladder cancer). The study enrolled a total of 438 patients and had two patient cohorts. Cohort 1 included previously untreated patients with locally advanced or metastatic urothelial carcinoma who were ineligible or unfit for cisplatin-based chemotherapy or had disease progression at least 12 months after treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. Cohort 2 included patients who received at least one platinum-based chemotherapy regimen for locally advanced or metastatic urothelial carcinoma or had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen.

In cohort 1, 119 patients were treated with Tecentriq 1200 mg by intraveneous infusion every 3 weeks until disease progression. The median age was 73 years. Most patients were male (81%), and the majority of patients were white (91%).

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

The primary efficacy endpoint for Cohort 1 was confirmed objective response rate (ORR) as assessed by an independent review facility (IRF) using RECIST v1.1. The primary analysis was performed when all patients had at least 24 weeks of follow-up. Median duration of treatment was 15.0 weeks and median duration of survival follow-up was 8.5 months in all comers. Clinically relevant IRF-assessed ORRs per RECIST v1.1 were shown; however, when compared to a prespecified historical control response rate of 10%, statistical significance was not reached for the primary endpoint. The confirmed ORRs per IRF-RECIST v1.1 were 21.9% (95% CI: 9.3, 40.0) in patients with PD-L1 expression ≥ 5%, 18.8% (95% CI: 10.9, 29.0) in patients with PD-L1 expression ≥ 1%, and 19.3% (95% CI: 12.7, 27.6) in all comers. The median duration of response (DOR) was not reached in any PD-L1 expression subgroup or in all comers. OS was not mature with an event ratio of approximately 40%. Median OS for all patient subgroups (PD-L1 expression ≥ 5% and ≥ 1%) and in all comers was 10.6 months.

An updated analysis was performed with a median duration of survival follow up of 17.2 months for Cohort 1 and is summarized in Table 6. The median DOR was not reached in any PD-L1 expression subgroup or in all comers.

Table 6 Summary of updated efficacy from IMvigor 210 Cohort 1

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

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

In Cohort 2, the co-primary efficacy endpoints were confirmed ORR as assessed by an IRF using RECIST v1.1 and investigator-assessed ORR according to Modified RECIST (mRECIST) criteria. There were 310 patients treated with Tecentriq 1200 mg by intravenous infusion every 3 weeks until loss of clinical benefit.The primary analysis of Cohort 2 was performed when all patients had at least 24 weeks of follow-up. The study met its co-primary endpoints in all subgroups in Cohort 2, demonstrating statistically significant ORRs per IRF-assessed RECIST v1.1 and investigator-assessed mRECIST compared to a prespecified historical control response rate of 10%.

An analysis was also performed with a median duration of survival follow up 21.1 months for Cohort 2. The confirmed ORRs per IRF-RECIST v1.1 were 28.0% (95% CI: 19.5, 37.9) in patients with PD-L1 expression ≥ 5%, 19.3% (95% CI: 14.2, 25.4) in patients with PD-L1 expression ≥ 1%, and 15.8% (95% CI: 11.9, 20.4) in all comers. The confirmed ORR per investigator-assessed mRECIST was 29.0% (95% CI: 20.4, 38.9) in patients with PD-L1 expression ≥ 5%, 23.7% (95% CI: 18.1, 30.1) in patients with PD-L1 expression ≥ 1%, and 19.7% (95% CI: 15.4, 24.6) in all comers. The rate of complete response per IRF-RECIST v1.1 in the all comer population was 6.1% (95% CI: 3.7, 9.4) Median DOR was not reached in any PD-L1 expression subgroups or in all comers, however was reached in patients with PD-L1

expression <1% (13.3 months; 95% CI 4.2, NE). The OS rate at 12 months was 37% in all comers.

NSCLC

Early-stage NSCLC

IMpower010

A phase III, open-label, multi-center, randomized study, GO29527 (IMpower010), was conducted to evaluate the efficacy and safety of Tecentriq for the adjuvant treatment of patients with stage IB (tumors ≥ 4 cm) – IIIA NSCLC (per the Union for International Cancer Control/American Joint Committee on Cancer staging system, 7th edition). A total of 1280 enrolled patients had complete tumor resection and were eligible to receive up to 4 cycles of cisplatin-based chemotherapy. The cisplatin-based chemotherapy regimens are described in Table 7.

Table 7 Chemotherapy Intraveneous Treatment Regimens in Study IMpower010

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

After completion of cisplatin-based chemotherapy (up to four cycles), a total of 1005 patients were randomized in a 1:1 ratio to receive Tecentriq (Arm A) or best supportive care (BSC) (Arm B). Tecentriq was administered as a fixed dose of 1200 mg by IV infusion every 3 weeks for 16 cycles unless there was disease recurrence or unacceptable toxicity. Randomization was stratified by sex, stage of disease, histology, and PD-L1 expression.

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

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

The primary efficacy outcome measure was disease-free survival (DFS) as assessed by the investigator. DFS was defined as the time from the date of 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 occured first. A key secondary efficacy outcome measure was overall survival (OS).

At the time of the interim DFS analysis, the study met its primary endpoint and demonstrated a statistically significant and clinically meaningful improvement in DFS in the Tecentriq arm compared to the BSC arm in the PD-L1 ≥ 1% TC stage II - IIIA patient population. The median follow-up time was approximately 32 months. The OS data were immature at the time of the DFS interim analysis with approximately 18.9% of deaths reported in both arms in the PD-L1 ≥ 1% TC stage II - IIIA patient population. An exploratory analysis of OS suggested a trend in favor of Tecentriq over BSC (stratified HR=0.77 [95% CI: 0.51, 1.17]) in this patient population.

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

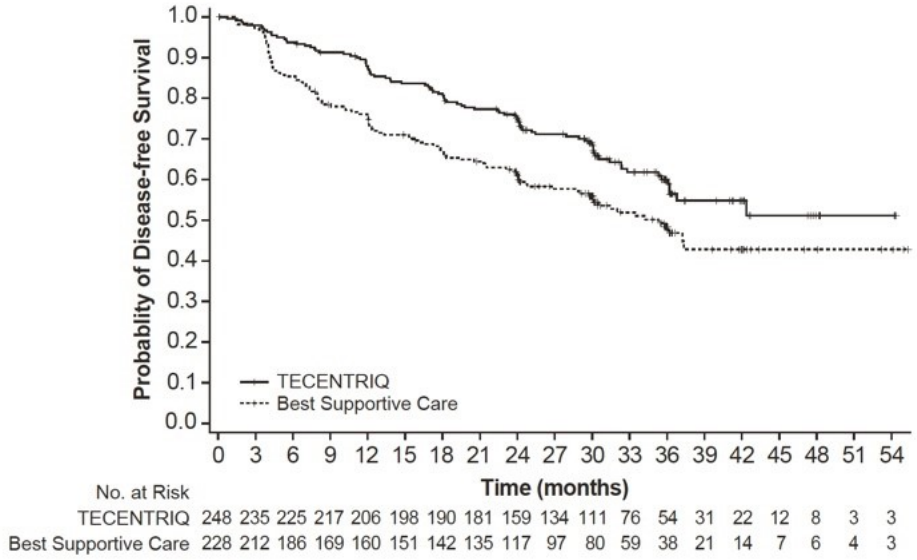
The key efficacy results are summarized in Table 8. The Kaplan-Meier curve for DFS is presented in Figure 2.

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

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

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

Figure 2: Kaplan-Meier Plot of Disease-Free Survival in the PD-L1 expression ≥ 1% TC stage II - IIIA patient population



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

1L metastatic non-squamous NSCLC

IMpower 150

A phase III, open-label, randomized study, GO29436 (IMpower150), was conducted to evaluate the efficacy and safety of Tecentriq in combination with paclitaxel and carboplatin, with or without bevacizumab, in chemotherapy-naïve patients with metastatic non-squamous NSCLC. A total of 1202 patients were enrolled and were randomized in a 1:1:1 ratio to receive one of the treatment regimens described in Table 9. Randomization was stratified by sex, presence of liver metastases and PD-L1 tumor expression on tumor cells (TC) and tumor infiltrating cells (IC).

Table 9 Intravenous Treatment regimens in Study IMpower 150

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

[a]Tecentriq is administered until loss of clinical benefit as assessed by the investigator

[b]The paclitaxel starting dose for patients of Asian race/ethnicity was 175 mg/m^2 due to higher overall level of hematologic toxicities in patients from Asian countries compared with those from non-Asian countries.

[c]Carboplatin and paclitaxel are administered until completion of 4 or 6 cycles, or progressive disease or unacceptable toxicity whichever occurs first

[d]Bevacizumab is administered until progressive disease or unacceptable toxicity

Patients were excluded if they had history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; active or untreated CNS metastases; clear tumor infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging. Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter.

The demographics and baseline disease characteristics of the study population were well balanced between the treatment arms. In this study, the median age was 63 years (range: 31 to 90), and 60% of patients were male. The majority of patients were white (82%). Approximately 10% of patients had known EGFR mutations, 4% had known ALK rearrangements, 14% had liver metastases at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%).

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

At the time of the interim OS analysis, patients had a median follow up time of 19.7 months. The key results from this analysis are summarized in Table 10. Kaplan-Meier curves for OS in the ITT population are presented in Figure 3. Figure 4 summarizes the results of OS in the ITT and PD-L1 subgroups, demonstrating OS benefit with Tecentriq

in all subgroups, including those with PD-L1 expression <1% on TC and IC. Updated PFS results are also demonstrated in Figure 5 and 6.

