PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTECENTRIQ®

atezolizumab

Concentrate for solution for infusion, 60 mg/mL

1200 mg/20 mL single use vials

Professed Standard

Antineoplastic agent

TECENTRIQ® has been issued marketing authorization **with conditions,** pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for TECENTRIQ®, please refer to Health Canada's Notice of Compliance with conditions - drug products website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php

TECENTRIQ® is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

TECENTRIQ® has been issued marketing authorization **without conditions** for:

- adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving TECENTRIQ.

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Submission Control No: 220475

Date of Approval: December 17, 2018

This product has been authorized under the Notice of Compliance with Conditions (NOC/c) policy for one of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

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PrTECENTRIQ®
atezolizumab

PART I: HEALTH PROFESSIONAL INFORMATION

TECENTRIQ® has been issued marketing authorization **with conditions,** pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for TECENTRIQ®, please refer to Health Canada's Notice of Compliance with conditions - drug products website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php

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SUMMARY PRODUCT INFORMATION

Route of Administration	Pharmaceutical Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Concentrate for solution for infusion 1200 mg atezolizumab / 20 mL (60 mg/mL)	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

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

INDICATIONS AND CLINICAL USE

Locally Advanced or Metastatic Urothelial Carcinoma

NOC/c TECENTRIQ (atezolizumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Marketing authorization with conditions was based on tumour response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established (see CLINICAL TRIALS).

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

TECENTRIQ (atezolizumab) is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving TECENTRIQ.

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

Pediatrics (<18 years of age):
The safety and efficacy of TECENTRIQ in children and adolescents below 18 years of age have not been established.

NOC/c CONTRAINDICATIONS

TECENTRIQ (atezolizumab) is contraindicated in:

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

NOC/c WARNINGS AND PRECAUTIONS

Immune-Related Adverse Reactions

Immune-Related Pneumonitis

Cases of pneumonitis, including fatal cases, have been observed in clinical trials with TECENTRIQ (atezolizumab) across tumour types. Patients should be monitored for signs and symptoms of pneumonitis (see ADVERSE REACTIONS, Immune-Related 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 Grade 4 pneumonitis.

Immune-Related Hepatitis
Cases of hepatitis, some leading to fatal outcomes, have been observed in clinical trials with TECENTRIQ across tumour types. Patients should be monitored for signs and symptoms of hepatitis. Monitor aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin prior to and periodically during treatment with TECENTRIQ. Consider appropriate management of patients with abnormal liver function tests (LFTs) at baseline (see ADVERSE REACTIONS, Immune-Related Hepatitis).

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. Patients should be monitored for signs and symptoms of colitis (see ADVERSE REACTIONS, Immune-Related Colitis).

Treatment with TECENTRIQ should be withheld for Grade 2 or Grade 3 diarrhea (increase of ≥ 4 stools/day over baseline) or colitis (symptomatic). For Grade 2 diarrhea or colitis, if symptoms persist > 5 days or recur, start 1-2 mg/kg prednisone or equivalent per day. Treat Grade 3 diarrhea or colitis with IV corticosteroids (1-2 mg/kg/day methylprednisolone or equivalent) and convert to oral corticosteroids (prednisone 1-2 mg/kg or equivalent per day) after improvement. If symptoms improve to ≤ 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 and type 1 diabetes mellitus, including diabetic ketoacidosis, have been observed in clinical trials with TECENTRIQ across tumour types. Patients should be monitored for clinical signs and symptoms of endocrinopathies (see ADVERSE REACTIONS, Immune-Related Endocrinopathies).

Hypophysitis
Hypophysitis has been observed in clinical trials with TECENTRIQ across tumour types. Monitor for signs and symptoms of hypophysitis. Administer corticosteroids and hormone replacement as clinically indicated. Withhold TECENTRIQ for Grade 2 or Grade 3 and permanently discontinue for Grade 4 hypophysitis.

Thyroid Disorders
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.

Adrenal Insufficiency
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).

Diabetes Mellitus
Treatment with insulin should be initiated for type 1 diabetes mellitus. For ≥ Grade 3 hyperglycemia (fasting glucose >250 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 across tumour types. 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 across tumour types. 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 across tumour types. Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis (see ADVERSE REACTIONS, Immune-Related 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.

