WARNING: To be sold by retail on the prescription of a "Registered Oncologist Only"

Atezolizumab Injection

Tecentriq®

टिसेन्ट्रिक™

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antineoplastic agent, humanized immunoglobulin G1 (IgG1) monoclonal antibody.

ATC Code – L01XC32

1.2 Type of Dosage Form and Strength

Concentrate for solution for infusion
Strength: 60mg/ml

1.3 Route of Administration

Intravenous (IV) infusion

1.4 Sterile / Radioactive Statement

Sterile product

1.5 Qualitative and Quantitative Composition

Active ingredient: Atezolizumab

Tecentriq 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: L-Histidine, Glacial acetic acid, Sucrose, Polysorbate 20, Water for Injection.

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATIONS

Urothelial carcinoma
Tecentriq is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma after prior chemotherapy or who are considered cisplatin ineligible

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

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

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 ≥1%, and who have not received prior chemotherapy for metastatic disease.

2.2 DOSAGE AND ADMINISTRATION

General

Tecentriq must be administered as an intravenous infusion under the supervision of a qualified healthcare professional. Do not administer as an IV push or bolus.

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

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

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

Tecentriq monotherapy

2L NSCLC, 2L UC & 1L UC in Cisplatin ineligible patients

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 NSCLC

Tecentriq in combination with bevacizumab, paclitaxel, and carboplatin

During the induction phase, Tecentriq is administered according to its dosing schedules by intravenous (IV) infusion, and 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 schedules by IV infusion, and bevacizumab is administered every 3 weeks.

1L ES-SCLC

Tecentriq in combination with carboplatin and etoposide

During the induction phase, Tecentriq administered according to its dosing schedules by IV infusion, followed by 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.

The induction phase is followed by a maintenance phase without chemotherapy in which Tecentriq is administered according to its dosing schedules by IV infusion.

1L TNBC

Tecentriq in combination with nab-paclitaxel

The recommended dose of Tecentriq is 840 mg administered by IV infusion, followed by 100 mg/m^2 nab-paclitaxel. For each 28-day cycle Tecentriq is administered on days 1 and 15, and nab-paclitaxel is administered on days 1, 8 and 15.

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).

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).

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 Colitis	Grade 2 diarrhea or colitis	Withhold[1]
	Grade 3 diarrhea or colitis	Withhold[1] Initiate IV corticosteroids and convert to oral corticosteroids after improvement
	Grade 4 diarrhea or colitis	Permanently discontinue
Immune-mediated Hypothyroidism	Symptomatic	Withhold[2] Initiate thyroid hormone replacement therapy
Immune-mediated Hyperthyroidism	Symptomatic	Withhold[2] Initiate anti-thyroid therapy as needed
Immune-mediated adrenal	Symptomatic	Withhold[1]

Insufficiency		
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 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 myositis	Grade 2 or 3	Withhold [1]
	Grade 4 or grade 3 recurrent myositis	Permanently discontinue
Immune-mediated Myocarditis	Grade 2	Withhold
	Grade 3 or 4	Permanently discontinue
Immune-mediated nephritis	Grade 2 (creatinine level >1.5 - 3.0x baseline or >1.5 - 3.0x 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
Infusion related reactions	Grade 1 or 2	Reduce rate of infusion or withhold treatment Premedication with antipyretic and antihistamines may be considered for subsequent doses
	Grade 3 or 4	Permanently discontinue
Rash/Severe cutaneous adverse reactions	Grade 3 Or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[3]	Withhold[1]
	Grade 4 or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)[3]	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] 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 in patients with 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.

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 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 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 endocrinopathies

Hypothyroidism, hyperthyroidism, adrenal insufficiency 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 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, 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 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.

Immune-mediated myocarditis

Myocarditis 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. Refer to section 2.2 Dosage and Administration for recommended dose modifications.

Immune-mediated myositis

Cases 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 signs and symptoms of myositis. 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.

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 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.

Embryofetal 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).

Disease Specific precautions

Use of Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in metastatic non-squamous non-small cell lung cancer Physicians should carefully consider the combined risks of the four-drug regimen of atezolizumab bevacizumab, paclitaxel and carboplatin before initiating treatment.

Use of atezolizumab in combination with nab-paclitaxel in metastatic triple negative breast cancer

Neutropenia and peripheral neutropathies occurring during treatment with atezolizumab and nabpaclitaxel may be reversible with interruptions of nab-paclitaxel. Physicians should consult the nabpaclitaxel prescribing information for specific precautions and contraindications of this medicine.

Patients excluded from clinical trials

Patients with the following condition were excluded from clinical trials: a history of autoimmune disease, history of pneumonitis, active brain metastasis, HIV, hepatitis B or hepatitis C infection, significant cardiovascular disease and patients with inadequate hematologic and end-organ function. Patients who were administered a live, attenuated vaccine within 28 days prior to enrolment; systemic immune stimulatory agents within 4

weeks or systemic immunosuppressive medicinal products within 2 weeks prior to study entry were excluded from clinical trial.

2.4.2 Drug abuse and dependence

No data to report.

2.4.3 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 POPULATION

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 Teratogenicity 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 Teratogenicity).

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

2.5.3 Lactation

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

2.5.4 Pediatric use

Tecentriq is not approved for use in patients under the age of 18 years. The safety and efficacy of Tecentriq in this population has not been established. 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 (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

Tecentriq monotherapy

The safety of Tecentriq monotherapy is based on pooled data in 3178 patients with multiple tumor types, with supporting data from the estimated cumulative exposure in >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.

