Core Data Sheet 3.0

May 2017

TECENTRIQ®

atezolizumab

Information as set forth in this label only applies to Tecentriq

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Category

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

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

ATC Code – Not yet assigned

1.2 TYPE OF DOSAGE FORM

Concentrate for solution for infusion

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 20 mL preservative-free, colorless to slightly yellow solution, at a concentration of 60 mg/mL. Each vial contains a total of 1200 mg atezolizumab.

Excipients: As registered locally.

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

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

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

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.

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

The recommended dose is 1200 mg administered by IV infusion every three weeks. 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.

Duration of Treatment

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

Delayed or Missed Doses

If a planned dose of Tecentriq is missed, it should be administered as soon as possible; do not wait until the next planned dose. The schedule of administration should be adjusted to maintain a 3-week interval between doses.

Dose Modifications

No dose reductions of Tecentriq are recommended.

See section 2.4.1 Warnings and Precautions, General for management of the following:

- Immune-related pneumonitis
- Immune-related hepatitis
- Immune-related colitis
- Immune-related endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus)
- Immune-related meningoencephalitis

- Immune-related neuropathies (myasthenic syndrome / myasthenia gravis, Guillain-Barré syndrome)

- Immune-related pancreatitis

- Infusion-related reactions

Table 1: Dose modification advice for specified Adverse Drug Reactions

Adverse reaction	Severity	Treatment modification
Rash (see section 2.6.1 Undesirable Effects, Clinical Trials)	Grade 3	Withhold Tecentriq Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day
	Grade 4	Permanently discontinue Tecentriq

2.2.1 Special Dosage Instructions

Children

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

Elderly

Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq is required in patients ≥ 65 years of age (see sections 2.5.5 Elderly 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 hepatic impairment. There are no data in patients with moderate or severe hepatic impairment (see section 3.2.5 Pharmacokinetics in Special Populations).

2.3 CONTRAINDICATIONS

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

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

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

Immune-related 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.

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

Immune-related 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.

Treatment with Tecentriq should be withheld if Grade 2 (ALT or AST >3x ULN or blood bilirubin >1.5x ULN) persists for more than 5-7 days, and 1-2 mg/kg prednisone or equivalent per day should be started. If LFTs improve to ≤ Grade 1, taper corticosteroids over ≥ 1 month. Treatment with Tecentriq 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 3 or Grade 4 events (ALT or AST >5.0x ULN or blood bilirubin >3x ULN).

Immune-related 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.

Treatment with Tecentriq should be withheld for Grade 2 or 3 diarrhea (increase of ≥ 4 stools/day over baseline) or colitis (symptomatic). For Grade 2 diarrhea or colitis, if symptoms persist > 5 days or recur, start 1-2 mg/kg prednisone or equivalent per day. Treat Grade 3 diarrhea or colitis with IV corticosteroids (1-2 mg/kg/day methylprednisolone or equivalent) and convert to oral corticosteroids (prednisone 1-2 mg/kg or equivalent per day) after improvement. If symptoms improve to ≤ Grade 1, taper corticosteroids over ≥ 1 month. Treatment with Tecentriq may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Treatment with Tecentriq should be permanently discontinued for Grade 4 (life threatening; urgent intervention indicated) diarrhea or colitis.

Immune-related endocrinopathies

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

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

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

Treatment with Tecentriq should be withheld for Grade 2 or Grade 3 hypophysitis. Treatment with 1-2 mg/kg per day IV methylprednisolone or equivalent should be started, and hormone replacement should be initiated as needed. Once symptoms improve, convert to 1-2 mg/kg per day of oral prednisone or equivalent. If symptoms

improve to ≤ Grade 1, corticosteroids should be tapered over ≥1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg per day of oral prednisone or equivalent and patient is stable on replacement therapy (if required). Treatment with Tecentriq should be permanently discontinued for Grade 4 hypophysitis.

Treatment with insulin should be initiated for type 1 diabetes mellitus. For ≥ Grade 3 hyperglycemia (fasting glucose >250 - 500 mg/dL), Tecentriq should be withheld. Treatment with Tecentriq may be resumed if metabolic control is achieved on insulin replacement therapy.

Immune-related 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.