Table 10: Summary of updated efficacy from IMpower150

Key efficacy endpoints	Arm B	Arm C
OS interim analysis	n=400	n=400
No. of deaths (%)	192 (48.0%)	230 (57.5%)
Median time to events (months)	19.8	14.9
95% CI	(17.4, 24.2)	(13.4, 17.1)
Stratified hazard ratio (95% CI)	0.76 (0.63, 0.93)	
p-value [1,2]	0.006	
6-month OS (%)	85	81
12-month OS (%)	68	61
Investigator-assessed PFS (RECIST v1.1)	n=400	n=400
No. of events (%)	291 (72.8%)	355 (88.8%)
Median duration of PFS (months)	8.4	6.8
95% CI	(8.0, 9.9)	(6.0, 7.0)
Stratified hazard ratio‡ (95% CI)	0.59 (0.50, 0.69)	
p-value [1,2]	< 0.0001	
12-month PFS (%)	38	20
Investigator-assessed Overall Best Response[3] (RECIST 1.1)	n=397	n=393
No. of responders (%)	224 (56.4%)	158 (40.2%)
95% CI	(51.4, 61.4)	(35.3, 45.2)
No. of complete response (%)	11 (2.8%)	3 (0.8%)
No. of partial response (%)	213 (53.7%)	155 (39.4%)
Investigator-assessed DOR (RECIST 1.1)	n=224	n=158
Median in months	11.5	6.0
95% CI	(8.9, 15.7)	(5.5, 6.9)

1. Based on the stratified log-rank test
2. For informational purposes; comparisons between Arm B and Arm C in the ITT population were not formally tested yet, as per the pre-specified analysis hierarchy.
3. Overall best response for complete response and partial response

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

PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1.; CI=confidence interval;

ORR=objective response rate; DOR=duration of response; OS=overall survival

Figure 3: Kaplan-Meier Plot for Overall Survival in the ITT population (IMpower150)

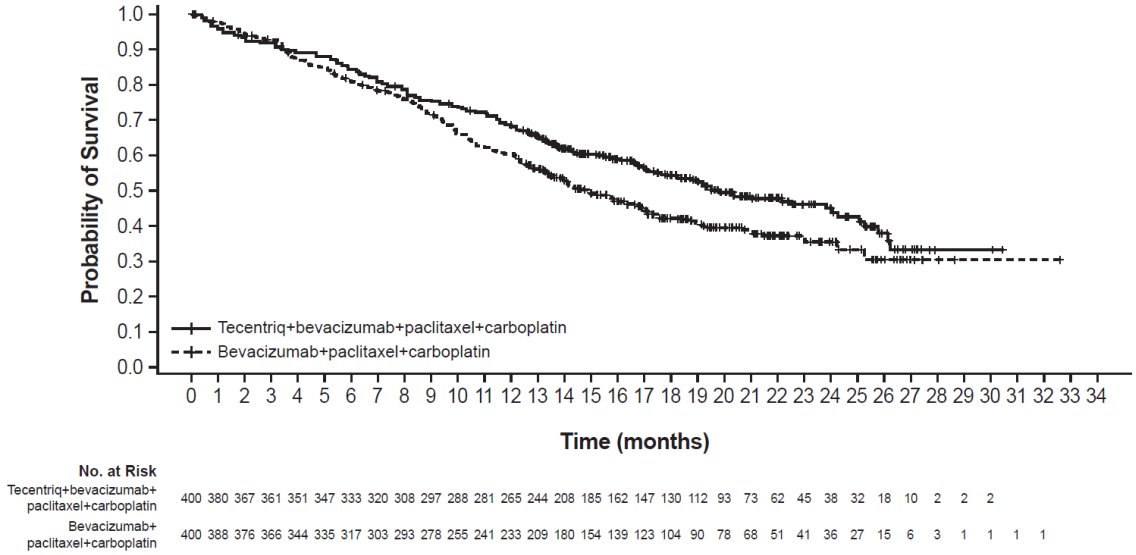


Figure 4: Forest plot of overall survival by PD-L1 expression in the ITT population (IMpower150)

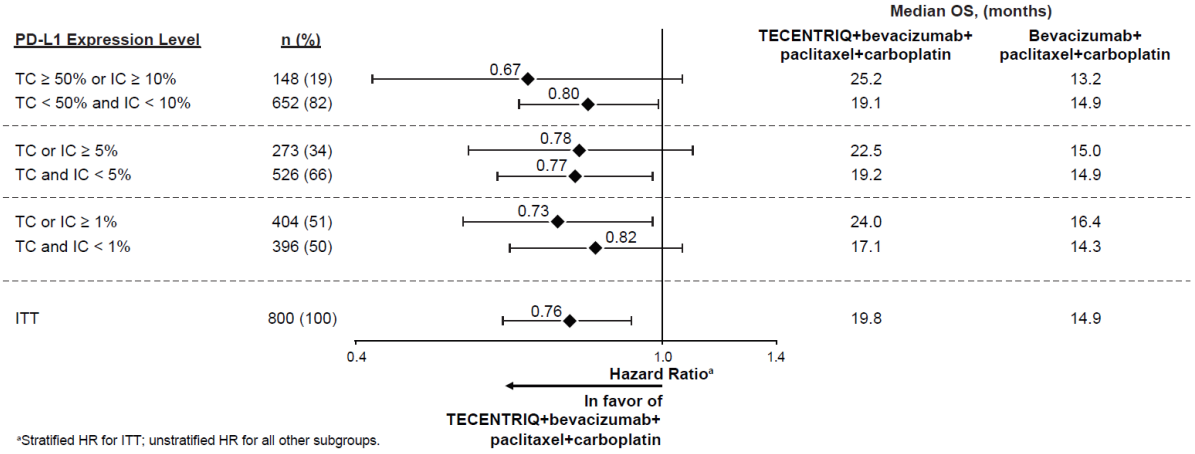


Figure 5: Kaplan-Meier Plot for updated Progression Free Survival in the ITT population (IMpower150)

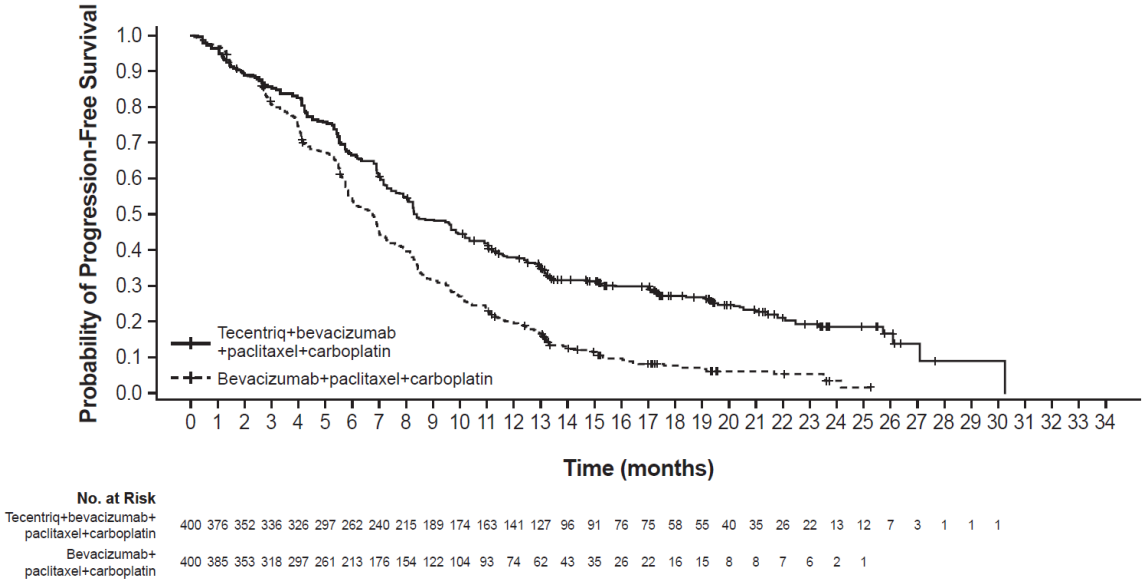
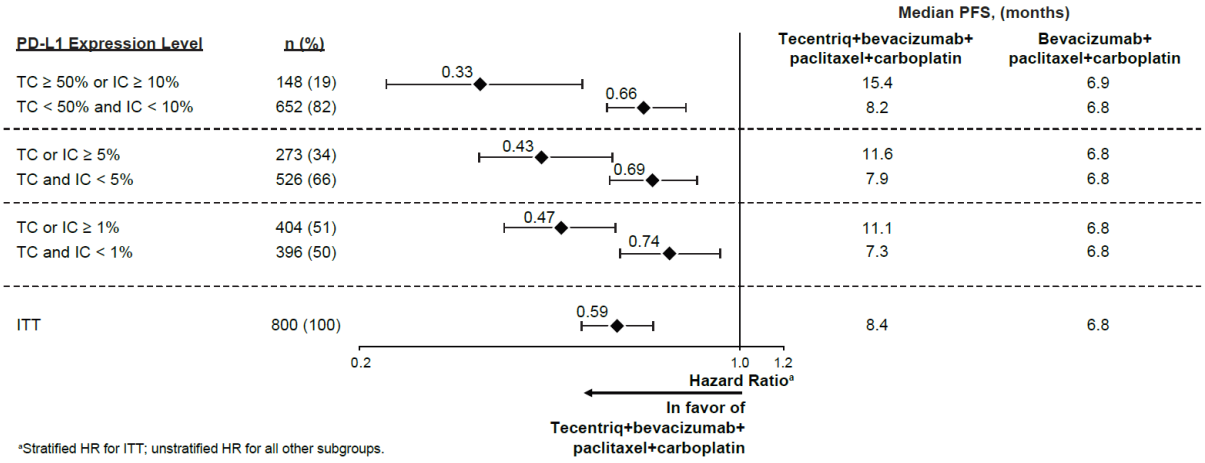


Figure 6: Forest plot of updated progression free survival by PD-L1 expression in the ITT population (IMpower150)



Pre-specified subgroup analyses from the interim OS analysis showed numerical OS improvements in the Tecentriq with bevacizumab, paclitaxel, carboplatin arm as compared to the bevacizumab, paclitaxel and carboplatin arm for patients with EGFR mutations or ALK rearrangements (HR: 0.54 [95% CI: 0.29, 1.03], median OS NE vs. 17.5 months) and liver metastases (HR:0.52 [95% CI: 0.33, 0.82], median OS 13.3 vs 9.4 months). Numerical PFS improvements were also shown in patients with EGFR mutations or ALK

rearrangements (HR: 0.55 [95% CI 0.34, 0.90], median PFS 10 vs. 6.1 months) and liver metastases (HR: 0.41 [95%CI 0.26, 0.62], median PFS 8.2 vs. 5.4 months).

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

IMpower130

A Phase III, open-label, randomized study, GO29537 (IMpower130) was conducted to evaluate the efficacy and safety of Tecentriq in combination with nab-paclitaxel and carboplatin, in chemotherapy-naïve patients with metastatic non-squamous NSCLC. Patients including those with EGFR or ALK genomic tumor aberrations, were enrolled and were randomized in a 2:1 ratio to receive one of the treatment regimens described in Table 11. Randomization was stratified by sex, presence of liver metastases and PD-L1 tumor expression on tumor cells (TC) and tumor infiltrating cells (IC). Patients in treatment regimen B were able to crossover and receive Tecentriq monotherapy following disease progression.