Immune-Related Myocarditis
Severe cases of myocarditis have been observed in clinical trials with TECENTRIQ. Patients should be monitored for signs and symptoms of myocarditis.

TECENTRIQ should be withheld for Grade 2 myocarditis. Treatment with TECENTRIQ should be permanently discontinued for Grade 3 or 4 myocarditis. Corticosteroids and/or additional immunosuppressive agents should be administered as clinically indicated.

Immune-Related Nephritis
Nephritis has been observed in clinical trials with TECENTRIQ. Patients should be monitored for changes in renal function.

Treatment with TECENTRIQ should be withheld for Grade 2 nephritis[1]. Treatment with TECENTRIQ should be permanently discontinued for Grade 3 or 4 nephritis.

Ocular Inflammatory Toxicity
Ocular inflammatory toxicity has been observed in clinical trials with TECENTRIQ. Withhold TECENTRIQ for moderate and permanently discontinue for severe ocular inflammatory toxicity.

Infection
Severe infections have been observed in clinical trials with TECENTRIQ. Monitor patients for signs and symptoms of infection and treat with antibiotics for suspected or confirmed bacterial infections. Withhold TECENTRIQ for ≥ Grade 3 infection.

[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.

Infusion-Related Reactions
Infusion-related reactions (IRRs) have been observed in clinical trials with TECENTRIQ (see ADVERSE REACTIONS, Infusion-Related Reactions).

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

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

Women of Childbearing Potential: Women of childbearing potential should be advised to 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 TOXICOLOGY).

Infertility: Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment.

Nursing Women: It is not known whether TECENTRIQ is secreted in human breast milk. Because antibodies are secreted in human milk and because a risk to the newborns/infants cannot be excluded, a decision should be made whether to discontinue breast-feeding or discontinue TECENTRIQ, taking into account the benefit of breast-feeding for the child and the benefit of TECENTRIQ therapy for the mother.

Pediatrics (<18 years of age): The safety and efficacy of TECENTRIQ in children and adolescents below 18 years of age have not been established.

Geriatrics (> 65 years of age): No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients (see DOSAGE AND ADMINSTRATION and ACTION AND CLINICAL PHARMACOLOGY).

Renal Impairment: Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with renal impairment (see ACTION AND CLINICAL PHARMACOLOGY).

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 ACTION AND CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests

Monitor AST, ALT, bilirubin, and thyroid function prior to and periodically during treatment with TECENTRIQ (see WARNINGS AND PRECAUTIONS, Immune-Related Hepatitis and Immune-Related Endocrinopathies and ADVERSE REACTIONS).

NOC/c ADVERSE REACTIONS

Adverse Drug Reaction Overview

Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ (atezolizumab), as presented in Table 1, is based on use in 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following prior platinum-based chemotherapy or who had disease progression within 12 months of platinum-based neoadjuvant or adjuvant chemotherapy. These patients were enrolled in cohort 2 of the phase II single-arm clinical study, GO29293, in which patients received TECENTRIQ 1200 mg every 3 weeks by intravenous infusion until there was no longer a clinical benefit as assessed by investigators or until unacceptable toxicity.

Overall, 303/310 (97.7%) patients enrolled in cohort 2 of GO29293 had at least one adverse event and grade 3-4 events were experienced by 186 (60.0%) patients. Serious adverse events occurred in 144 (46.5%) patients. Grade 5 adverse events (adverse events leading to death) occurred in 3 (1.0%) patients. Adverse events leading to dose interruption occurred in 100 (32.3%) patients and withdrawal from TECENTRIQ due to adverse events occurred in 12 (3.9%) patients.

The most common adverse events (reported by ≥10% patients) were fatigue (51.0%), decreased appetite (27.1%), nausea (26.5%), constipation (26.1%), urinary tract infection (23.2%), pyrexia (22.3%), edema, peripheral (14.2%), diarrhea (21.6%), vomiting (19.4%), back pain (18.1%), dyspnea (17.4%), chills (10.6%), arthralgia (17.7%), anemia (17.1%), cough (16.5%), hematuria (16.1%), pruritus (14.8%), abdominal pain (13.9%), rash (11.6%), pain in extremities (10.3%), headache (10.0%), and pain (10.0%). The majority of adverse reactions were mild to moderate (Grade 1 or 2) in severity.