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

Immune-related 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.

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

Immune-related 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.

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

Tecentriq should be permanently discontinued for Grade 4, or any grade of recurrent pancreatitis.

Infusion related reactions

Infusion related reactions (IRRs) have been observed in clinical trials with Tecentriq (see section 2.6.1 Undesirable effects, Clinical Trials).

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

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-related 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 Pregnancy, and 3.3.4 Teratogenicity).

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.

2.4.4 Laboratory Tests

See sections 2.4.1 Warnings and Precautions, General (Immune-related hepatitis, Immune-related endocrinopathies) and 2.6.1 Undesirable Effects, Clinical Trials for management of the following:

- AST, ALT, bilirubin
- thyroid function

2.4.5 Interactions with other Medicinal Products and other Forms of Interaction

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

2.5 USE IN SPECIAL POPULATIONS

2.5.1 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).

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).

2.5.2 Labor and Delivery

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

2.5.3 Nursing Mothers

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

2.5.4 Pediatric Use

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

2.5.5 Elderly 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 safety of Tecentriq is based on pooled data in 2160 patients with urothelial carcinoma and NSCLC, with supporting data from the estimated cumulative exposure in 6000 patients across all clinical trials in multiple tumor types. Table 2 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of Tecentriq.

The following categories of frequency have been used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Table 2 Summary of adverse reactions occurring in patients treated with Tecentriq in clinical trials

ADR (MedDRA)	Tecentriq (n=2160)			
System Organ Class	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
Blood and Lymphatic System Disorders				
Thrombocytopenia	52 (2.4%)	11 (0.5%)	0 (0%)	Common
Endocrine Disorders				
Hypothyroidism [a]	101 (4.7%)	4 (0.2%)	0 (0%)	Common
Hyperthyroidism [b]	36 (1.7%)	0 (0%)	0 (0%)	Common
Adrenal insufficiency [c]	7 (0.3%)	0 (0%)	0 (0%)	Uncommon
Hypophysitis	1 (<0.1%)	0 (0%)	0 (0%)	Rare
Diabetes mellitus [d]	6 (0.3%)	4 (0.2%)	0 (0%)	Uncommon
Gastrointestinal Disorders				
Diarrhea	402 (18.6%)	21 (1.0%)	0 (0%)	Very Common
Dysphagia	57 (2.6%)	11 (0.5%)	0 (0%)	Common
Colitis [e]	23 (1.1%)	11 (0.5%)	0 (0%)	Common
Nausea	494 (22.9%)	25 (1.2%)	0 (0%)	Very Common

ADR (MedDRA)	Tecentriq (n=2160)			
System Organ Class	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
Vomiting	324 (15.0%)	19 (0.9%)	0 (0%)	Very Common
Abdominal pain	154 (7.1%)	15 (0.7%)	0 (0%)	Common
Pancreatitis [f]	4 (0.2%)	3 (0.1%)	0 (0%)	Uncommon
Amylase increased	2 (<0.1%)	1 (<0.1%)	0 (0%)	Rare
Lipase increased	4 (0.2%)	3 (0.1%)	0 (0%)	Uncommon
General Disorders and Administration				
Chills	125 (5.8%)	2 (<0.1%)	0 (0%)	Common
Fatigue	764 (35.4%)	76 (3.5%)	0 (0%)	Very Common
Asthenia	298 (13.8%)	31 (1.4%)	0 (0%)	Very Common
Influenza like illness	120 (5.6%)	0 (0.0%)	0 (0%)	Common
Pyrexia	396 (18.3%)	11 (0.5%)	0 (0%)	Very Common
Infusion related reaction	25 (1.2%)	5 (0.2%)	0 (0%)	Common
Hepatobiliary Disorders				
ALT increased	105 (4.9%)	26 (1.2%)	0 (0%)	Common
AST increased	114 (5.3%)	27 (1.3%)	0 (0%)	Common
Hepatitis [g]	7 (0.3%)	6 (0.3%)	0 (0%)	Uncommon
Immune System Disorders				
Hypersensitivity	24 (1.1%)	2 (<0.1%)	0 (0%)	Common
Metabolism and Nutrition Disorders				
Decreased appetite	551 (25.5%)	21 (1.0%)	0 (0%)	Very Common
Hypokalemia	104 (4.8%)	23 (1.1%)	0 (0%)	Common
Hyponatremia	110 (5.1%)	62 (2.9%)	0 (0%)	Common
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	307 (14.2%)	15 (0.7%)	0 (0%)	Very Common
Musculoskeletal pain	190 (8.8%)	10 (0.5%)	0 (0%)	Common
Nervous System Disorders				
Guillain-Barré syndrome [h]	5 (0.2%)	4 (0.2%)	0 (0%)	Uncommon
Noninfective encephalitis [i]	2 (<0.1%)	2 (<0.1%)	0 (0%)	Rare