Table 11 Intravenous treatment regimens in IMpower130

Treatment Regimen	Induction (Four or Six 21-Day Cycles)	Maintenance (21-Day Cycles)
A	Tecentriq (1200mg)[a] + nab-paclitaxel ($100mg/m^2$)[b,c] + carboplatin (AUC 6)[c]	Tecentriq (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 and is administered until completion of 4-6 cycles, or progressive disease or unacceptable toxicity whichever occurs first

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

The demographics and baseline disease characteristics of the study population (n = 723) were well balanced between the treatment arms. The median age was 64 years (range 18

to 86). The majority of the patients were, male (57%), white (90%). 14.8% of patients had liver metastases at baseline, and most patients were current or previous smokers (88%). The majority of patients had baseline ECOG performance status of 1 (58.7%).

The primary analysis was conducted in all patients, excluding those with EGFR or ALK genomic tumor aberrations (n = 679). Patients had a median survival follow up time of 18.6 months. Improvements in OS and PFS were demonstrated with Tecentriq + nab-paclitaxel + carboplatin compared to the control. The key results are summarized in Table 12 and Kaplan-Meier curves for OS and PFS are presented in Figures 7 and 9, respectively.

All PD-L1 subgroups, regardless of expression, derived benefit in terms of OS and PFS; the results are summarized in Figure 8 and 10. Consistent OS and PFS benefit was demonstrated in all other pre-specified subgroups, with the exception of patients with liver metastases who did not show improved OS with Tecentriq, nab-paclitaxel and carboplatin, compared to nab-paclitaxel and carboplatin (HR of 1.04, 95% CI: 0.63,1.72).

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

Table 12 Summary of efficacy from IMpower130 in the Primary Analysis Population

Key efficacy endpoints	Tecentriq + nab-paclitaxel + carboplatin	nab-paclitaxel + carboplatin
Co-primary Endpoints		
OS	n = 451	n = 228
No. of deaths (%)	226 (50.1%)	131 (57.5%)
Median time to events (months)	18.6	13.9
95% CI	(16.0, 21.2)	(12.0, 18.7)
Stratified hazard ratio‡ (95% CI)	0.79 (0.64, 0.98)	
p-value	0.033	
12-month OS (%)	63	56
Investigator-assessed PFS (RECIST v1.1)	n = 451	n = 228
No. of events (%)	347 (76.9)	198 (86.8)
Median duration of PFS (months)	7.0	5.5
95% CI	(6.2, 7.3)	(4.4, 5.9)
Stratified hazard ratio‡ (95% CI)	0.64 (0.54, 0.77)	
p-value	< 0.0001	
12-month PFS (%)	29	14

Key efficacy endpoints	Tecentriq + nab-paclitaxel + carboplatin	nab-paclitaxel + carboplatin
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 tumor expression on TC and IC
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1.; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival

Figure 7: Kaplan-Meier Plot for Overall Survival (IMpower130)

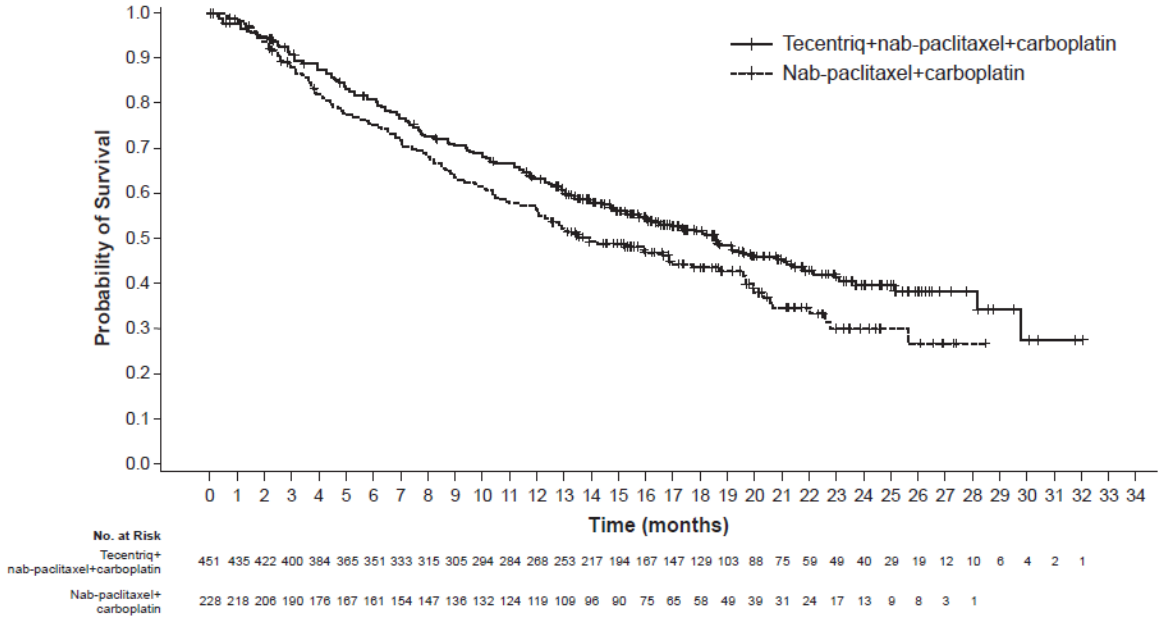


Figure 8: Forest Plot of Overall Survival by PD-L1 expression (IMpower130)

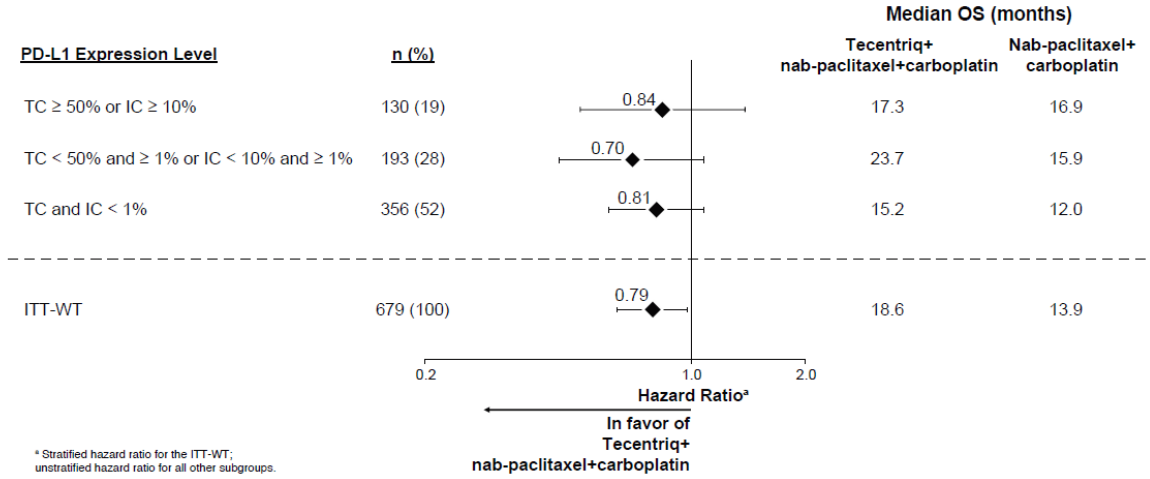


Figure 9: Kaplan-Meier Plot for Progression Free Survival (IMpower130)

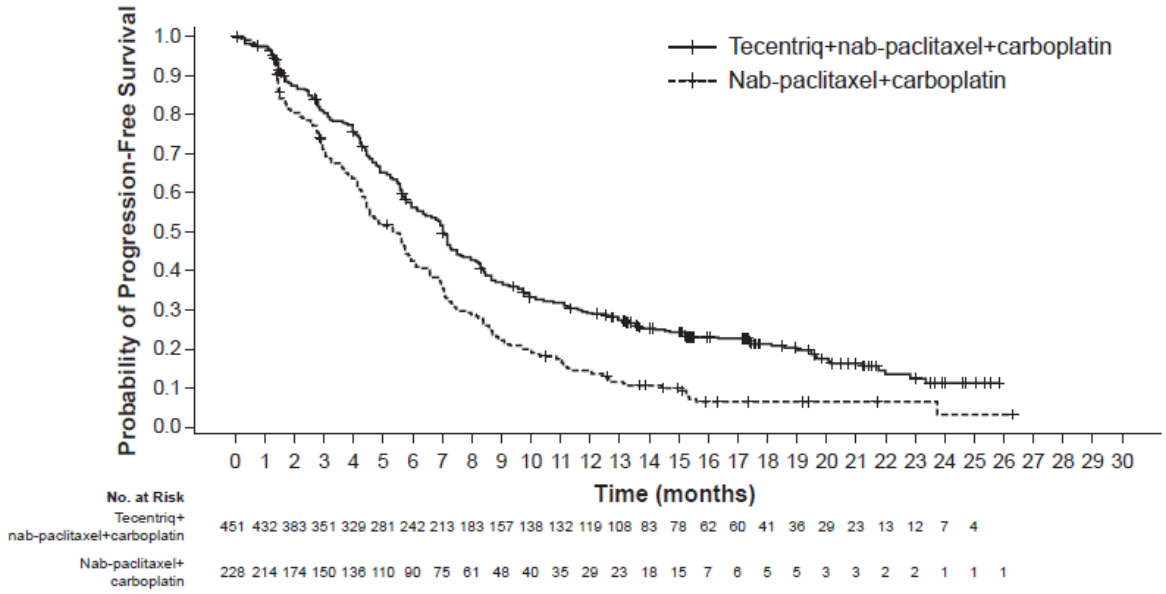
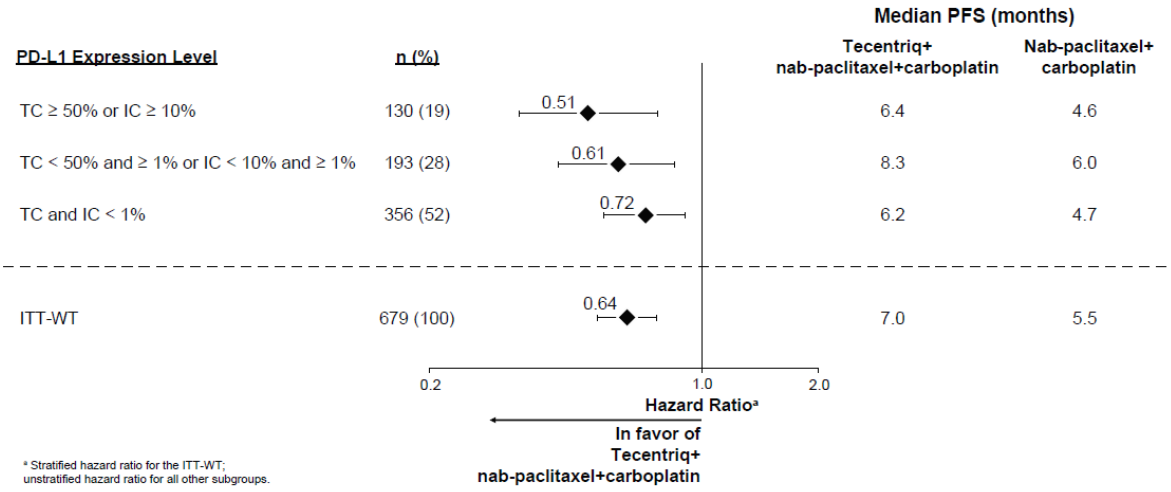


Figure 10: Forest Plot of Progression Free Survival by PD-L1 expression (IMpower130)



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

however patients receiving Tecentriq, nab-paclitaxel and carboplatin reported less worsening of these symptoms over time.