Table 2 Summary of adverse reactions occurring in patients treated with Tecentriq 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
Cardiac Disorders				

ADR (MedDRA)	Tecentriq (n=3178)			
System Organ Class	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
Myocarditis [a]	-	-	-	Rare
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	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
General Disorders and Administration site conditions				
Chills	207 (6.5%)	2 (<0.1%)	0 (0%)	Common
Fatigue	1142 (35.9%)	109 (3.4%)	0 (0%)	Very Common
Asthenia	461 (14.5%)	63 (2.0%)	0 (0%)	Very Common
Influenza like illness	186 (5.9%)	1 (<0.1%)	0 (0%)	Common
Pyrexia	638 (20.1%)	17 (0.5%)	0 (0%)	Very Common
Infusion related reaction [h]	34 (1.1%)	5 (0.2%)	0 (0%)	Common
Hepatobiliary Disorders				
ALT increased	167 (5.3%)	46 (1.4%)	0 (0%)	Common

ADR (MedDRA)	Tecentriq (n=3178)			
System Organ Class	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
AST increased	180 (5.7%)	46 (1.4%)	0 (0%)	Common
Hepatitis [i]	62 (2.0%)	25 (0.8%)	2 (<0.1%)	Common
Immune System Disorders				
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
Meningoencephalitis [k]	14 (0.4%)	6 (0.2%)	0 (0%)	Uncommon
Myasthenic syndrome[z]	1 (<0.1%)	0 (0%)	0 (0%)	Rare
Renal and Urinary Disorders				
drincreased[aa]	171 (5.4%)	14 (0.4%)	0 (0%)	Common
Nephritis[s]	3 (<0.1%)	1 (<0.1%)	0 (0%)	Rare

ADR (MedDRA)	Tecentriq (n=3178)			
System Organ Class	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
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	400 (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 (0.7%)	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, myxoedema, thyroid function test abnormal, thyroiditis acute, thyroxine decreased
c. Includes reports of hyperthyroidism, Basedow's disease, endocrine ophthalmopathy, exophthalmos
d. Includes reports of adrenal insufficiency, primary adrenal insufficiency
e. Includes reports of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis and ketoacidosis
f. Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic, colitis ulcerative
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 macular, rash papular, , folliculitis, 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
n. Includes reports of thrombocytopenia and platelet count decreased
o. Includes reports of diarrhea, 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, PO2 decreased
y. Includes reports of hypophysitis and temperature regulation disorder
z. Includes report of myasthenia gravis
aa. Includes reports of blood creatinine increased and hypercreatininaemia
bb. Includes reports of nasopharyngitis, nasal congestion and rhinorrhoea
cc. Includes reports of dermatitis psoriasiform and psoriasis
dd. dd. Includes reports of dermatitis bullous, exfoliative rash, erythema multiforme, dermatitis exfoliative generalised, toxic skin eruption, toxic epidermal necrolysis

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

ADR (MedDRA)	Tecentriq + Combination Treatments (n = 4371)			
System Organ Class	All Grades (%)	Grade 3-4 (%)	Grade 5 (%)	Frequency (All Grades)
Endocrine Disorders				
Hypothyroidism[*,‡,c]	586 (13.4)	9 (0.2%)	0 (0%)	Very Common
Hyperthyroidism[‡]	193 (4.4%)	7 (0.2%)	0 (0%)	Common
Adrenal insufficiency[‡,d]	40 (0.9%)	8 (0.2%)	1 (<0.1%)	Uncommon
Hypophysitis[‡,e]	13 (0.3%)	5 (0.1%)	0 (0%)	Uncommon
Gastrointestinal Disorders				
Constipation[*]	1123 (25.7%)	24 (0.5%)	0 (0%)	Very Common
Stomatitis[*]	351 (8.0%)	23 (0.5%)	0 (0%)	Common
General Disorders and Administration Site Conditions				
Oedema Peripheral*	451 (10.3%)	11 (0.3%)	0 (0%)	Very Common
Infections and Infestations				
Lung infection[*,h]	564 (12.9%)	226 (5.2%)	26 (0.6%)	Very Common
Investigations				
Blood alkaline phosphatase increased	200 (4.6%)	26 (0.6%)	0 (0%)	Common
Metabolism and Nutrition Disorders				
Hypomagnesemia[*, j]	403 (9.2%)	22 (0.5%)	0 (0%)	Common
Nervous System Disorders				
Dizziness[*]	408 (9.3%)	9 (0.2%)	0 (0%)	Common
Dysgeusia[*]	269 (6.2%)	0 (0.0%)	0 (0%)	Common
Peripheral neuropathy[*,f]	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

ADR (MedDRA)	Tecentriq + Combination Treatments (n = 4371)			
System Organ Class	All Grades (%)	Grade 3-4 (%)	Grade 5 (%)	Frequency (All Grades)
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia*	236 (5.4%)	4 (< 0.1%)	0 (0%)	Common
Nasopharyngitis[o]	442 (10.1%)	1 (< 0.1%)	0 (0%)	Very Common
Skin and Subcutaneous Tissue Disorders				
Alopecia[n]	1152 (26.4%)	3 (< 0.1%)	0 (0%)	Very Common
Severe cutaneous adverse reactions [p]	27 (0.6 %)	8 (0.2 %)	0 (0%)	Uncommon
Vascular Disorders				
Hypertension*,[m]	611 (14.0%)	258 (5.9%)	0 (0%)	Very Common

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

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

[a.] Includes reports of neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis and granulocytopenia

[b.] Includes reports of 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 thyroiditisa, 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, peripheral nerve infection

[g.] Includes reports of proteinuria, protein urine present, haemoglobinuria, nephrotic syndrome urine abnormality and albuminuria

[h.] Includes reports of pneumonia, bronchitis, lung infection, 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 rhinorrhoea

[p.] Includes reports of dermatitis bullous, exfoliative rash, erythema multiforme, dermatitis exfoliative generalised, toxic skin eruption, Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), and cutaneous vasculitis (cases of SJS and DRESS have been reported in studies outside the pooled dataset).