ADR (MedDRA)	Tecentriq (n=2160)			
System Organ Class	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
Meningitis noninfective[J]	3 (0.1%)	2 (<0.1%)	0 (0%)	Uncommon
Myasthenic syndrome[K]	-	-	-	Rare
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea	479 (21.8%)	82 (3.8%)	1 (<0.1%)	Very Common
Hypoxia	53 (2.5%)	25 (1.6%)	0 (0%)	Common
Nasal congestion	62 (2.9%)	0 (0%)	0 (0%)	Common
Pneumonitis[I]	68 (3.1%)	21 (1.0%)	1 (<0.1%)	Common
Skin and Subcutaneous Tissue Disorders				
Rash[M]	401 (18.6%)	19 (0.9%)	0 (0%)	Very Common
Pruritus	244 (11.3%)	5 (0.2%)	0 (0%)	Very Common
Vascular Disorders				
Hypotension	77 (3.6%)	13 (0.6%)	0 (0%)	Common

[a] Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, blood thyroid stimulating hormone decreased, myxoedema, thyroid function test abnormal, thyroiditis acute, thyroxine decreased
[b] Includes reports of hyperthyroidism, blood thyroid stimulating hormone increased, thyroiditis, blood thyroid stimulating hormone decreased, endocrine ophthalmopathy, exophthalmus, thyroid function test abnormal, thyroiditis acute, thyroxine decreased
[c] Includes reports of adrenal insufficiency, primary adrenal insufficiency, and Addison's disease
[d] Includes reports of diabetes mellitus and type 1 diabetes mellitus
[e] Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic
[f] Includes reports of pancreatitis and pancreatitis acute
[g] Includes reports of autoimmune hepatitis, hepatitis, hepatitis acute
[h] Includes reports of Guillain-Barré syndrome and demyelinating polyneuropathy
[i] Includes reports of encephalitis
[j] Includes reports of meningitis
[k] Reported in studies outside the pooled dataset. The frequency is based on the program-wide exposure.
[l] Includes reports of pneumonitis, lung infiltration, bronchiolitis, interstitial lung disease, radiation pneumonitis
[m] Includes reports of rash maculo-papular, erythema, rash pruritic, dermatitis acneiform, eczema, rash papular, rash macular, dermatitis, rash erythematous, acne, rash pustular, skin exfoliation, skin ulcer, seborrhoeic dermatitis, erythema multiforme, dermatitis bullous, rash generalized, skin toxicity, exfoliative rash, dermatitis allergic, drug eruption, dermatitis exfoliative, palmar-plantar erythrodysaesthesia syndrome, rash papulosquamous, toxic skin eruption, erythema of eyelid, eyelid rash, folliculitis, furuncle, rash

Additional information for selected adverse reactions

See section 2.4.1 Warnings and Precautions, General for management of the following:

Immune-related pneumonitis

Pneumonitis occurred in 3.1% (68/2160) of patients who received Tecentriq for metastatic urothelial carcinoma and NSCLC. Of the 68 patients, one event was fatal. The median time to onset was 3.5 months (range: 3 days to 20.5 months). The median duration was 1.5 months (range 0 days to 15.1+ months; + denotes a censored value).

Pneumonitis led to discontinuation of Tecentriq in 10 (0.5%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.6% (34/2160) of patients receiving Tecentriq.