The most common adverse events leading to dose interruption were urinary tract infection (2.6%), diarrhea, pyrexia (2.3% each), fatigue (1.9%), blood bilirubin increased, dyspnea and pneumonitis (1.6% each), aspartate aminotransferase increased, blood creatinine increased,

confusional state, hypotension, sepsis and transaminases increased (1.3% each). Two patients were withdrawn from TECENTRIQ due to sepsis.

The safety of TECENTRIQ was also investigated in cohort 1 of study GO29293 in which patients with locally advanced or metastatic urothelial carcinoma, who were treatment naïve, received TECENTRIQ 1200 mg every 3 weeks (n=119) and in study PCD4989g in which patients with locally advanced or metastatic urothelial carcinoma, that had received prior treatment for their disease, received TECENTRIQ 1200 mg (n=9) or 15 mg/kg (n=86) every 3 weeks. The total number of locally advanced or metastatic urothelial carcinoma patients who were treated with TECENTRIQ, independent of prior treatment status, was 524.

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

The safety of TECENTRIQ (atezolizumab), as presented in Table 2, is based on use in 1187 patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC), who had progressed during or following a platinum-containing regimen. These patients were enrolled in the phase III pivotal trial study GO28915, in which 609 patients received TECENTRIQ 1200 mg administered intravenously every 3 weeks until loss of clinical benefit or unacceptable toxicity vs. 578 patients who received docetaxel 75 mg/m^2 administered intravenously every 3 weeks until unacceptable toxicity or disease progression.

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

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

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

The safety of TECENTRIQ in NSCLC was also investigated in four additional supporting studies: Phase II global multi-centered open-label randomized controlled study GO28753, two phase II global multi-centered single arm studies GO28754 and GO28625, and phase I multi-centered open-label study PCD4989g with a NSCLC cohort. The total number of locally

advanced or metastatic NSCLC patients who were treated with TECENTRIQ in clinical trials was 1636.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Locally Advanced or Metastatic Urothelial Carcinoma

The information provided in Table 1 and Listing 1 summarizes the adverse drug reactions observed in patients included in Cohort 2 of study GO29293 (n=310), during treatment with TECENTRIQ and up to 30 days from the last dose received.

Table 1 Adverse Drug Reactions Occurring in ≥ 1% of Patients with Urothelial Carcinoma Treated with TECENTRIQ in Study GO29293 Cohort 2

Adverse Drug Reaction[a] (MedDRA)	TECENTRIQ N = 310	
System Organ Class	**All Grades (%)**	**Grade 3 - 4 (%)**
All Adverse Reactions	266 (85.8%)	78 (25.1%)
Blood and Lymphatic System Disorders		
Thrombocytopenia	9 (2.9%)	1 (0.3%)
Endocrine Disorders		
Hypothyroidism [b]	11 (3.5%)	1 (0.3%)
Hyperthyroidism [c]	3 (1.0%)	0 (0%)
Gastrointestinal Disorders		
Nausea	82 (26.5%)	6 (1.9%)
Diarrhea	68 (21.9%)	3 (1.0%)
Vomiting	60 (19.4%)	4 (1.3%)
Abdominal pain	43 (13.9%)	8 (2.6%)
Colitis [d]	4 (1.3%)	3 (1.0%)
General Disorders and Administration		
Fatigue	158 (51.0%)	19 (6.1%)
Pyrexia	72 (23.2%)	3 (1.0%)
Chills	34 (11.0%)	1 (0.3%)
Asthenia	26 (8.4%)	2 (0.6%
Influenza like illness	16 (5.2%)	0 (0.0%)
Hepatobiliary Disorders		
AST increased	16 (5.2%)	5 (1.6%)
ALT increased	16 (5.2%)	6 (1.9%)
Metabolism and Nutrition Disorders		
Decreased appetite	85 (27.4%)	4 (1.3%)
Hyponatremia	22 (7.1%)	12 (3.9%)
Hypokalemia	17 (5.5%)	4 (1.3%)