1L metastatic non-squamous and squamous NSCLC

IMpower110

A phase III, open-label, multi-center, randomized study, GO29431 (IMpower110), was conducted to evaluate the efficacy and safety of Tecentriq in chemotherapy-naïve patients with metastatic NSCLC, with PD-L1 expression ≥ 1% TC (PD-L1 stained ≥ 1% of tumor cells) or ≥ 1% IC (PD-L1 stained tumor-infiltrating immune cells covering ≥ 1% of the tumor area) by the VENTANA PD-L1 (SP142) Assay.

A total of 572 patients were randomized in a 1:1 ratio to receive Tecentriq (Arm A) or chemotherapy (Arm B). Tecentriq was administered as a fixed dose of 1200 mg by IV infusion every 3 weeks until loss of clinical benefit as assessed by the investigator or unacceptable toxicity. The chemotherapy regimens are described in Table 13. Randomization was stratified by sex, ECOG performance status, histology, and PD-L1 tumor expression on TC and IC.

Table 13 Chemotherapy Intravenous Treatment Regimens in Study IMpower110

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

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

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

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

baseline disease characteristics in patients with high PD-L1 expression (PD-L1 ≥ 50% TC or ≥ 10% IC) who do not have EGFR or ALK genomic tumor aberrations (n=205) were generally representative of the broader study population and were balanced between the treatment arms.

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

Table 14 Summary of efficacy from IMpower110 in patients with high PD-L1 expression (≥ 50% TC or ≥ 10% IC 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 time to events (months)	20.2	13.1
95% CI	(16.5, NE)	(7.4, 16.5)
Stratified hazard ratio‡ (95% CI)	0.59 (0.40, 0.89)	
p-value‡	0.0106	
12-month OS (%)	64.9	50.6
Secondary endpoints		
Investigator-assessed PFS (RECIST v1.1)	n=107	n=98
No. of events (%)	67 (62.6%)	79 (80.6%)
Median duration of PFS (months)	8.1	5.0
95% CI	(6.8, 11.0)	(4.2, 5.7)
Stratified hazard ratio‡ (95% CI)	0.63 (0.45, 0.88)	
12-month PFS (%)	36.9	21.6
Investigator-assessed ORR (RECIST 1.1)	n = 107	n = 98
No. of responders (%)	41 (38.3%)	28 (28.6%)
95% CI	(29.1, 48.2)	(19.9, 38.6)
No. of complete response (%)	1 (0.9%)	1 (1.0%)
No. of partial response (%)	40 (37.4%)	27 (27.6%)
Investigator-assessed DOR (RECIST 1.1)	n = 41	n = 28

Key efficacy endpoints	**Arm A** (Tecentriq)	**Arm B** (Chemotherapy)
Median in months	NE	6.7
95% CI	(11.8, NE)	(5.5, 17.3)

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

Figure 11: Kaplan-Meier Plot of Overall Survival in Patients with high PD-L1 Expression (≥ 50% TC or ≥ 10% IC)

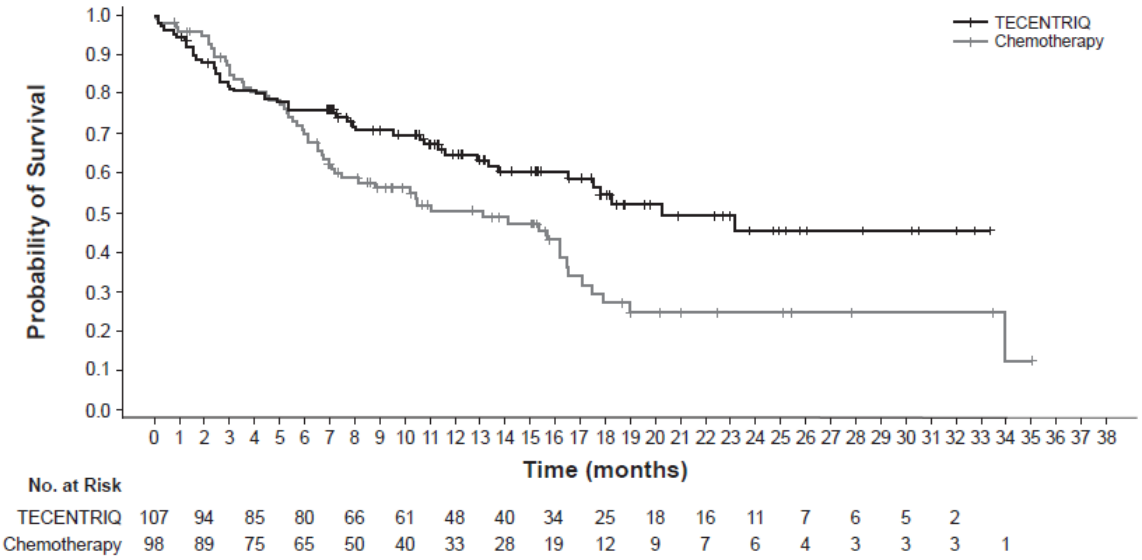
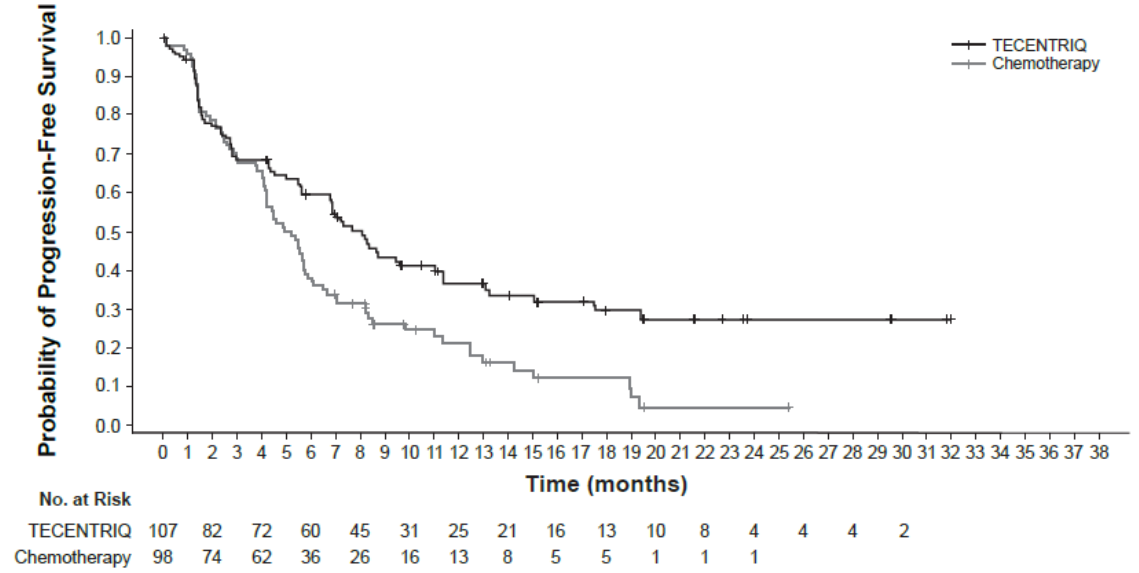


Figure 12: Kaplan-Meier Plot of Progression Free Survival in Patients with high PD-L1 Expression (≥ 50% TC or ≥ 10% IC)



The observed OS improvement in the Tecentriq arm compared with the chemotherapy arm was consistently demonstrated across subgroups in patients with high PD-L1 expression including both non-squamous NSCLC patients (HR: 0.62 [95% CI: 0.40, 0.96], median

OS 20.2 vs. 10.5 months) and squamous NSCLC patients (HR: 0.56 [95% CI: 0.23, 1.37]) median OS NE vs 15.3 months). The data for patients ≥75 years old and patients who were never smokers are too limited to draw conclusions in these subgroups.

Additional pre-specified analyses were conducted to evaluate efficacy by PD-L1 status assessed by the VENTANA PD-L1 (SP263) Assay and by the PD-L1 IHC 22C3 pharmDxTM kit in all randomized patients with PD-L1 expression ≥ 1% TC or ≥ 1% IC by the VENTANA PD-L1 (SP142) Assay who do not have EGFR or ALK genomic tumour abberations (n=554). An OS improvement was observed with atezolizumab compared to chemotherapy in patients with high PD-L1 expression (PD-L1 ≥50% TC) using the VENTANA PD-L1 (SP263) Assay (n=293; HR: 0.71 [95% CI: 0.50, 1.00], median OS 19.5 vs. 16.1 months) and in patients with high PD-L1 expression (Tumour Proportion Score (TPS) ≥50%) using the PD-L1 IHC 22C3 pharmDxTM Kit (n=260; HR: 0.60 [95% CI: 0.42, 0.86], median OS 20.2 vs 11.0 months).

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

1L ES - SCLC

IMpower133

A Phase I/III, randomized, multicenter, double-blind, placebo controlled study, GO30081 (IMpower133), was conducted to evaluate the efficacy and safety of Tecentriq in combination with carboplatin and etoposide in patients with chemotherapy-naïve ES-SCLC. A total of 403 patients were randomized (1:1) to receive one of the treatment regimens described in Table 15. Randomization was stratified by sex, ECOG performance status, and presence of brain metastases.

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

Table 15 Intravenous Treatment Regimen in Study IMpower133

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

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

The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 64 years (range: 26 to 90 years). The majority of patients were male (65%), white (80%), and 9% had brain metastases and most patients were current or previous smokers (97%). Baseline ECOG performance status was 0 (35%) or 1 (65%).

At the time of the primary analysis, patients had a median survival follow up time of 13.9 months. The key results are summarized in Table 16. Kaplan-Meier curves for OS and PFS are presented in Figure 13 and 14.