Immune-related hepatitis

Hepatitis occurred in 0.3% (7/2160) of patients who received Tecentriq for metastatic urothelial carcinoma and NSCLC. The median time to onset was 1.1 months (range 9 days to 7.9 months). The median duration was 1 month (range: 9 days to 1.9+ months; + denotes a censored value). Hepatitis led to discontinuation of Tecentriq in 2 (<0.1%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.2% (5/2160) of patients receiving Tecentriq.

Immune-related colitis

Colitis occurred in 1.1% (23/2160) of patients who received Tecentriq for metastatic urothelial carcinoma and NSCLC. The median time to onset was 4 months (range 15 days to 15.2 months). The median duration was 1.4 months (range: 3 days to 17.8+ months; + denotes a censored value). Colitis led to discontinuation of Tecentriq in 5 (0.2%) patients. Colitis requiring the use of corticosteroids occurred in 0.5% (10/2160) of patients receiving Tecentriq.

Immune-related endocrinopathies

Hypothyroidism occurred in 4.7% (101/2160) of patients who received Tecentriq for metastatic urothelial carcinoma and NSCLC. The median time to onset was 5.5 months (range: 15 days to 31.3 months). Hyperthyroidism occurred in 1.7% (36/2160) of patients who received Tecentriq for metastatic urothelial carcinoma and NSCLC. The median time to onset was 3.5 months (range: 21 days to 31.3 months). Adrenal insufficiency occurred in 0.3% (7/2160) of patients who received Tecentriq for metastatic urothelial carcinoma and NSCLC. The median time to onset was 5.7 months (range: 3 days to 19 months). Adrenal insufficiency requiring the use of corticosteroids occurred in 0.3% (6/2160) of patients receiving Tecentriq. Hypophysitis occurred in <0.1% (1/2160) of patients who received Tecentriq for metastatic urothelial carcinoma and NSCLC. The time to onset for this patient was 13.7 months.

Diabetes mellitus occurred in 0.3% (6/2160) of patients who received Tecentriq for metastatic urothelial carcinoma and NSCLC. The time to onset ranged from 3 days to 6.5 months. Diabetes mellitus led to the discontinuation of Tecentriq in 1 (<0.1%) patient.

Immune-related meningoencephalitis

Meningitis occurred in 0.1% (3/2160) of patients who received Tecentriq for metastatic urothelial carcinoma and NSCLC. The time to onset ranged from 15 to 16 days. All three patients required the use of corticosteroids and discontinued Tecentriq. Encephalitis occurred in <0.1% (2/2160) of patients. The time to onset was 14 and 16 days. One of

these patients required the use of corticosteroids. Encephalitis led to the discontinuation of Tecentriq in 1 (<0.1%) patient.

Immune-related neuropathies

Neuropathies, including Guillain-Barré syndrome and demyelinating polyneuropathy, occurred in 0.2% (5/2160) of patients who received Tecentriq for metastatic urothelial carcinoma and NSCLC. The median time to onset was 7 months (range: 18 days to 8.1 months). The median duration was 4.6 months (0 days 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% (2/2160) of patients.

Immune-related pancreatitis

Pancreatitis, including amylase increased and lipase increased, occurred in 0.5% (10/2160) of patients who received Tecentriq for metastatic urothelial carcinoma and NSCLC. The median time to onset was 5.5 months (range: 9 days to 16.9 months). The median duration was 19 days (range 3 days to 11.2+ months; + denotes a censored value). Pancreatitis requiring the use of corticosteroids occurred in <0.1% (2/2160) of patients receiving Tecentriq.

2.6.1.1 Laboratory Abnormalities

All identified laboratory abnormalities were reported as ADRs. Refer to Table 2 Summary of adverse reactions occurring in patients treated with Tecentriq in clinical trials.

2.6.2 Post Marketing

No data

2.6.2.1 Laboratory Abnormalities

No data

2.7 OVERDOSE

There is no information on overdose with Tecentriq.

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.