Adverse Drug Reaction[a] (MedDRA)	TECENTRIQ N = 310	
System Organ Class	**All Grades (%)**	**Grade 3 - 4 (%)**
Hyperglycemia	14 (4.5%)	2 (0.6%)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	55 (17.7%)	3 (1.0%)
Musculoskeletal pain	21 (6.8%)	2 (0.6%)
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	55 (17.7%)	10 (3.2%)
Nasal congestion	16 (5.2%)	0 (0%)
Pneumonitis	8 (2.6%)	3 (0.9%)
Hypoxia	5 (1.6%)	3 (1.0%)
Skin and Subcutaneous Tissue Disorders		
Rash [e]	57 (18.4%)	2 (0.6%)
Pruritus	46 (14.8%)	1 (0.3%)
Vascular Disorders		
Hypotension	14 (4.5%)	2 (0.6%)

[a] Incidences presented in this table are based on adverse events considered to be drug-related.
[b] Includes reports of hypothyroidism and blood thyroid stimulating hormone increased
[c] Includes reports of hyperthyroidism and blood thyroid stimulating hormone increased
[d] Includes reports of colitis, colitis ischaemic and colitis microscopic
[e] Includes reports of rash, rash maculo-papular, rash pruritic, rash pustular, acne, eczema, erythema, rash papular, skin toxicity, dermatitis allergic, drug eruption, erythema multiforme, rash erythematous and seborrhoeic dermatitis.

Listing 1: Less Common Adverse Drug Reactions Occurring in (< 1%) Patients with Urothelial Carcinoma Treated with TECENTRIQ in Study GO29293 Cohort 2:

Gastrointestinal Disorders: Dysphagia

Hepatobiliary Disorders: Hepatitis (includes reports of autoimmune hepatitis, hepatitis)

Immune System Disorders: Hypersensitivity

Injury, Poisoning and Procedural Complications: Infusion related reaction

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

The information provided in Table 2 and Listing 2 summarizes the adverse drug reactions observed in patients included in study GO28915 (n=1187), during treatment with TECENTRIQ compared to treatment with docetaxel.

Table 2 Adverse Drug Reactions Occurring in ≥ 1% of Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with TECENTRIQ vs. Docetaxel in the Pivotal Study GO28915

Adverse Drug Reaction[a] (MedDRA) System Organ Class (SOC)	TECENTRIQ n = 609 (Frequency rate %)		Docetaxel n = 578 (Frequency rate %)	
	All Grades	**Grades 3-4**	**All Grades**	**Grades 3-4**
All Adverse Drug Reactions	511 (83.9%)	104 (17.1%)	480 (83.0%)	95 (16.4%)

Adverse Drug Reaction[a] (MedDRA) System Organ Class (SOC)	TECENTRIQ n = 609 (Frequency rate %)		Docetaxel n = 578 (Frequency rate %)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Blood and Lymphatic System Disorders				
Thrombocytopenia	8 (1.3%)	1 (0.2%)	8 (1.4%)	1 (0.2%)
Endocrine Disorders				
Hypothyroidism [b]	27 (4.4%)	0 (0%)	2 (0.3%)	0 (0%)
Hyperthyroidism [c]	17 (2.8%)	0 (0%)	1 (0.2%)	0 (0%)
Gastrointestinal Disorders				
Nausea	109 (17.9%)	4 (0.7%)	132 (22.8%)	2 (0.3%)
Diarrhea	94 (15.4%)	4 (0.7%)	141 (24.4%)	11 (1.9%)
Vomiting	74 (12.2%)	2 (0.3%)	63 (10.9%)	5 (0.9%)
Abdominal pain	20 (3.3%)	1 (0.2%)	38 (6.6%)	5 (0.9%)
Dysphagia	13 (2.1%)	2 (0.3%)	11 (1.9%)	1 (0.2%)
General Disorders and Administration				
Fatigue	163 (26.8%)	17 (2.8%)	206 (35.6%)	23 (4.0%)
Pyrexia	109 (17.9%)	2 (0.3%)	77 (13.3%)	1 (0.2%)
Chills	22 (3.6%)	1 (0.2%)	9 (1.6%)	0 (0%)
Asthenia	116 (19.0%)	8 (1.3%)	115 (19.9%)	13 (2.2%)
Influenza like illness	32 (5.3%)	0 (0%)	14 (2.4%)	0 (0%)
Hepatobiliary Disorders				
AST increased	38 (6.2%)	5 (0.8%)	12 (2.1%)	2 (0.3%)
ALT increased	35 (5.7%)	6 (1.0%)	14 (2.4%)	2 (0.3%)
Immune System Disorders				
Hypersensitivity	6 (1.0%)	1 (0.2%)	11 (1.9%)	0 (0%)
Metabolism and Nutrition Disorders				
Decreased appetite	143 (23.5%)	2 (0.3%)	137 (23.7%)	9 (1.6%)
Hyponatremia	26 (4.3%)	11 (1.8%)	18 (3.1%)	4 (0.7%)
Hypokalemia	25 (4.1%)	4 (0.7%)	24 (4.2%)	6 (1.0%)
Hyperglycemia	18 (3.0%)	7 (1.1%)	26 (4.5%)	5 (0.9%)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	73 (12.0%)	3 (0.5%)	58 (10.0%)	1 (0.2%)
Musculoskeletal pain	65 (10.7%)	4 (0.7%)	27 (4.7%)	1 (0.2%)
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea	119 (19.5%)	16 (2.6%)	113 (19.6%)	14 (2.4%)
Nasal congestion	11 (1.8%)	0 (0%)	6 (1.0%)	0 (0%)
Pneumonitis[d]	14 (2.3%)	5 (0.8%)	4 (0.7%)	2 (0.3%)
Hypoxia	10 (1.6%)	4 (0.7%)	11 (1.9%)	6 (1.0%)
Skin and Subcutaneous Tissue Disorders				
Rash [e]	105 (17.2%)	5 (0.8%)	87 (15.1%)	1 (0.2%)
Pruritus	50 (8.2%)	3 (0.5%)	18 (3.1%)	0 (0%)
Vascular Disorders				
Hypotension	17 (2.8%)	2 (0.3%)	23 (4.0%)	3 (0.5%)