Additional information for selected adverse reactions

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

Immune-mediated pneumonitis

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

Immune-mediated hepatitis

Hepatitis occurred in 2.0% (62/3178) of patients who received Tecentriq. Of the 62 patients, two event was fatal. The median time to onset was 1.5 months (range 0.2 to 18.8 months). The median duration was 2.1 months (range: 0 to 22.0+ months; + denotes a censored value). Hepatitis led to discontinuation of Tecentriq in 6 (0.2%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.6% (18/3178) of patients receiving Tecentriq.

Immune-mediated colitis

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

Immune-mediated endocrinopathies

Thyroid Disorder

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

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

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

Adrenal Insufficiency

Adrenal insufficiency occurred in 0.3% (11/3178) of patients who received Tecentriq. The median time to onset was 5.5 months (range: 0.1 to 19 months). The median duration was 16.8 months (range: 0 to 16.8 months). Adrenal insufficiency led to discontinuation of Tecentriq in 1 (<0.1%) patient. Adrenal insufficiency requiring the use of corticosteroids occurred in 0.3% (9/3178) of patients receiving Tecentriq.

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

Hypophysitis

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

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

Diabetes mellitus

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

Immune-mediated meningoencephalitis

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

Immune-mediated neuropathies

Neuropathies, including Guillain-Barré syndrome and demyelinating polyneuropathy, occurred in 0.2% (5/3178) of patients who received Tecentriq. The median time to onset was 7 months (range: 0.6 to 8.1 months). The median duration was 8.0 months (0.6 day to 8.3+ months; +denotes a censored value). Guillain-Barré syndrome led to the discontinuation of Tecentriq in 1 (<0.1%) patient. Guillain-Barré syndrome requiring the use of corticosteroids occurred in <0.1% (2/ 3178) of patients receiving Tecentriq.

Immune-mediated pancreatitis

Pancreatitis, including amylase increased and lipase increased, occurred in 0.6% 18/3178) of patients who received Tecentriq monotherapy. The median time to onset was 5.0 months (range: 0.3 to 16.9 months). The median duration was 0.8 months (range: 0.1 to 12+ months; + denotes a censored value). Pancreatitis led to discontinuation of

Tecentriq in 3 (<0.1%) patients. Pancreatitis requiring the use of corticosteroids occurred in <0.1% (4/3178) of patients receiving Tecentriq.

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 nephritis
Nephritis, occurred in <0.1% (3/3178) of patients who received Tecentriq. 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 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 of the first event 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

Lung infection, Immunodeficiency, Blood sugar increased, chest infection, Pneumonitis, Platelet count low, Neutropenia, Hypothyroidism, Bedridden, Hip facture etc.

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 antitumor 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 antitumor 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.

BRAF V600 mutations cause hyperactivation of the MAPK pathway, driving tumor cell proliferation, survival, and suppression of tumor immune recognition. Dual inhibition of the MAPK pathway with BRAF and MEK inhibitors suppresses tumor growth and improves tumor immunogenicity through improved antigen presentation associated with increased infiltration of T cells into the tumor. The addition of atezolizumab to cobimetinib and vemurafenib further reduced tumor growth in preclinical models with higher rates of immune cell infiltration and activation versus targeted therapy alone.

3.1.2 Clinical / Efficacy Studies

Urothelial Carcinoma

IMvigor211

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.

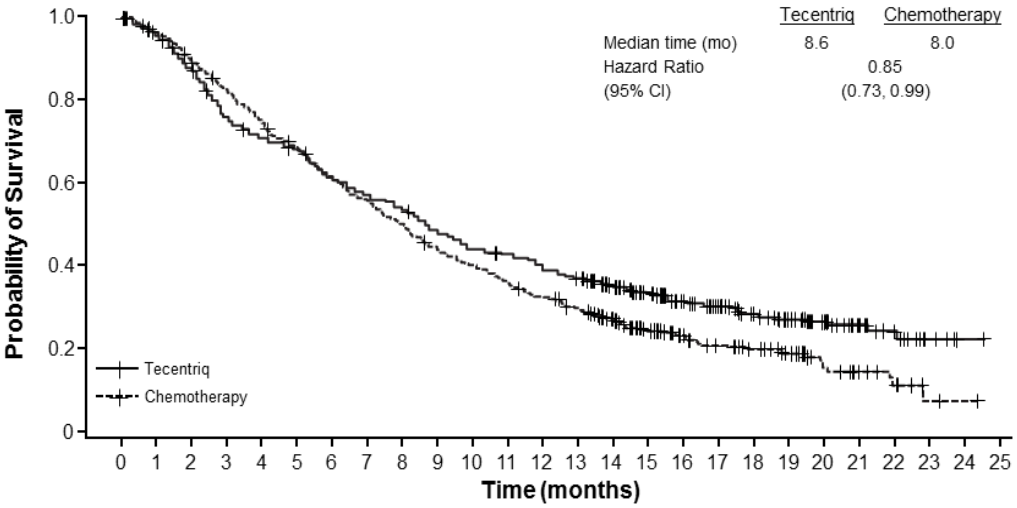
The median survival follow up was 17 months. Study IMvigor211 did not meet its primary endpoint. In the subset of patients with tumors having PD-L1 expression ≥5%, Tecentriq did not demonstrate a statistically significant survival benefit compared to chemotherapy with an OS HR of 0.87 (95% CI: 0.63, 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 4. The Kaplan Meier curve for OS in the all comer population is presented in Figure 1.