3.1.2 Clinical / Efficacy Studies

Urothelial Carcinoma

GO29293

A phase II, multi-center, international, two-cohort, single-arm clinical trial, GO29293 (IMvigor 210), was conducted in patients with locally advanced or metastatic urothelial carcinoma (also known as urothelial bladder cancer). The study enrolled patients with primary bladder sites as well as renal pelvis, ureter, and urethra sites. Patients were excluded if they had a history of autoimmune disease, active brain metastasis, administration of a live, attenuated vaccine within 28 days prior to enrollment, administration of systemic immunostimulatory agents within 6 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. 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 after 12 months of 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. Tumor specimens were evaluated prospectively for PD-L1 expression in tumor infiltrating immune cells (IC) and the results were used to define the PD-L1 expression subgroups for the analyses described below.

Tecentriq was given as a fixed dose of 1200 mg by IV infusion on Day 1 of a 21-day cycle. Patients in Cohort 1 were treated until disease progression. Patients in Cohort 2 were treated until loss of clinical benefit as assessed by the investigator.

There were 119 patients treated in Cohort 1 and 310 patients treated in Cohort 2. Patient demographics and baseline tumor characteristics for both cohorts were representative of the patient populations in their respective setting. The median age for Cohort 1 was 73 years and Cohort 2 was 66 years. Most patients were male (81% and 78% for Cohorts 1 and 2 respectively), and the majority of patients were White (91% for both cohorts).

In Cohort 1, representation of pre-specified poor prognostic factors was comparable between all pre-specified PD-L1 expression subgroups as well as for the all comer

group. This included 24 patients (20%) in Cohort 1 with ECOG score of 2, 18 patients (15%) with two Bajorin risk factors (ECOG performance status ≥ 2 and visceral metastasis), 84 patients (71%) with impaired renal function (GFR < 60 mL/min), and 25 patients (21%) with liver metastasis.

In Cohort 2, 43% of patients had received ≥ 2 prior chemotherapy regimens in the metastatic setting. Thirty-nine percent of patients had received their last chemotherapy regimen within 3 months prior to commencing treatment with Tecentriq. Prior platinum-based therapies included 73% of patients treated with cisplatin, 26% had prior carboplatin and no other platinum-based regimen, and 1% treated with other platinum-based regimens. In total, 78% of patients had visceral metastases. Bellmunt risk factors (ECOG score of 1, liver metastases at baseline, and hemoglobin < 10 g/dL) were observed in 62%, 31% and 22% of patients respectively.

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 co-primary efficacy endpoints for Cohort 2 were confirmed ORR as assessed by an IRF using RECIST v1.1 and investigator-assessed ORR according to Modified RECIST (mRECIST) criteria.

The primary analysis of Cohort 1 was performed when all patients had at least 24 weeks of follow-up. Median duration of treatment for Cohort 1 was 15.0 weeks and median duration of survival follow up was 7.6 months in patients with PD-L1 expression ≥ 5%, 8.3 months in patients with PD-L1 expression ≥ 1%, and 8.5 months in all comers. Clinically meaningful IRF-assessed ORRs per RECISTv1.1 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 3. The median DOR was not reached in any PD-L1 expression subgroup or in all comers.

Table 3 Summary of updated efficacy from GO29293 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
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 objective 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.

The primary analysis of Cohort 2 was performed when all patients had at least 24 weeks of follow-up. Median duration of treatment for Cohort 2 was 12.3 weeks and median duration of survival follow up was 7.6 months in patients with PD-L1 expression ≥ 5%, 7.2 months in patients with PD-L1 expression ≥ 1%, and 7.1 months in all comers. The study met its co-primary endpoints in all subgroups in Cohort 2, demonstrating statistically significant ORRs per IRF-assessed RECIST v1.1 and investigator-assessed mRECIST compared to a pre-specified historical control response rate of 10%. The confirmed ORRs per IRF-RECIST v1.1 were 27.0% (95% CI: 18.6, 36.8) in patients with PD-L1 expression ≥ 5%, 18.3% (95% CI: 13.3, 24.2) in patients with PD-L1 expression ≥ 1%, and 15.1% (95% CI: 11.3, 19.6) in all comers. The confirmed ORR per investigator-assessed mRECIST was 26.0% (95% CI: 17.7, 35.7) in patients with PD-L1 expression ≥5%, 21.2% (95% CI: 15.8, 27.3) in patients with PD-L1 expression ≥1%, and 18.3% (95% CI: 14.2, 23.1) in all comers. The median DOR was not reached in any PD-L1 expression subgroup or in all comers. OS was not mature with an event ratio of 45.3%. Median OS was not reached in patients with PD-L1 expression ≥ 5%, and was 8.0 and 7.9 months in patients with PD-L1 expression ≥ 1% and all comers, respectively.