Adverse Drug Reaction[a] (MedDRA) System Organ Class (SOC)	TECENTRIQ n = 609 (Frequency rate %)		Docetaxel n = 578 (Frequency rate %)	
	All Grades	Grades 3-4	All Grades	Grades 3-4

[a] Incidences presented in this table are based on adverse events considered to be drug-related
[b] Includes reports of hypothyroidism, thyroiditis, thyroid function test abnormal, thyroid stimulating hormone decreased and blood thyroid stimulating hormone increased
[c] Includes reports of hyperthyroidism, thyroiditis, exophthalmos, endocrine opthalmopathy, thyroid function test abnormal, blood thyroid stimulating hormone decreased and blood thyroid stimulating hormone increased
[d] Includes reports of interstitial lung disease, lung infiltration, radiation pneumonitis, pneumonitis and bronchioloitis.
[e] Includes reports of rash, rash maculo-papular, rash pruritic, rash pustular, acne, eczema, erythema, rash generalized, rash papular, skin toxicity, skin exfoliation, skin ulcer, dermatitis acneiform, dermatitis, mucocutaneous rash, folliculitis, drug eruption, dermatitis bullous, erythema multiforme, erythema of eyelid, rash erythematous, palmar−plantar erythrodysaesthesia syndrome and seborrhoeic dermatitis.

Listing 2: Less Common Adverse Drug Reactions Occurring in (< 1%) Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with TECENTRIQ in the Pivotal Study GO28915

Endocrine Disorders: Adrenal insufficiency, glucose tolerance impaired, type 2 diabetes mellitus and type 1 diabetes mellitus.

Gastrointestinal Disorders: Colitis, pancreatitis.

Hepatobiliary Disorders: Hepatitis

Injury, Poisoning and Procedural Complications: Infusion related reaction

Nervous System Disorders: Guillain-Barré syndrome, Meningitis Noninfective, Noninfective encephalitis.

Additional Information on Selected Adverse Reactions
The data below reflect clinically significant adverse drug reactions observed in patients based on exposure to TECENTRIQ in clinical studies. See WARNINGS AND PRECAUTIONS for management of the following:

Immune-Related Pneumonitis
Pneumonitis occurred in 3.1% (68/2160) of patients who received TECENTRIQ for locally advanced or metastatic urothelial carcinoma and NSCLC, including Grade 1-2 in 2.1% (45/2160), Grade 3-4 in 1.0% (22/2160), and Grade 5 in 1 (<0.1%) patient. 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 resolved in 45 patients.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 locally advanced or metastatic urothelial carcinoma and NSCLC. Grade 3-4 hepatitis occurred in 0.3% (6/2160) of patients. 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; months denotes a censored value). Hepatitis led to discontinuation in 2 (<0.1%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.2% (5/2160) of patients.