Table 4: 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
ǂ 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)



No. of Patients at Risk

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

IMvigor210

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 intravenous infusion every 3 weeks until disease progression. The median age was 73 years. Most patients were male (81%), and the majority of patients were White (91%).

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

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

The primary analysis was performed when all patients had at least 24 weeks of follow-up. Median duration of treatment was 15.0 weeks and median duration of survival follow up was 8.5 months in all comers. Clinically relevant IRF-assessed ORRs per RECIST v1.1 were shown; however, when compared to a pre-specified historical control response rate of 10%, statistical significance was not reached for the primary endpoint. The confirmed ORRs per IRF-RECIST v1.1 were 21.9% (95% CI: 9.3, 40.0) in patients with PD-L1 expression ≥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 5. The median DOR was not reached in any PD-L1 expression subgroup or in all comers.

Table 5 Summary of updated efficacy from IMvigor210 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 Cohort 2, demonstrating statistically significant ORRs per IRF-assessed RECIST v1.1 and investigator-assessed mRECIST compared to a pre-specified historical control response rate of 10%.

An analysis was also performed with a median duration of survival follow up 21.1 months for Cohort 2. The confirmed ORRs per IRF-RECIST v1.1 were 28.0% (95% CI: 19.5, 37.9) in patients with PD-L1 expression ≥ 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 subgroup or in all comers, however was reached in patients with PD-L1 expression <1% (13.3 months; 95% CI 4.2, NE). The OS rate at 12 months was 37% in all comers.

NSCLC

1L non-squamous NSCLC

IMpower150

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 6. Randomization was stratified by sex, presence of liver metastases and PD-L1 tumor expression on tumor cells (TC) and tumor infiltrating cells (IC).

Table 6 Intravenous Treatment regimens in Study IMpower150

Treatment regimen	Induction (Four or Six 21-day cycles)	Maintenance (21-day cycles)
A	Tecentriq[a] (1200 mg) + paclitaxel[b,c] (200 mg/m2) + carboplatin[c] (AUC 6)	Tecentriq[a] (1200 mg)
B	Tecentriq[a] (1200 mg) + bevacizumab[d] (15 mg/kg) + paclitaxel[b,c] (200 mg/m2) + carboplatin[c] (AUC 6)	Tecentriq[a] (1200 mg) + bevacizumab[d] (15 mg/kg)
C	Bevacizumab[d] (15 mg/kg) + paclitaxel[b,c] (200 mg/m2) + 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/m2 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. 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, including patients with EGFR mutations or ALK rearrangements who should have been previously treated with tyrosine kinase inhibitors, demonstrated PFS improvement in Arm B as compared to Arm C (HR: 0.61 [95% CI: 0.52, 0.72] median PFS 8.3 vs. 6.8 months).

At the time of the interim OS analysis, patients had a median follow up time of 19.7 months. The key results from this analysis are summarized in Table 7. Kaplan-Meier curves for OS in the ITT population are presented in Figure 2. Figure 3 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 Figures 4 and 5.

Table 7 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 2: Kaplan-Meier Plot for Overall Survival in the ITT population (IMpower150)

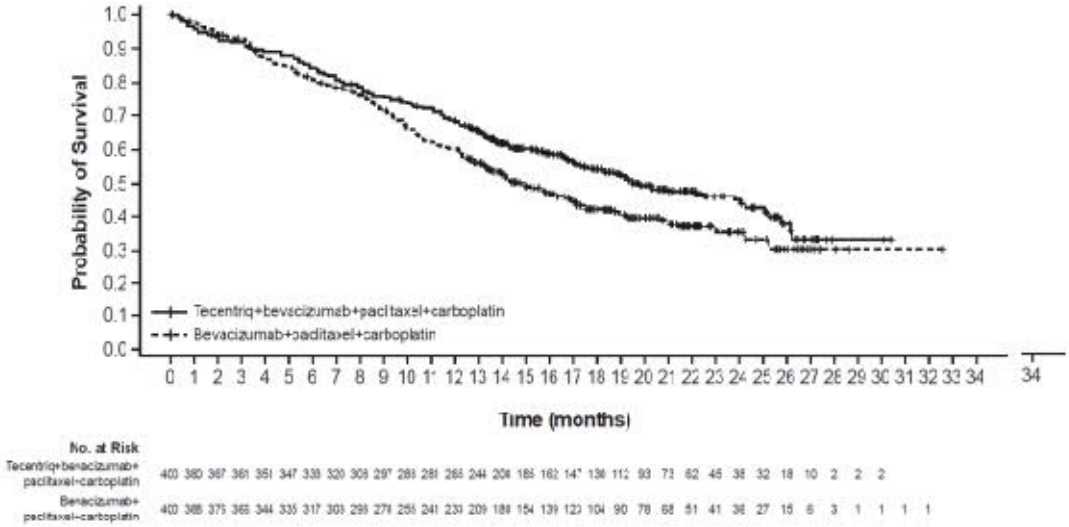


Figure 3: Forest plot of overall survival by PD-L1 expression in the ITT population (IMpower150)