An updated analysis was performed with a median duration of survival follow up 21.1 months for Cohort 2, and is summarized in Table 4. For Cohort 2, median DOR was not reached in any of the pre-specified PD-L1 expression subgroups, however was reached in patients with PD-L1 expression <1% (13.3 months; 95% CI 4.2, NE).

Table 4 Summary of updated efficacy from GO29293 Cohort 2

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 = 100	n = 207	n = 310
No. of Responders (%)	28 (28.0%)	40 (19.3%)	49 (15.8%)
95% CI	19.5, 37.9	14.2, 25.4	11.9, 20.4
ORR (Investigator-Assessed; Modified RECIST)	n = 100	n = 207	n = 310
No. of Responders (%)	29 (29.0%)	49 (23.7%)	61 (19.7%)
95% CI	20.4, 38.9	18.1, 30.1	15.4, 24.6
DOR (IRF-Assessed; RECIST v1.1)	n = 28	n = 40	n = 49
Patients with event (%)	9 (32.1%)	12 (30.0%)	17 (34.7%)
Median (months) (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (16.0, NE)
PFS (IRF-Assessed; RECIST v1.1)	n = 100	n = 207	n = 310
Patients with event (%)	80 (80.0%)	177 (85.5%)	274 (88.4%)
Median (months) (95% CI)	2.1 (2.1, 4.2)	2.1 (2.1, 2.1)	2.1 (2.1, 2.1)
OS	n = 100	n = 207	n = 310
Patients with event (%)	58 (58.0%)	142 (68.6%)	226 (72.9%)
Median (months) (95% CI)	11.9 (9.0, NE)	9.0 (7.1, 10.9)	7.9 (6.7, 9.3)
1-year OS rate (%)	50	40	37

CI=confidence interval; DOR=duration of objective 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.

PCD4989g

In addition, efficacy was evaluated in a phase Ia, multi-center, international, single-arm clinical trial (PCD4989g). The study was conducted in patients with locally advanced or metastatic cancer that included a cohort of 95 patients with locally advanced or metastatic UBC treated with Tecentriq with a median survival follow-up of 29.2 months. The study showed a confirmed ORR per IRF-RECIST v1.1 of 31.8% (95% CI: 13.9, 54.9) for patients with PD-L1 expression ≥5% and 18.8% (95% CI: 9.0, 32.6) for patients with PD-L1 expression <5%. Median DOR in responders per IRF-RECIST v1.1 was not reached in patients with PD-L1 expression ≥5% and was 27.6 months (95% CI: 9.6, NE) in patients with PD-L1 expression <5%. Median PFS per IRF-RECIST v1.1 was 2.7 months (95%CI: 1.4, 10.6) and 1.7 months (95% CI: 1.4, 4.0) for PD-L1 expression ≥5% and PD-L1 expression <5%, respectively. Median OS was 9.9 months (range: 0.7 – 35.5+; +denotes a censored value) for PD-L1 expression <5% and 9.1 months for PD-L1 expression ≥5% (range: 0.7 – 32.8). The OS rate at 12 months and 24 months was 46% and 30% respectively, for all comers.

Non-small cell lung cancer

GO28915

A phase III, open-label, multi-center, international, randomized study, GO28915 (OAK), was conducted to evaluate the efficacy and safety of Tecentriq compared with docetaxel in patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen. A total of 1225 patients were enrolled, with the primary analysis population consisting of the first 850 randomized patients. Eligible patients were stratified by PD-L1 expression status in tumor-infiltrating immune cells (IC), by the number of prior chemotherapy regimens, and by histology. Patients were randomized (1:1) to receive either Tecentriq or docetaxel. This study excluded patients who had a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Tumor assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter. Tumor specimens were evaluated prospectively for PD-L1 expression on tumor cells (TC) and IC and the results were used to define the PD-L1 expression subgroups for the analyses described below.