Grade 3-4 increases in AST, ALT and bilirubin occurred in 1.3% (27/2160), 1.2% (26/2160) and 0.4% (8/2160) of patients receiving TECENTRIQ, respectively.

Immune-Related Colitis
Colitis occurred in 1.1% (23/2160) of patients who received TECENTRIQ for locally advanced or metastatic urothelial carcinoma and NSCLC, including Grade 1-2 in 0.6% (13/2160) and Grade 3-4 in 0.5% (10/2160). 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 resolved in 16 patients. 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.

Diarrhea occurred in 18.5% (399/2160) patients, including Grade 3-4 diarrhea in 0.9% (20/2160) of patients who received TECENTRIQ.

Immune-Related Endocrinopathies
Hypothyroidism occurred in 4.7% (101/2160) of patients who received TECENTRIQ for locally advanced or metastatic urothelial carcinoma and NSCLC, including Grade 1-2 in 4.5% (97/2160) and Grade 3 in 0.2% (4/2160) of patients. 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 locally advanced or metastatic urothelial carcinoma and NSCLC. Grade 1-2 hyperthyroidism occurred in 1.7% (36/2160) of patients. The median time to onset was 3.5 months (range: 21 days to 19 months).

Adrenal insufficiency occurred in 0.3% (6/2160) of patients who received TECENTRIQ for metastatic urothelial carcinoma and NSCLC, including Grades 1-2 in 0.3% (6/2160) of patients. 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.

Diabetes mellitus including hyperglycemia occurred in 3.8% (83/2160) of patients who received TECENTRIQ for locally advanced or metastatic urothelial carcinoma and NSCLC, including Grade 1-2 in 2.8% (60/2160) and Grade 3-4 in 1.0% (23/2160) of patients. The median time to onset was 2.8 months (range: 0 to 15.3 months). The median duration was 1.5 months (range 0+ to 18.2+ months; + denotes a censored value). Diabetes mellitus/hyperglycemia resolved in 56 patients.

Immune-Related Meningoencephalitis
Meningitis occurred in 0.1% (3/2160) of patients who received TECENTRIQ for metastatic urothelial carcinoma and NSCLC, including Grade 2 in 1 (<0.1%) patient and Grade 3-4 in <0.1% (2/2160) of patients. 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. Guillain-Barré syndrome Grade 3 occurred in 0.2% (4/2160) patients and demyelinating polyneuropathy Grade 2 occurred in 1 (<0.1%) patient. 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 Nephritis
Nephritis has been observed in clinical trials with TECENTRIQ. Patients should be monitored for changes in renal function.

Immune-Related Pancreatitis
Pancreatitis, including amylase increased and lipase increased, occurred in 0.5% (10/2160) of patients who received TECENTRIQ for locally advanced or metastatic urothelial carcinoma and NSCLC, including Grade 1-2 in 0.1% (3/2160) and Grade 3-4 in 0.3% (7/2160) of patients. The median time to onset was 5.5 months (range: 0.3 to 16.9 months). The median duration was 0.1 to 11.2+ months, respectively; (+ denotes a censored value). Pancreatitis resolved in 8 patients.

Infection
In 2160 patients who received TECENTRIQ for locally advanced or metastatic urothelial carcinoma and NSCLC, infection occurred in 898 (41.6%) patients. Grade 3 or 4 infection occurred in 218 (10.1%) patients, while 14 (0.6%) patients died due to infection. Infection led to interruption of TECENTRIQ in 180 (6.9%) patients. Urinary tract infections were the most common type of Grade 3 or higher infection, occurring in 39 (1.8%) patients.

Infusion-Related Reactions
Infusion-related reactions occurred in 1.1% (24/2160) of patients who received TECENTRIQ for locally advanced or metastatic urothelial carcinoma and NSCLC. Grade 1-2 infusion related reactions occurred in 1.0% (20/2160) of patients. Signs and symptoms associated with an infusion-related reaction to TECENTRIQ and reported in >1% of patients include dyspnea, pyrexia, chills and hypotension.