Table 16 Summary of efficacy from IMpower133

Key efficacy endpoints	Arm A (Tecentriq + carboplatin + etoposide)	Arm B (Placebo + carboplatin + etoposide)
Co-primary endpoints		
OS analysis	n=201	n=202
No. of deaths (%)	104 (51.7%)	134 (66.3%)
Median time to events (months)	12.3	10.3
95% CI	(10.8, 15.9)	(9.3, 11.3)
Stratified hazard ratio‡ (95% CI)	0.70 (0.54, 0.91)	
p-value	0.0069	
12-month OS (%)	51.7	38.2
Investigator-assessed PFS (RECIST v1.1)	n=201	n=202
No. of events (%)	171 (85.1%)	189 (93.6%)
Median duration of PFS (months)	5.2	4.3
95% CI	(4.4, 5.6)	(4.2, 4.5)
Stratified hazard ratio‡ (95% CI)	0.77 (0.62, 0.96)	
p-value	0.0170	
6-month PFS (%)	30.9	22.4
12-month PFS (%)	12.6	5.4

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

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

‡ Stratified by sex and ECOG performance status

Figure 13: Kaplan-Meier Plot of Overall Survival (IMpower133)

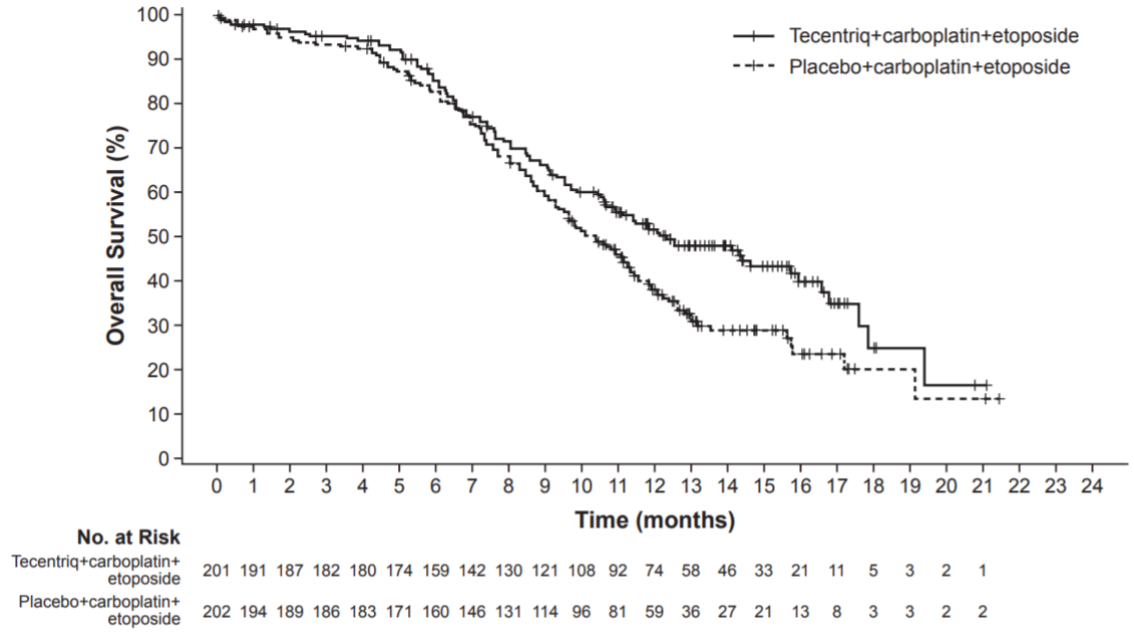
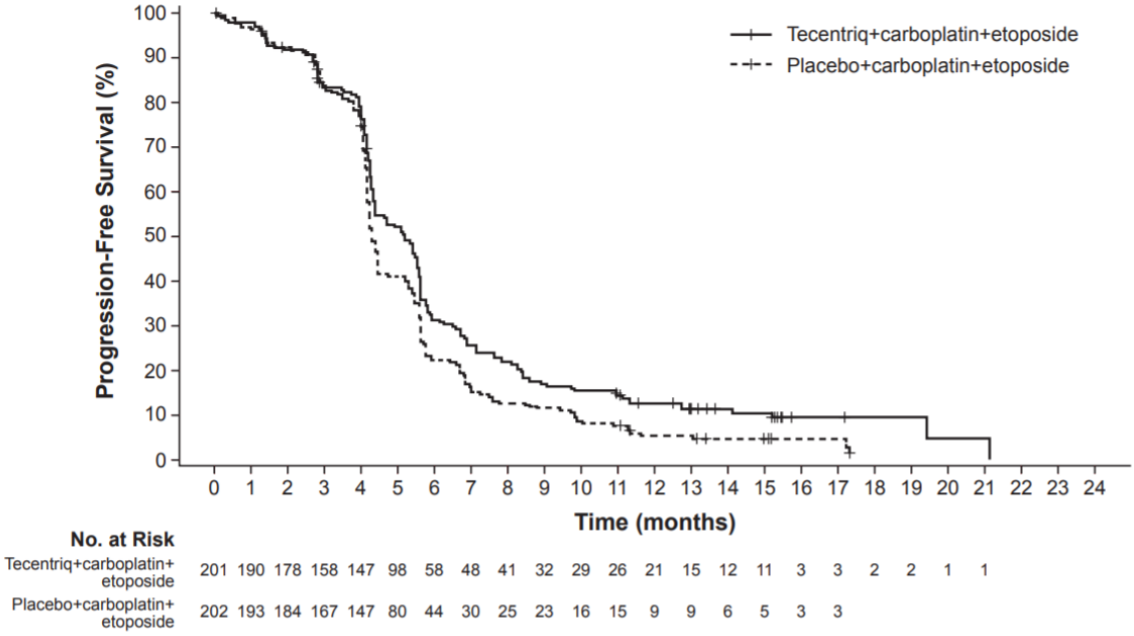


Figure 14: Kaplan-Meier Plot of Progression-Free Survival (IMpower133)



This study also included an exploratory analysis of average score changes from baseline in patient-reported symptoms, physical function, and health-related quality of life (measured using the EORTC QLC-C30 and QLC-LC13). On average, patients who received Tecentriq with carboplatin and etoposide reported early and notable improvements in lung cancer-related symptoms (e.g., coughing, chest pain, dyspnea) and physical function. Changes in

treatment-related symptoms (e.g., diarrhea, nausea and vomiting, sore mouth, peripheral neuropathy) were comparable between arms throughout induction and most visits through week 54. Overall, patients treated with Tecentriq, carboplatin and etoposide achieved more pronounced and enduring improvements in health-related quality of life (≥10-point score increases at most visits through Week 48) compared to patients treated with placebo, carboplatin and etoposide, who reported nominal improvements (<10-point score increases) at most study treatment visits.

2L NSCLC

Tecentriq IV

OAK

A phase III, open-label, multi-center, international, randomized study, GO28915 (OAK), was conducted to evaluate the efficacy and safety of Tecentriq compared with docetaxel in patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen. A total of 1225 patients were enrolled, with the primary analysis population consisting of the first 850 randomized patients. Eligible patients were stratified by PD-L1 expression status in tumor-infiltrating immune cells (IC), by the number of prior chemotherapy regimens, and by histology. Patients were randomized (1:1) to receive either Tecentriq or docetaxel. This study excluded patients who had a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Tumor assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter. Tumor specimens were evaluated prospectively for PD-L1 expression on tumor cells (TC) and IC 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 CNS metastases at baseline, and most patients were current or previous smokers (82%). Baseline ECOG performance status was 0 (37%) or 1 (63%). Seventy-five percent of patients received only one prior platinum-based therapeutic regimen.

Tecentriq was administered as a fixed dose of 1200 mg by IV infusion every 3 weeks. No dose reduction was allowed. Patients were treated until loss of clinical benefit as assessed by the investigator. Docetaxel was administered 75 mg/m^2 by IV infusion on day 1 of each 21 day cycle until disease progression. For all treated patients, the median duration of treatment was 2.1 months for the docetaxel arm and 3.4 months for the Tecentriq arm.

The primary efficacy endpoint was OS. The key results of this study with a median survival follow-up of 21 months are summarized in Table 17. Kaplan-Meier curves for OS in the ITT population are presented in Figure 15. Figure 16 summarizes the results of OS in the ITT and PD-L1 subgroups, demonstrating OS benefit with Tecentriq in all subgroups, including those with PD-L1 expression < 1% in TC and IC.

Table 17 Summary of efficacy in the primary analysis population (OAK)

Efficacy endpoints	Tecentriq		Docetaxel
Primary Efficacy Endpoint			
OS			
All comers*	n=425		n=425
No. of deaths (%)	271 (64%)		298 (70%)
Median time to events (months)	13.8		9.6
95% CI	(11.8, 15.7)		(8.6, 11.2)
Stratified‡ hazard ratio (95% CI)		0.73 (0.62, 0.87)	
p-value**		0.0003	
12-month OS (%)	218 (55%)		151 (41%)
18-month OS (%)	157 (40%)		98 (27%)
PD-L1 expression ≥ 1% in TC or IC	n=241		n=222
No. of deaths (%)	151 (63%)		149 (67%)
Median time to events (months)	15.7		10.3
95% CI	(12.6, 18.0)		(8.8, 12.0)
Stratified hazard ratio (95% CI)		0.74 (0.58, 0.93)	
p-value**		0.0102	
12-month OS (%)	58%		43%
18-month OS (%)	44%		29%
Secondary Endpoints			
Investigator-assessed PFS (RECIST v1.1)			
All comers*	n=425		n=425
No. of events (%)	380 (89%)		375 (88%)
Median duration of PFS (months)	2.8		4.0
95% CI	(2.6, 3.0)		(3.3, 4.2)
Stratified hazard ratio (95% CI)		0.95 (0.82, 1.10)	
Investigator-assessed ORR (RECIST v1.1)			
All comers	n=425		n=425
No. of responders (%)	58 (14%)		57 (13%)
95% CI	(10.5, 17.3)		(10.3, 17.0)
Investigator-assessed DOR (RECIST v1.1)			
All comers	n=58		n=57
Median in months	16.3		6.2
95% CI	(10.0, NE)		(4.9, 7.6)