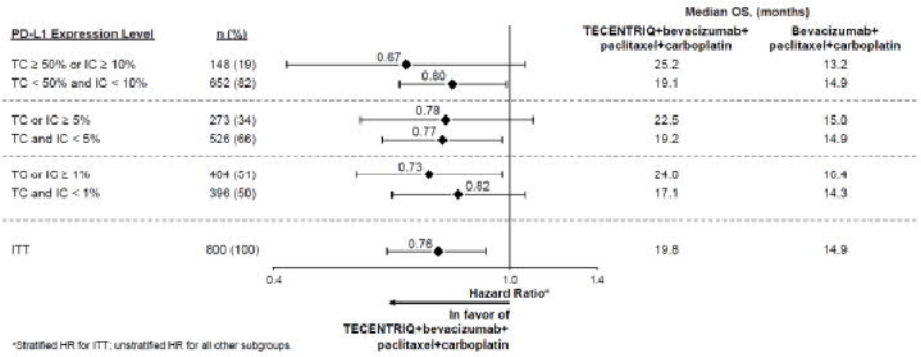


Figure 4: Kaplan-Meier Plot for updated Progression Free Survival in the ITT population (IMpower150)

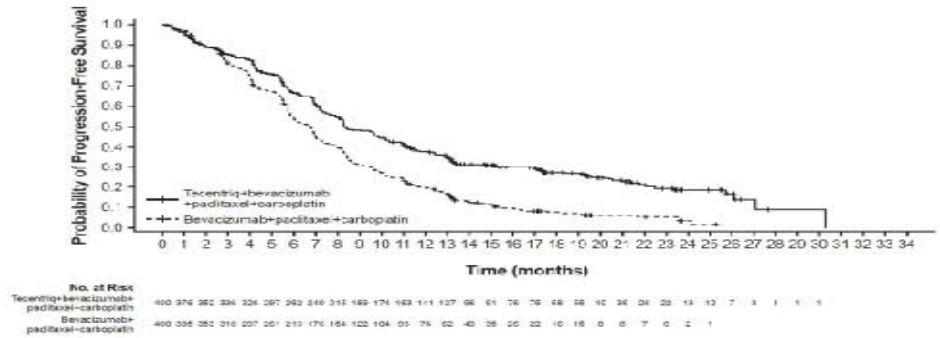
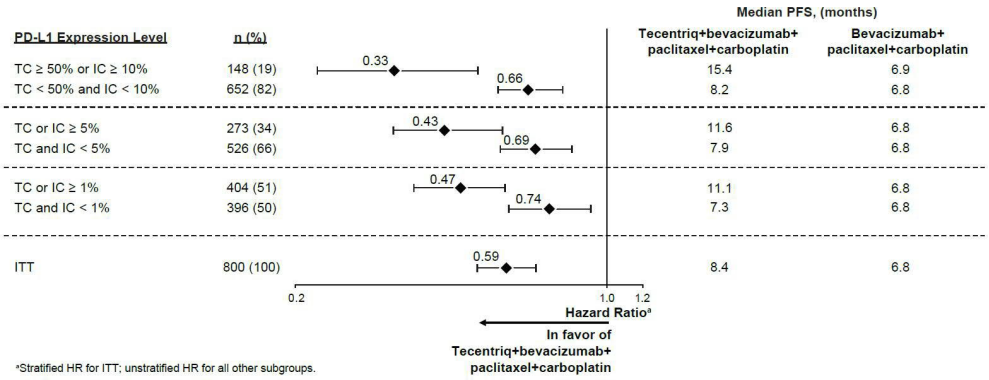


Figure 5: Forest plot of updated progression free survival by PD-L1 expression in the ITT population (IMpower150)



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.

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 8. 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 8 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 9. Kaplan-Meier curves for OS and PFS are presented in Figure 6 and 7.

Table 9 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	

Key efficacy endpoints	Arm A (Tecentriq + carboplatin + etoposide)	Arm B (Placebo + carboplatin + etoposide)
12-month OS (%)	51.7	38.2
Investigator-assessed PFS (RECIST v1.1)	n=201	n=202
No. of events (%)	171 (85.1%)	189 (93.6%)
Median duration of PFS (months)	5.2	4.3
95% CI	(4.4, 5.6)	(4.2, 4.5)
Stratified hazard ratio‡ (95% CI)	0.77 (0.62, 0.96)	
p-value	0.0170	
6-month PFS (%)	30.9	22.4
12-month PFS (%)	12.6	5.4
Secondary endpoints		
Investigator-assessed ORR (RECIST 1.1)	n=201	n=202
No. of responders (%)	121 (60.2%)	130 (64.4%)
95% CI	(53.1, 67.0)	(57.3, 71.0.)
No. of complete response (%)	5 (2.5%)	2 (1.0%)
No. of partial response (%)	116 (57.7%)	128 (63.4%)
Investigator-assessed DOR (RECIST 1.1)	n =121	n = 130
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 6: Kaplan-Meier Plot of Overall Survival (IMpower133)