The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 64 years (range: 33 to 85), and 61% of patients were male. The majority of patients were white (70%). Approximately three-fourths of patients had non-squamous disease (74%), 10% had known EGFR mutation, 0.2% had known ALK rearrangements, 10% had CNS metastases at baseline, and most patients were current or previous smokers (82%). Baseline ECOG performance status was 0 (37%) or 1 (63%). Seventy five percent of patients received only one prior platinum-based therapeutic regimen.

Tecentriq was administered as a fixed dose of 1200 mg by IV infusion every 3 weeks. No dose reduction was allowed. Patients were treated until loss of clinical benefit as assessed by the investigator. Docetaxel was administered 75 mg/m^2 by IV infusion on day 1 of each 21 day cycle until disease progression. [REF] 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 5. 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.

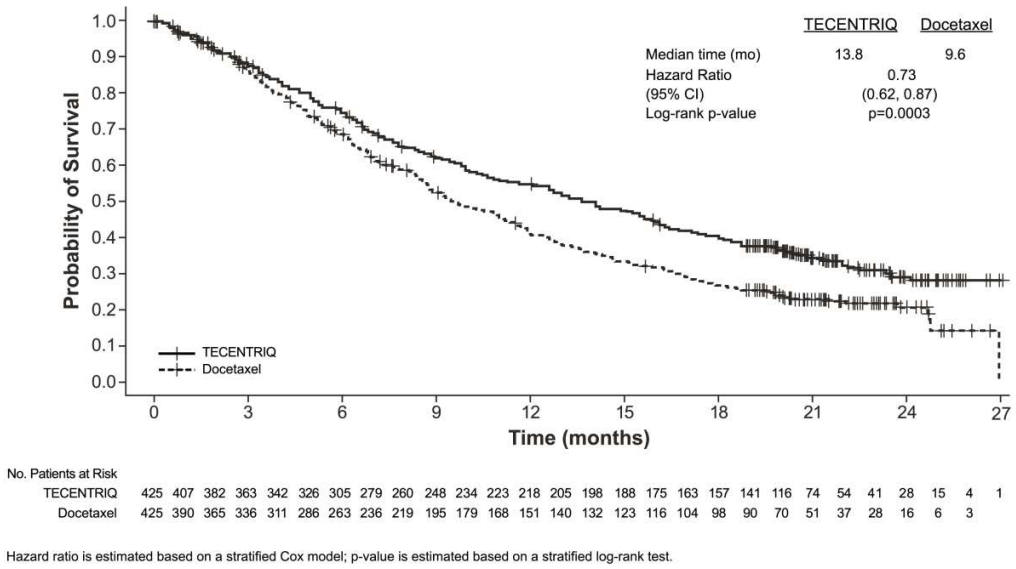
Table 5 Summary of Efficacy in the Primary Analysis Population (GO28915)

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

CI=confidence interval; DOR=duration of objective 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

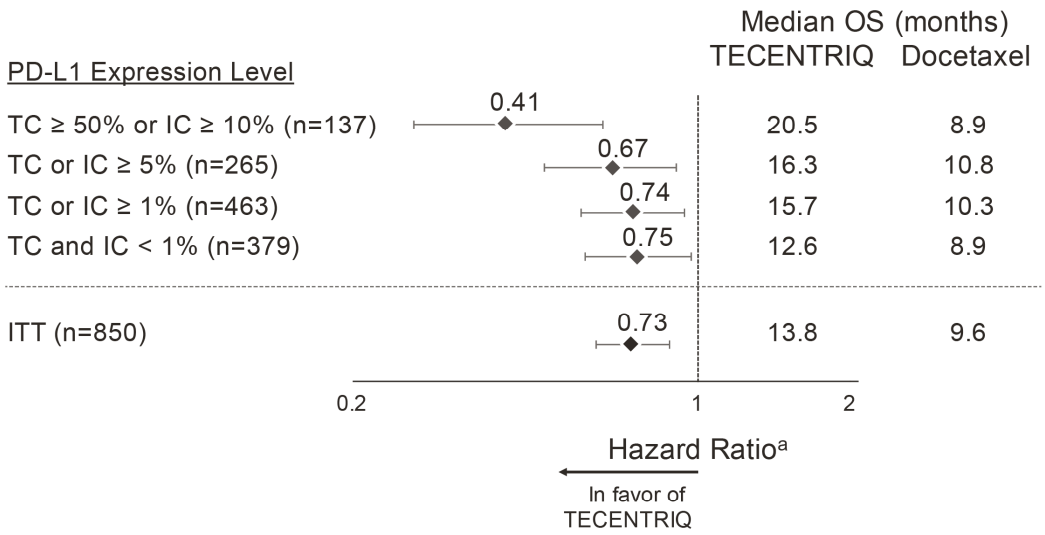
** Based on the stratified log-rank test