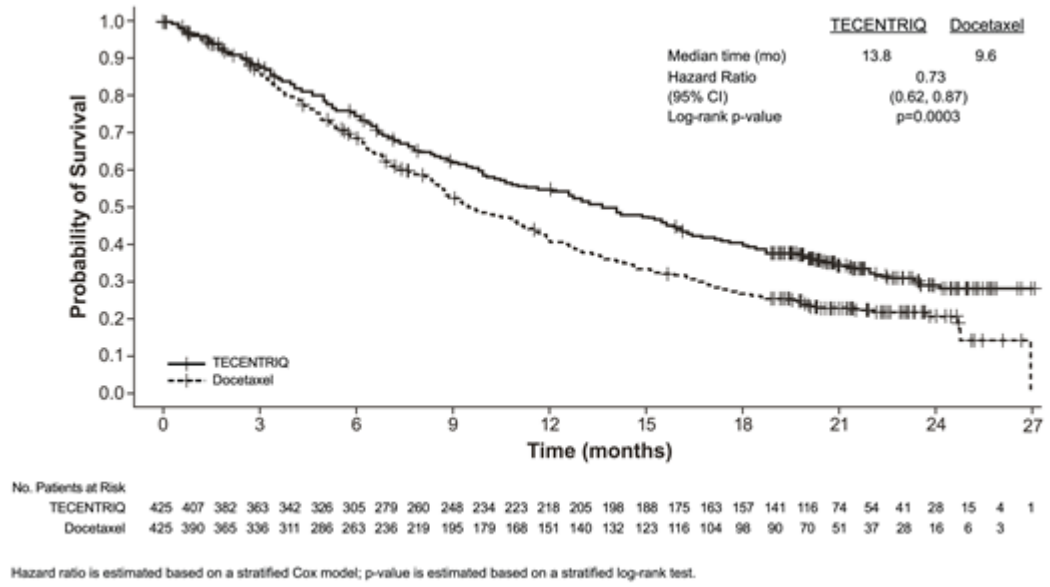
CI=confidence interval; DOR=duration of response; IC=tumor-infiltrating immune cells; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1; TC = tumor cells.

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

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

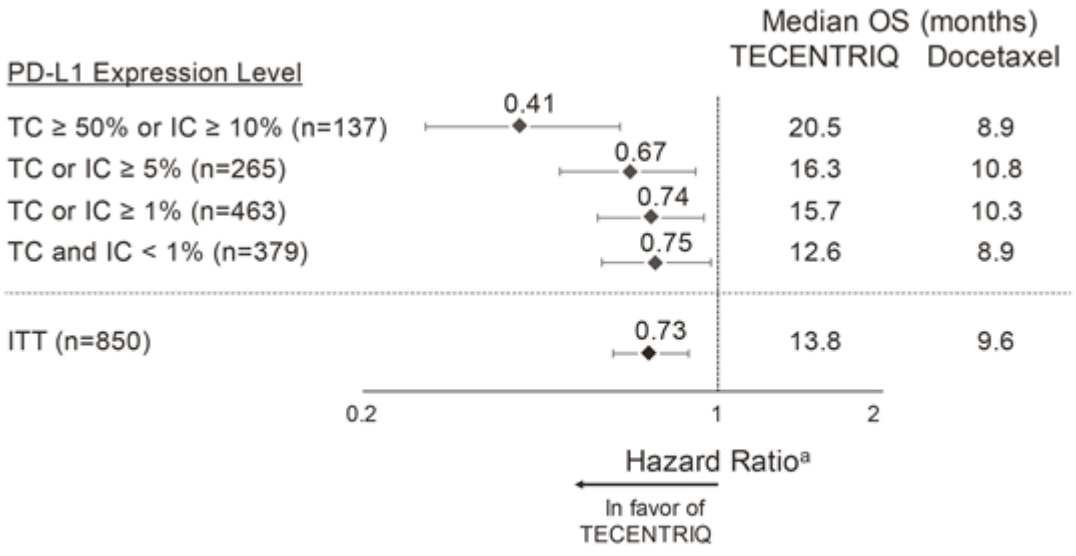
** Based on the stratified log-rank test

Figure 15: Kaplan-Meier Plot for Overall Survival in the Primary Analysis Population (all comers) (OAK)



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

Figure 16: Forest Plot of Overall Survival by PD-L1 Expression in the Primary Analysis Population (OAK)



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

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

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

POPLAR

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 or docetaxel. Randomization was stratified by PD-L1 expression status in IC, by the number of prior chemotherapy regimens and by histology. An updated analysis with a total of 200 deaths observed and a median survival follow-up of 22 months showed a median OS of 12.6 months in patients treated with Tecentriq vs. 9.7 months in patients treated with docetaxel (HR of 0.69, 95% CI: 0.52, 0.92). ORR was 15.3% vs. 14.7% and median DOR was 18.6 months vs. 7.2 months for Tecentriq vs. docetaxel, respectively.

Tecentriq SC

IMscin001

A phase Ib/III, open-label, multi-center, international, randomized study, BP40657 (IMscin001), was conducted to evaluate the pharmacokinetics, efficacy and safety of Tecentriq SC compared with Tecentriq IV in patients with locally advanced or metastatic NSCLC who have not been exposed to cancer immunotherapy (CIT) and for whom prior platinum-based therapy has failed. IMscin001 was designed to demonstrate non-inferiority of the atezolizumab Cycle 1 (pre-dose Cycle 2) serum Ctrough and model-predicted AUC from 0 to 21 days at Cycle 1 of atezolizumab SC compared with atezolizumab IV (co-primary endpoint). Secondary endpoints included efficacy [progression free survival (PFS),

objective response rate (ORR), overall survival (OS), duration of response (DOR)], and patient-reported outcomes.

In Part 2 (Phase III), a total of 371 patients were enrolled and randomized to receive either 1875 mg of Tecentriq SC Q3W or 1200 mg of Tecentriq IV Q3W . No dose reduction was allowed.

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

The demographics and baseline disease characteristics were generally balanced between the treatment arms. The median age was 64 years (range: 27 to 85), and 69% of patients were male. The majority of patients were White (67%). Approximately two-thirds of patients (65%) had non-squamous disease, 5% had known EGFR mutation, 2% had known ALK rearrangements, 40% were PD-L1 positive (TC≥1% and/or IC≥1%), 16% had non-active CNS metastases at baseline, 26% had an ECOG PS of 0, 74% had an ECOG PS of 1, and most patients were current or previous smokers (70%). 80% received one prior therapeutic regimen.

Non-inferiority of the exposure from atezolizumab in Tecentriq SC compared to atezolizumab IV was demonstrated (see 3.2 Pharmacokinetic properties). Other key results are summarized below. At the time of primary analysis, the median survival follow- up was 4.7 months and OS and DOR results were immature . There were 86 (35%) deaths in the Tecentriq SC arm and 37 (30%) deaths in the intravenous atezolizumab arm.

Table 18 Summary of Efficacy from IMscin001

Efficacy endpoint	Tecentriq SC	Tecentriq IV
Investigator-assessed PFS (RECIST v1.1)*	n=247	n=124
No. of PFS events (%)	168 (68%)	84 (68%)
Median duration of PFS (months)	2.8	2.9
95% CI**	(2.1, 3.1)	(1.7, 4.2)
Investigator-assessed ORR (RECIST v1.1)*	n=245	n=124
No. of responders (%)	29 (12%)	12 (9.7%)
95% CI***	(8.1, 17)	(5.1, 16)

CI=confidence interval; ORR=objective response rate; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1

*descriptive analyses

**95% CI was calculated using the standard error derived from Greenwood's formula.

***95% CI for rate was constructed using the Clopper–Pearson method.

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

1L TNBC

IMpassion130

A phase III, double-blind, two-arm, randomized, placebo-controlled study, WO29522 (IMpassion130), was conducted to evaluate the efficacy and safety of Tecentriq in combination with nab-paclitaxel, in patients with unresectable locally advanced or metastatic TNBC who had not received prior chemotherapy for metastatic disease. A total of 902 patients were enrolled and stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumor-infiltrating immune cells (IC) (PD-L1 stained tumour-infiltrating immune cells [IC] in <1% of the tumour area vs. ≥1% of the tumour area). Patients were randomized to receive Tecentriq (840 mg) or placebo IV infusions on Days 1 and 15 of every 28-day cycle, plus nab-paclitaxel (100 mg/m^2) administered via IV infusion on Days 1, 8 and 15 of every 28-day cycle. Patients received treatment until radiographic disease progression per RECIST v1.1, or unacceptable toxicity. Treatment with Tecentriq could be continued when nab-paclitaxel was stopped due to unacceptable toxicity.

Patients were excluded if they had a history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to 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. Tumor assessments were performed every 8 weeks (± 1 week) for the first 12 months after Cycle 1, day 1 and every 12 weeks (± 1 week) thereafter.

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

PFS, ORR and DOR results for patients with PD-L1 expression ≥1% with a median survival follow up of 13 months are summarized in Table 19 and Figure 17. In addition, PFS benefit was observed in subgroups.

A final OS analysis was performed in patients with PD-L1 expression ≥1% with a median follow-up of 19.2 months. OS results are presented in table 19 and Figure 18

Table 19: Summary of efficacy in patients with PD-L1 expression ≥ 1% (IMpassion130)

Key efficacy endpoints	Tecentriq + nab-paclitaxel	Placebo + nab-paclitaxel
Co-primary endpoints		
Investigator-assessed PFS (RECIST v1.1)	n=185	n=184
No. of events (%)	138 (74.6%)	157 (85.3%)
Median duration of PFS (months)	7.5	5.0
95% CI	(6.7, 9.2)	(3.8, 5.6)
Stratified hazard ratio‡ (95% CI)	0.62 (0.49, 0.78)	
p-value[1]	<0.0001	
12-month PFS (%)	29.1	16.4
OS	n=185	n=184
No. of deaths (%)	120 (64.9%)	139 (75.5%)
Median time to events (months)	25.4	17.9
95% CI	(19.6, 30.7)	(13.6, 20.3)
Stratified hazard ratio‡ (95% CI)	0.67 (0.53, 0.86)	
p-value[1,2]	0.0016	
Secondary endpoints		

Key efficacy endpoints	Tecentriq + nab-paclitaxel	Placebo + nab-paclitaxel
Investigator-assessed ORR (RECIST 1.1)	n=185	n=183
No. of responders (%)	109 (58.9%)	78 (42.6%)
95% CI	(51.5, 66.1)	(35.4, 50.1)
No. of complete response (%)	19 (10.3%)	2 (1.1%)
No. of partial response (%)	90 (48.6%)	76 (41.5%)
No. of stable disease	38 (20.5%)	49 (26.8%)
Investigator-assessed DOR	n=109	n=78
Median in months	8.5	5.5
95% CI	(7.3, 9.7)	(3.7, 7.1)
Unstratified hazard ratio (95% CI)	0.60 (0.43, 0.86)	

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

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

PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors v1.1.; CI=confidence interval;