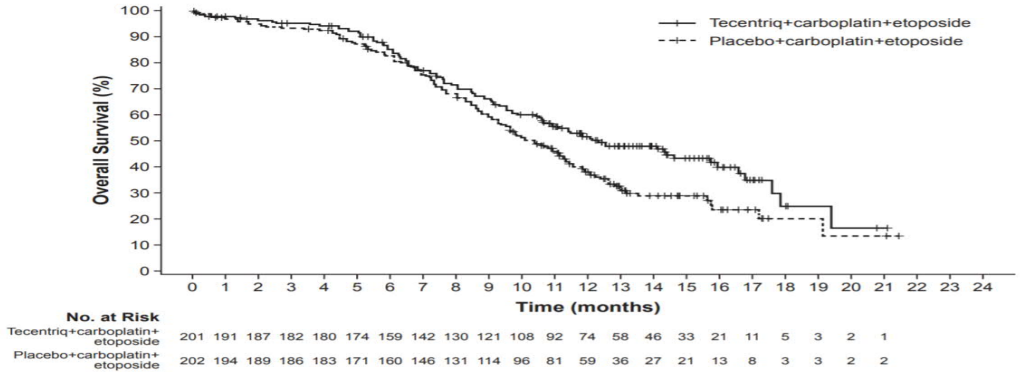
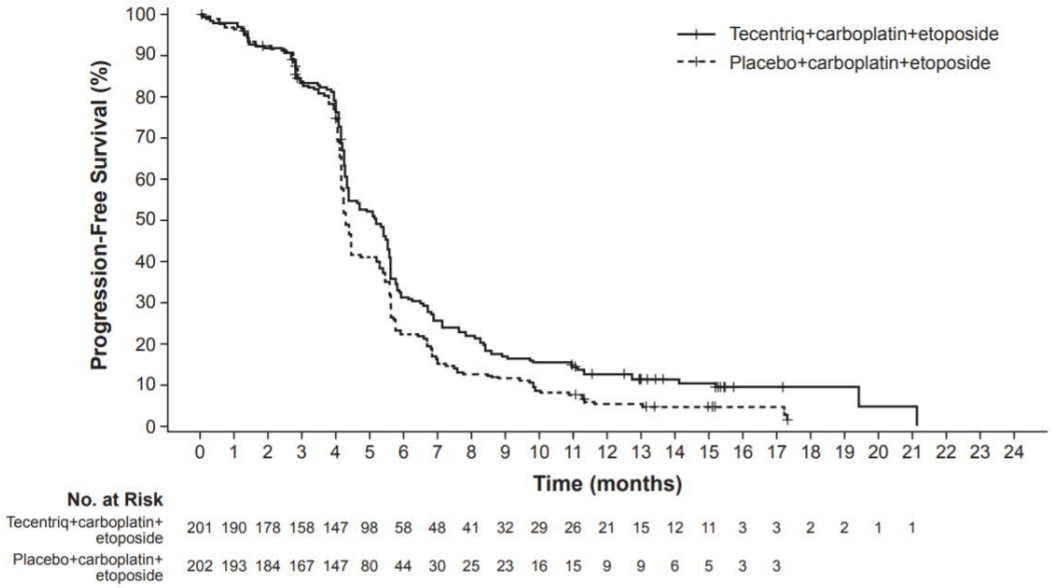


Figure 7: Kaplan-Meier Plot of Progression-Free Survival (IMpower133)



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.

Non-small cell lung cancer

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/m2 by IV infusion on day 1 of each 21day 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 10. Kaplan-Meier curves for OS in the ITT population are presented in Figure 1. Figure 2 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 10 Summary of Efficacy in the Primary Analysis Population (OAK)

Efficacy endpoints	Tecentriq	Docetaxel
Primary Efficacy Endpoint		
OS		
All comers*	n=425	n=425
No. o 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 8: Kaplan-Meier Plot for Overall Survival in the Primary Analysis Population (all comers) (OAK)

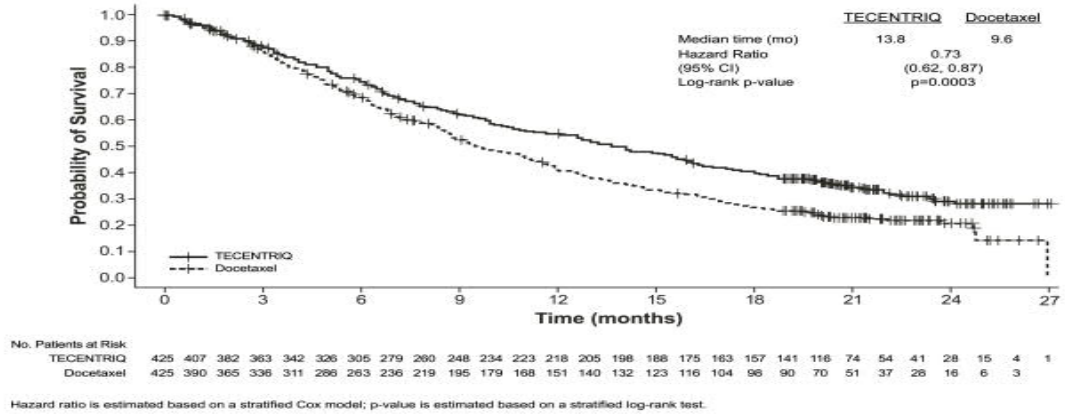
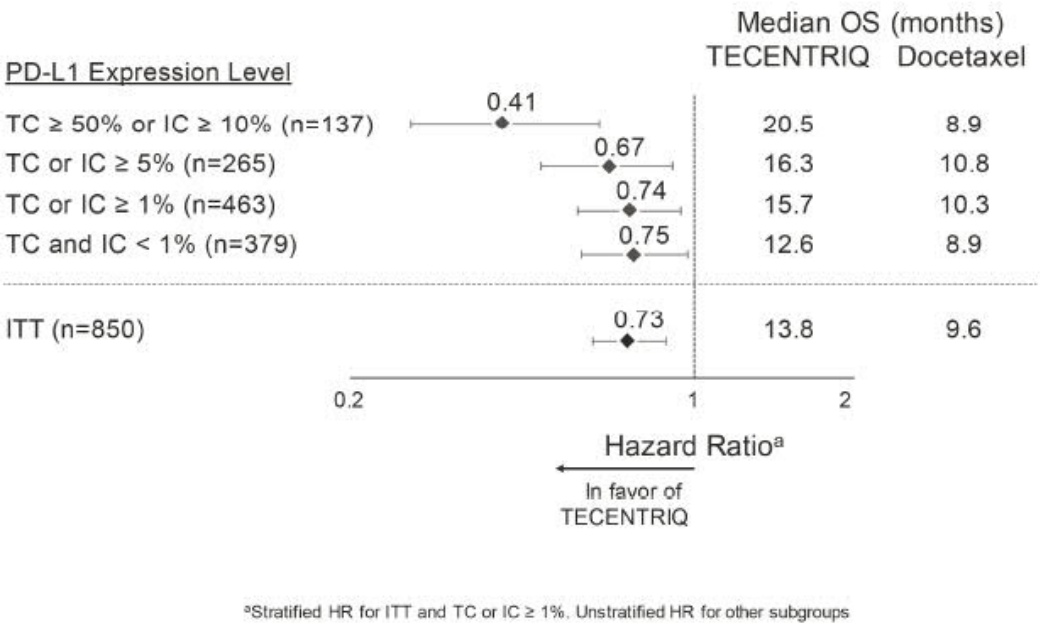