Figure 1: Kaplan-Meier Plot for Overall Survival in the Primary Analysis Population (all comers) (GO28915)



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

Figure 2: Forest Plot of Overall Survival by PD-L1 Expression in the Primary Analysis Population (GO28915)



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

An improvement in OS was observed with Tecentriq compared to docetaxel in both non-squamous NSCLC patients (hazard ratio [HR] of 0.73, 95% CI: 0.60, 0.89; median OS of 15.6 vs. 11.2 months for Tecentriq and docetaxel, respectively) and squamous NSCLC patients (HR of 0.73, 95% CI: 0.54, 0.98; median OS of 8.9 vs. 7.7 months for Tecentriq and docetaxel, respectively). The observed OS improvement was consistently demonstrated across subgroups of patients including those with brain 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.

GO28753

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.

3.1.3 Immunogenicity

As with all therapeutic proteins, there is the potential for immune response to atezolizumab. In study GO29293, 43.9% of patients tested positive for anti-atezolizumab antibodies at one or more post-dose time points. In study GO28915, the post-baseline ATA rate was 30.4%. Overall, ATA positivity appeared to have no clinically relevant impact on 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 has been characterized in patients in multiple clinical trials at doses 0.01 mg/kg to 20 mg/kg every 3 weeks including the fixed dose 1200 mg. Exposure to atezolizumab increased dose proportionally over the dose range 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. A population pharmacokinetic analysis suggests that steady-state is obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in area under the curve (AUC), maximum concentration (Cmax) and trough concentration (Cmin) was 1.91, 1.46 and 2.75-fold, respectively.

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

Children

No studies have been conducted to investigate the pharmacokinetics of Tecentriq in children.

Elderly

No dedicated studies of Tecentriq have been conducted in elderly patients. The effect of age on the pharmacokinetics of atezolizumab was assessed in a population pharmacokinetic analysis. Age was not identified as a significant covariate influencing atezolizumab pharmacokinetics based on patients of age range of 21-89 years (n=472), and median of 62 years of age. No clinically important difference was observed in the pharmacokinetics of atezolizumab among patients < 65 years (n=274), patients between 65–75 years (n=152) and patients > 75 years (n=46) (see section 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 × ULN and any AST, n = 71) and normal hepatic function (bilirubin and AST ≤ ULN, n=401). No data are available in patients with either moderate (bilirubin > 1.5 to 3.0 × ULN and any AST) or severe (bilirubin > 3.0 × ULN and any AST) hepatic impairment. Hepatic impairment was defined by the National Cancer Institute (NCI) criteria of hepatic dysfunction (see section 2.2.1 Special Dosage Instructions).

3.3 PRECLINICAL SAFETY

3.3.1 Carcinogenicity

No carcinogenicity studies have been conducted with Tecentriq.

3.3.2 Mutagenicity

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 Teratogenicity

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.

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

Vials

Store at 2°C-8°C.

Tecentriq should be protected from light.

Do not freeze. Do not shake.

Shelf life

As registered locally.

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

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

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Instructions for dilution

Tecentriq should be prepared by a healthcare professional using aseptic technique. Withdraw 20 mL 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.

No preservative is used in Tecentriq therefore each vial is for single use only.

Incompatibilities

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

Medicine: keep out of reach of children

Current at May 2017

Manufactured by: Roche Diagnostic GmBH, Mannheim, Germany

Secondary Packaged and Batch Confirmation by: F. Hoffmann – La Roche Ltd., Kaiseraugst, Switzerland

Imported by Roche Thailand Ltd., Bangkok