ORR=objective response rate; DOR=duration of response; OS=overall survival, NE=not estimable

Figure 17: Kaplan-Meier Plot for Progression Free Survival in patients with PD-L1 expression ≥1% IC (IMpassion130)

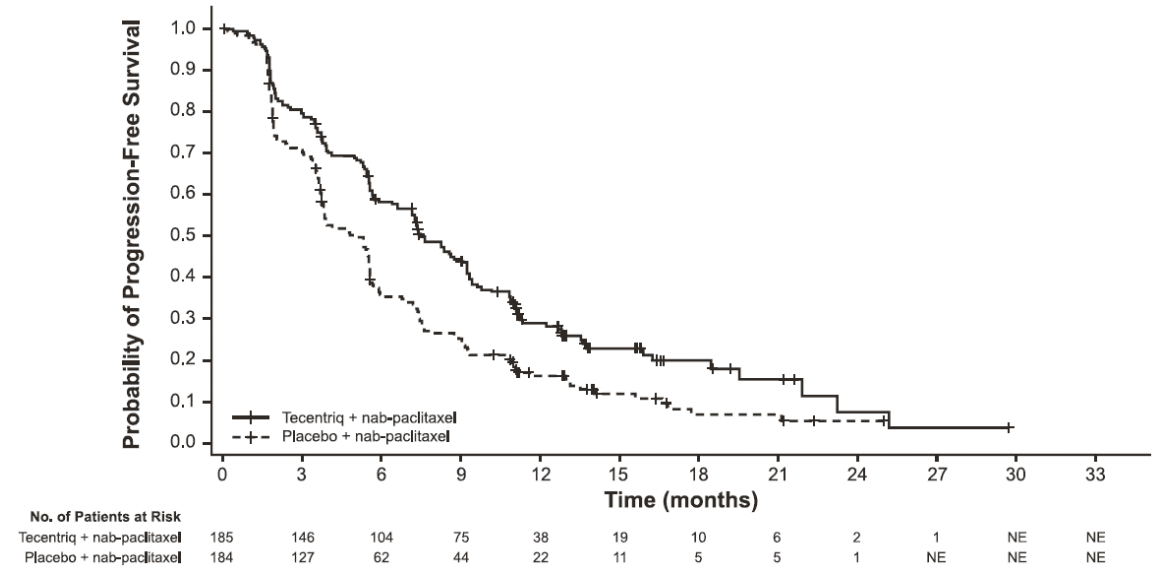
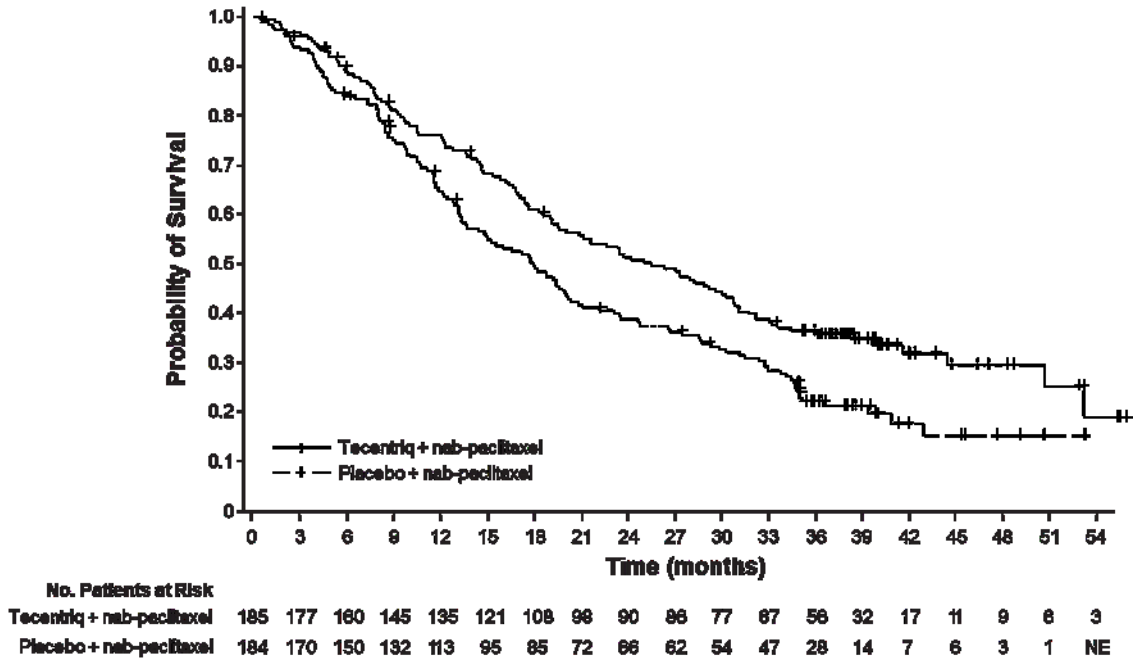


Figure 18: Kaplan-Meier Plot for Overall Survival in patients with PD-L1 expression ≥1% IC (IMpassion130)



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

HCC

IMbrave150

A global phase III, randomized, multi-center, open-label study, YO40245 (IMbrave150), was conducted to evaluate the efficacy and safety of Tecentriq in combination with bevacizumab, in patients with locally advanced or metastatic and/or unresectable HCC, who have not received prior systemic treatment. A total of 501 patients were randomized (2:1) to receive either Tecentriq 1200 mg and 15 mg/kg of bevacizumab every 3 weeks administered via IV infusion, or sorafenib 400 mg orally twice per day. Randomization was stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), baseline AFP (<400 vs. ≥400 ng/mL) and ECOG performance status (0 vs. 1). Patients in both arms received treatment

until loss of clinical benefit, or unacceptable toxicity. Patients could discontinue either Tecentriq or bevacizumab (e.g., due to adverse events) and continue on single-agent therapy until loss of clinical benefit or unacceptable toxicity associated with the single-agent.

The study enrolled adults who were Child-Pugh A, ECOG 0/1 and who had not received prior systemic treatment. Bleeding (including fatal events) is a known adverse reaction with bevacizumab and upper gastrointestinal bleeding is a common and life threatening complication in patients with HCC. Hence, patients were required to be evaluated for the presence of varices within 6 months prior to treatment, and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding or high risk of bleeding. Patients were also excluded if they had moderate or severe ascites; history of hepatic encephalopathy; a history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to 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. Tumor assessments were performed every 6 weeks for the first 54 weeks following Cycle 1, Day 1, then every 9 weeks thereafter.

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

The co-primary efficacy endpoints were OS and IRF-assessed PFS according to RECIST v1.1. At the time of the primary analysis, patients had a median survival follow up time of 8.6 months. The data demonstrated a statistically significant improvement in OS and PFS as assessed by IRF per RECIST v1.1 with Tecentriq + bevacizumab compared to sorafenib. A statistically significant improvement was also observed in confirmed objective response rate (ORR) by IRF per RECIST v1.1 and HCC modified RECIST (mRECIST). The key efficacy results from the primary analysis are summarized in Table 20.

A descriptive updated efficacy analysis was performed with a median survival follow up time of 15.6 months. The key results from the updated analysis are summarized in Table 21. Kaplan-Meier curves for OS (updated analysis) and PFS (primary analysis) are presented in Figures 19 and 20, respectively.

Table 20 Summary of efficacy (IMbrave150 Primary Analysis)

Key efficacy endpoints	Tecentriq + Bevacizumab		Sorafenib	
OS	n=336		n=165	
No. of deaths (%)	96 (28.6%)		65 (39.4%)	
Median time to event (months)	NE		13.2	
95% CI	(NE, NE)		(10.4, NE)	
Stratified hazard ratio‡ (95% CI)	0.58 (0.42, 0.79)			
p-value[1]	0.0006			
6-month OS (%)	84.8%		72.3%	
	RECIST v1.1		**HCC mRECIST**	
	Tecentriq + bevacizumab	Sorafenib	Tecentriq + bevacizumab	Sorafenib
IRF-assessed PFS	n=336	n=165	n=336	n=165
No. of events (%)	197 (58.6%)	109 (66.1%)	199 (59.2%)	111 (67.3%)
Median duration of PFS (months)	6.8	4.3	6.8	4.2
95% CI	(5.8, 8.3)	(4.0, 5.6)	(5.7, 7.7)	(4.0, 5.5)
Stratified hazard ratio‡ (95% CI)	0.59 (0.47, 0.76)		0.59 (0.46, 0.74)	
p-value[1]	<0.0001		N/A	
6-month PFS	54.5%	37.2%	54.3%	36.4%
IRF-assessed ORR	n=326	n=159	n=325	n=158
No. of confirmed responders (%)	89 (27.3%)	19 (11.9%)	108 (33.2%)	21 (13.3%)
95% CI	(22.5, 32.5)	(7.4, 18.0)	(28.1, 38.6)	(8.4, 19.6)
p-value[2]	<0.0001		<0.0001	
No. of complete responses (%)	18 (5.5%)	0	33 (10.2%)	3 (1.9%)
No. of partial responses (%)	71 (21.8%)	19 (11.9%)	75 (23.1%)	18 (11.4%)
No. of stable disease (%)	151 (46.3%)	69 (43.4%)	127 (39.1%)	66 (41.8%)
IRF-assessed DOR	n=89	n=19	n=108	n=21
Median in months	NE	6.3	NE	6.3
95% CI	(NE, NE)	(4.7, NE)	(NE, NE)	(4.9, NE)
6-month DOR (%)	87.6%	59.1%	82.3%	62.5%

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

1. Based on two-sided stratified log-rank test
2. Based on two-sided Cochran-Mantel-Haenszel test

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

Table 21: Summary of efficacy (IMbrave150 Updated Analysis)