Figure 9: Forest Plot of Overall Survival by PD-L1 Expression in the Primary Analysis Population (OAK)



An improvement in OS was observed with Tecentriq compared to docetaxel in both nonsquamous 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 metastateses 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.

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 immune stimulatory 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 11 and Figure 10. In addition, PFS benefit was observed in subgroups.

A OS analysis was performed in patients with PD-L1 expression ≥1% with a median follow-up of 19.12 months. OS results are presented in Table 11 and Figure 11.

Table 11 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

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

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

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

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

Figure 10: Kaplan-Meier Plot for Progression Free Survival in patients with PD-L1 expression ≥1% IC (IMpassion130)

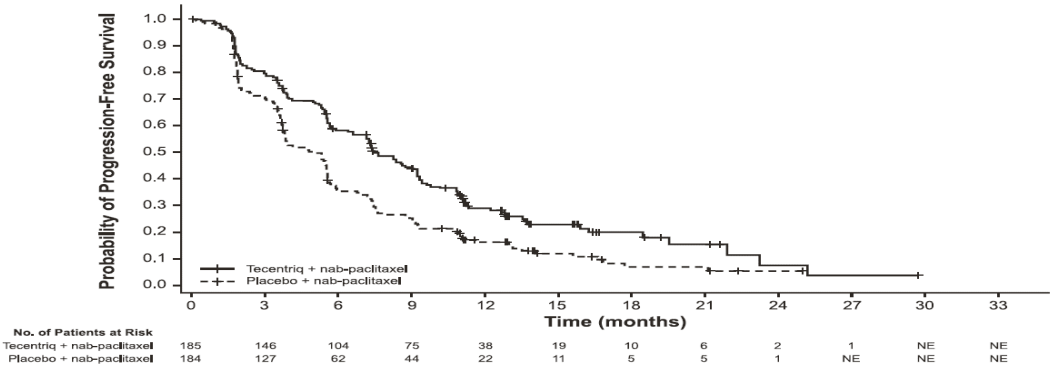
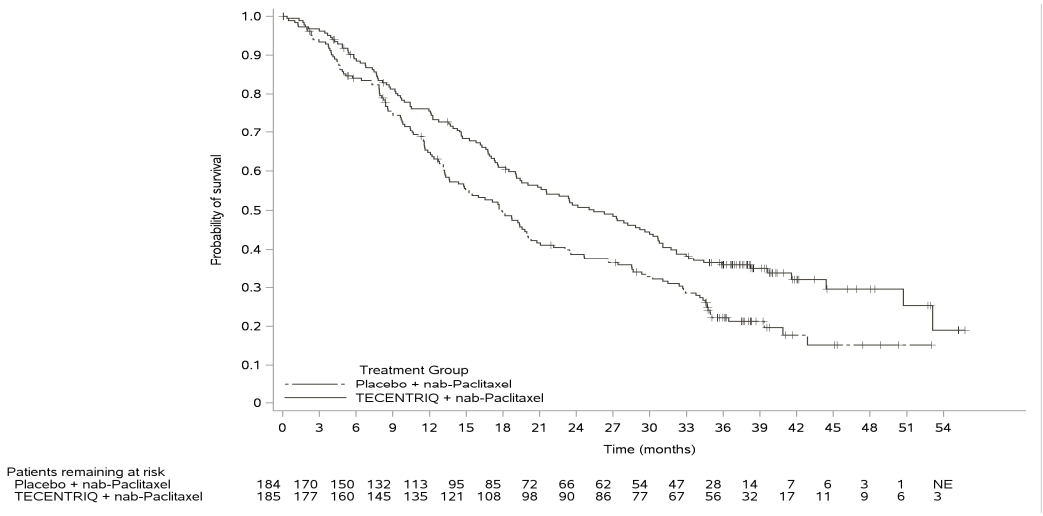


Figure 11: Kaplan-Meier Plot for Overall Survival in patients with PD-L1 expression ≥1% IC (IMpassion130)



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.

3.1.3 Immunogenicity

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

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

3.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of atezolizumab have been characterized in patients in multiple clinical trials at doses 0.01 mg/kg to 20 mg/kg and 1200 mg every 3 weeks, weeks, as well as 840 mg every 2 weeks. Exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg. A population analysis that included 472 patients described atezolizumab pharmacokinetics for the dose range: 1 - 20 mg/kg with a linear two-compartment disposition model with first-order elimination. Based on pharmacokinetic modeling, the overall exposure of atezolizumab administered at doses of 840 mg every 2 weeks, 1200 mg every 3 weeks are comparable A population pharmacokinetic analysis suggests that steady-state is obtained after 6 to 9 weeks after multiple doses. The maximum systemic accumulation ratio across dosing regimens is 3.3.

Based on an analysis of exposure, safety and efficacy data, the following factors have no clinically relevant effect: age (21-89 years), body weight, gender, positive anti-therapeutic antibody (ATA) status, albumin levels, tumor burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status.

3.2.1 Absorption

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

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 (Vss) 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 (t1/2) is 27 days.

3.2.5 Pharmacokinetics in special populations

Pediatric Population
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.

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 atezolizumab pharmacokinetics based on patients of age range of 21-89 years (n=472), and median of 62 years of age. No clinically important difference was observed in the pharmacokinetics of atezolizumab among patients < 65 years (n=274), patients between 65-75 years (n=152) and patients > 75 years (n=46) (see section 2.2.1 Special Dosage Instructions).

Renal impairment
No dedicated studies of Tecentriq have been conducted in patients with renal impairment. In the population pharmacokinetic analysis, no clinically important differences in the clearance of atezolizumab were found in patients with mild (eGFR 60 to 89 mL/min/1.73 m2; n=208) or moderate (eGFR 30 to 59 mL/min/1.73 m2; n=116) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m2; n=140) renal function. Only a few patients had severe renal impairment (eGFR 15 to 29 mL/min/1.73 m2; n=8) (see section 2.2.1 Special Dosage Instructions).

Hepatic impairment
No dedicated studies of Tecentriq have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of atezolizumab between patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin >1.0 to 1.5 x ULN and any AST) or moderate hepatic impairment (bilirubin >1.5 to 3x ULN and any AST). No data are available in patients with severe (bilirubin > 3.0 x 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

Not applicable

4. DESCRIPTION

Atezolizumab is a programmed cell death ligand 1 (PD-L1) blocking antibody. Atezolizumab is an Fc-engineered, humanized, non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of 145 kDa.

Tecentriq (atezolizumab) injection for intravenous use is a sterile, preservative-free, colorless to slightly yellow solution in single-dose vials. Each 20 mL vial contains 1200 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), polysorbate 20 (8 mg), and sucrose (821.6 mg), with a pH of 5.8. Each 14 mL vial contains 840 mg of atezolizumab and is formulated in glacial acetic acid (11.5 mg), L-histidine (43.4 mg), polysorbate 20 (5.6 mg), and sucrose (575.1 mg) with a pH of 5.8.

5. PHARMACEUTICAL PARTICULARS

5.1 STORAGE

Vials: Store in a refrigerator at 2°C-8°C.

DO NOT FREEZE. DO NOT SHAKE.

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

Shelf life
3 Years for Atezolizumab Injection 1200mg/20ml
2 Years for Atezolizumab Injection 840mg/14ml

This medicine should not be used after the expiry date (Expiry Date) 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 30 days at 2^0C-8^0C or 24 hours at ambient temperature (≤ 25°C) if prepared under aseptic conditions.

5.2 SPECIAL INSTRUCTIONS FOR USE, HANDING AND DISPOSAL

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), polyethylene (PE) polyolefin bags 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.

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.

5.3 Patient counselling information

Immune-mediated adverse reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of Tecentriq, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucous in stools, or severe abdominal pain.

- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, hyperthyroidism, hypothyroidism, adrenal insufficiency, or type 1 diabetes mellitus, including diabetic ketoacidosis.
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of other potential immune-mediated adverse reactions.

Infections
Advise patients to contact their healthcare provider immediately for signs or symptoms of infection.

Infusion-Related Reactions
Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions.

Embryo-Fetal Toxicity
Advise females of reproductive potential that Tecentriq can cause harm to the fetus and to inform their healthcare provider of a known or suspected pregnancy.

Advise females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of Tecentriq.

Lactation
Advise female patients not to breastfeed while taking Tecentriq and for at least 5 months after the last dose.

6. DETAILS OF MANUFACTURER:

Manufactured by:
F. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4070 Basel, Switzerland at:

- Atezolizumab Injection [1200mg/20ml]:Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim, Germany.
- Atezolizumab Injection [840mg/14ml]: F. Hoffmann-La Roche Ltd, Wurmisweg, CH-4303 Kaiseraugst, Switzerland

Imported and marketed by:
Roche Products (India) Pvt. Ltd.
C/O. Parekh Integrated Services Pvt Ltd,
Gala No. A1, First Floor, Warehouse no. 6,
BGR Logistics Park, NH-3, Zone 5, Bhiwandi,
Maharashtra (India) – 421302

7. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

IMP-063/2017 dated 31 March 2017 [1200mg/20ml] and dated 27 Sept 2019 [840mg/14ml]

8. DATE OF REVISION

Current at February 2021, Version 18.0