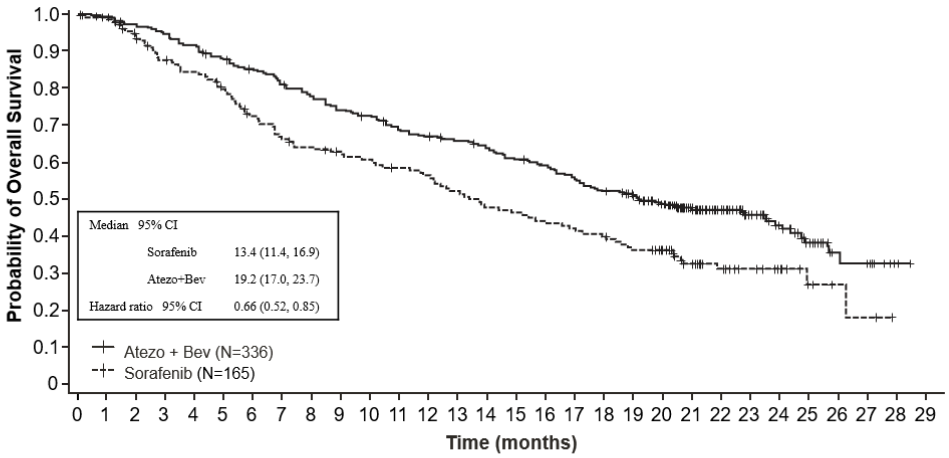
Key efficacy endpoints	Atezolizumab + Bevacizumab	Sorafenib
OS	n=336	n=165
No. of deaths (%)	180 (53.6%)	100 (60.6%)
Median time to event (months)	19.2	13.4
95% CI	(17.0, 23.7)	(11.4, 16.9)
Stratified hazard ratio‡ (95% CI)	0.66 (0.52, 0.85)	
IRF-assessed ORR, RECIST 1.1	n=326	n=159
No. of confirmed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

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

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

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

Figure 19: Kaplan-Meier curve for Overall Survival (IMbrave150 Updated Analysis)

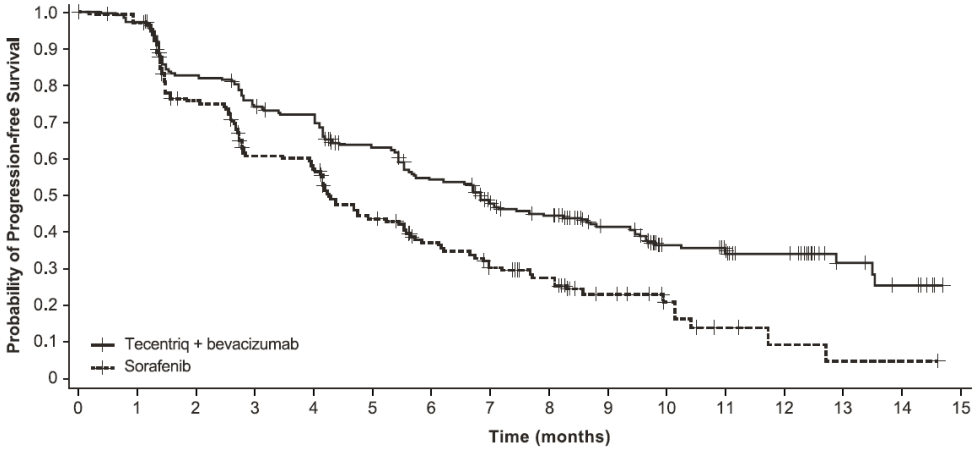


No. of Patients at Risk

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

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

Figure 20: Kaplan-Meier Plot for Progression-Free Survival per RECIST v1.1 (IMbrave150 Primary Analysis)



No. of Patients at Risk															
Tecentriq + bevacizumab	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE

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

GO30140

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

5.6 months in patients treated with Tecentriq and bevacizumab, vs 3.4 months in patients treated with Tecentriq monotherapy.

3.1.3 Immunogenicity

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

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

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

3.2 Pharmacokinetic Properties

Tecentriq IV

The pharmacokinetics of atezolizumab have been characterized in patients in multiple clinical trials at doses of 0.01 mg/kg to 20 mg/kg and 1200 mg every 3 weeks, as well as 840 mg every 2 weeks. Exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg. A population analysis that included 472 patients described atezolizumab pharmacokinetics for the dose range of 1–20 mg/kg with a linear two-compartment disposition model with first-order elimination. Based on pharmacokinetic modelling, the overall exposure of atezolizumab administered at dose of 840 mg every 2 weeks, 1200 mg every 3 weeks and 1680 mg every 4 weeks are comparable. A population pharmacokinetic analysis suggests that steady state is obtained after 6 to 9 weeks after multiple dose. The maximum systemic accumulation ratio across dosing regimen is 3.3.
Based on an analysis of exposure, safety and efficacy data, the following factors have no clinically relevant effect: age (2–89 years), body weight, gender, positive ADA status, albumin levels, tumor burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status.

Tecentriq SC

Atezolizumab model-predicted exposure metrics following Tecentriq SC (1875 mg Q3W SC) and intravenous atezolizumab (1200 mg Q3W IV) administration in the IMscin001 study are shown in Table 22.

Atezolizumab Cycle 1 observed serum C_{trough} (i.e., pre-dose cycle 2) showed non-inferiority of atezolizumab within Tecentriq SC to intravenous atezolizumab, with a geometric mean ratio (GMR) of 1.05 (90% CI: 0.88–1.24).

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

The maximum systemic accumulation ratio following 1875 mg Q3W of Tecentriq SC is 2.2.

The model-predicted C_{trough} and AUC at steady state were comparable for Tecentriq SC and intravenous atezolizumab (see Table 22).

Table 22 Atezolizumab steady state exposure (geometric mean with 5th-95th Percentiles) following subcutaneous or intravenous administration of atezolizumab

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

a) Model predicted exposure based on population pharmacokinetics analysis

3.2.1 Absorption

Tecentriq IV is administered as an IV infusion.

Tecentriq SC

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

3.2.2 Distribution

A population pharmacokinetic analysis indicates that central compartment volume of distribution (V1) is 3.28 l and volume at steady state (V_{ss}) is 6.91 l in the typical patient.

3.2.3 Metabolism

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

3.2.4 Elimination

A population pharmacokinetic analysis indicates that the clearance of atezolizumab is 0.200 l/day and the typical terminal elimination half-life ($t_{½}$) is 27 days.

3.2.5 Pharmacokinetics in Special Populations

Pediatric Population

Tecentriq IV

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

Tecentriq SC

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

Geriatric Population

No dedicated studies of Tecentriq have been conducted in geriatric patients. The effect of age on the pharmacokinetics of atezolizumab was assessed in a population pharmacokinetic analysis. Age was not identified as a significant covariate influencing intravenous atezolizumab pharmacokinetics based on patients of age range of 21–89 years (n=472), and median of 62 years of age. No clinically important difference was observed in the pharmacokinetics of intravenous atezolizumab among patients < 65 years (n=274), patients between 65–75 years (n=152) and patients > 75 years (n=46) (see section 2.2.1 Special Dosage Instructions).

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

Renal impairment

No dedicated studies of Tecentriq have been conducted in patients with renal impairment. In the population pharmacokinetic analysis, no clinically important differences in the clearance of intravenous atezolizumab were found in patients with mild (eGFR 60 to 89 ml/min/1.73 m^2; n=208) or moderate (eGFR 30 to 59 ml/min/1.73 m^2; n=116) renal impairment compared to patients with normal (eGFR greater than or equal to 90 ml/min/1.73 m^2; n=140) renal function. Only a few patients had severe renal impairment (eGFR 15 to 29 ml/min/1.73 m^2; n=8) (see section 2.2.1 Special Dosage Instructions).

No clinically relevant differences in the clearance of subcutaneous atezolizumab were found in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n=111) or moderate (eGFR 30 to 59 mL/min/1.73 m^2; n=32) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m^2;n=103) renal function.

Hepatic impairment

No dedicated studies of Tecentriq have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of intravenous or subcutaneously administered atezolizumab between patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 × ULN and any AST) or moderate hepatic impairment (bilirubin >1.5 to 3x ULN and any AST). No data are available in patients with severe (bilirubin >3.0 × ULN and any AST) hepatic impairment. Hepatic impairment was defined by the National Cancer Institute (NCI) criteria of hepatic dysfunction (see section 2.2.1 Special Dosage Instructions).

3.3 Nonclinical Safety

3.3.1 Carcinogenicity

No carcinogenicity studies have been conducted with Tecentriq.

3.3.2 Genotoxicity

No mutagenicity studies have been conducted with Tecentriq.

3.3.3 Impairment of Fertility

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

3.3.4 Reproductive Toxicity

No reproductive or teratogenicity studies in animals have been conducted with Tecentriq. The PD-L1/PD-1 signaling pathway is well established as essential in maternal / fetal tolerance and embryo-fetal survival during gestation. Administration of Tecentriq is expected to have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo lethality.

3.3.5 Other

Subcutaneous formulation

No carcinogenicity, genotoxicity, or fertility studies were conducted for recombinant human hyaluronidase. Reproductive toxicology studies with rHuPH20 revealed

embryofetal toxicity in mice at high systemic exposure, but did not show teratogenic potential.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Tecentriq IV

Vials

Store at 2 °C to 8 °C.

Tecentriq should be protected from light.

Do not freeze. Do not shake.

Shelf life

Please see on the pack.

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

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

Tecentriq SC

Vials

Store at 2°C 8°C.

Keep vial in outer carton in order to protect from light.

Do not freeze. Do not shake.

Shelf life

Please see on the pack.

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

Storage of the syringe

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

- The closed syringe can be stored at ≤30°C (86°F) for up to 8 hours in diffuse daylight and in the refrigerator [2°C to 8°C (36°F to 46°F)] for up to 30 days.

4.2 Special Instructions for Use, Handling and Disposal

Tecentriq IV

Instructions for dilution

Tecentriq should be prepared by a healthcare professional using aseptic technique. Use sterile needle and syringe to prepare Tecentriq. Withdraw the required volume of Tecentriq liquid concentrate from the vial and dilute to the required administration volume with 0.9% sodium chloride solution. Dilute with 0.9% sodium chloride injection only. After dilution, the final concentration of the diluted solution should be between 3.2 and 16.8 mg/ mL

This medicinal product must not be mixed with other medicinal products.

No preservative is used in Tecentriq, therefore, each vial is for single use only. Discard any unused portion.

Incompatibilities

No incompatibilities have been observed between Tecentriq and IV bags with product-contacting surfaces of polyvinyl chloride (PVC), polyolefin bags polyethylene (PE) or polypropylene (PP). In addition, no incompatibilities have been observed with in-line filter membranes composed of polyethersulfone or polysulfone, and infusion sets and other infusion aids composed of PVC, PE, polybutadiene, or polyetherurethane.

Tecentriq SC

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

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

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

Preparation of the Syringe

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

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

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

Remove the transfer needle and attach a SC infusion set (e.g. winged / butterfly) containing a 23-25G (3/8”- 5/8”) 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.

Incompatibilities

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

Tecentriq IV and SC

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.

4.3 Packs

Single-use vial of 60 mg/ml

Single-use vial of 125 mg/mL

Medicine: keep out of reach of children

Current at November 2023

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by Roche Diagnostics GmbH, Mannheim, Germany

by F. Hoffmann – La Roche Ltd., Kaiseraugst, Switzerland