Abnormal Hematologic and Clinical Chemistry Findings

Locally Advanced or Metastatic Urothelial Carcinoma

The information provided in Table 3 summarizes grade 3-4 laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in Cohort 2 of study GO29293 (n=310).

Table 3 Grade 3-4 Laboratory Abnormalities in ≥ 1% Patients with Urothelial Carcinoma Treated with TECENTRIQ in Study GO29293 Cohort 2

Laboratory Test	Grade 3-4 (%)
Lymphopenia	14%
Anemia	12%
Hyponatremia	12%
Increased alkaline phosphatase	5%
Hypophosphatemia	4%
Hypoalbuminemia	3%
Hypokalemia	3%
Increased ALT	3%
Increased AST	3%
Increased creatinine	3%
Increased bilirubin	1%
Hyperkalemia	2%
Thrombocytopenia	2%

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

The information provided in Table 4 summarizes grade 3-4 laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in pivotal study GO28915

Table 4 Grade 3-4 Laboratory Abnormalities in ≥ 1% Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with TECENTRIQ in Pivotal Study GO28915

Laboratory Test	Grade 3-4 (%)
Lymphopenia	14%
Anemia	3%
Hyponatremia	7%
Increased alkaline phosphatase	2%
Hypophosphatemia	5%
Hypoalbuminemia	4%
Hypokalemia	2%
Increased ALT	3%
Increased AST	3%
Increased creatinine	2%
Increased bilirubin	2%
Hyperkalemia	2%
Thrombocytopenia	2%
Hypercalcemia	2%

Leukopenia	2%
Hypoglycemia	1%
INR increased	2%
Neutropenia	2%
Hypomagnesemia	1%

DRUG INTERACTIONS

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

Drug-Lifestyle Interactions
No studies on the effects on the ability to drive and to use machines have been performed.

NOC/c DOSAGE AND ADMINISTRATION

Dosing Considerations
TECENTRIQ (atezolizumab) must be administered as an intravenous infusion under the supervision of a qualified healthcare professional. Do not administer as an IV push or bolus.

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

Recommended Dose and Dosage Adjustment
Standard Dosage
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
It is recommended that patients are treated with TECENTRIQ until loss of clinical benefit or unmanageable toxicity.

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

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

NSCLC:
In patients with NSCLC being treated with TECENTRIQ, close monitoring for unequivocal progression may be useful in patients who are being followed beyond radiographic progression.

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 WARNINGS AND PRECAUTIONS for management of the following:

- Immune-related pneumonitis
- Immune-related hepatitis
- Immune-related colitis (including diarrhea)
- 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
- Immune-related myocarditis
- Immune-related nephritis
- Ocular inflammatory toxicity
- Infection
- Infusion-related reactions

Table 5 Dose Modification Advice for Specified Adverse Drug Reactions

Adverse Reaction	Severity	Treatment Modification
Rash (see ADVERSE REACTIONS)	Grade 3	Withhold TECENTRIQ. Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg oral prednisone equivalent per day.
	Grade 4	Permanently discontinue TECENTRIQ.

Pediatrics:
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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Renal Impairment:
Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with renal impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions).

Administration
Instructions for Dilution
TECENTRIQ should be prepared by a healthcare professional using aseptic technique. Withdraw 20 mL of TECENTRIQ liquid concentrate from the vial. Dilute into a 250 mL polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% Sodium Chloride Injection, USP. Dilute with 0.9% Sodium Chloride Injection only. Mix diluted solution by gentle inversion. Do not shake.
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.

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

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

NOC/c ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells suppresses cytotoxic T-cell activity through the inhibition of T-cell proliferation and cytokine production. PD-L1 may be expressed on tumour cells and tumour-infiltrating immune cells, and can contribute to the inhibition of the anti-tumour immune response in the microenvironment.

Atezolizumab is an Fc-engineered humanized immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 pathway-mediated inhibition of the immune response, including reactivating the anti-tumour immune response. Atezolizumab leaves the PD-L2/PD-1 interaction intact. In syngeneic mouse tumour models, blocking PD-L1 activity resulted in decreased tumour growth.

Pharmacokinetics

The pharmacokinetics of atezolizumab has been characterized in patients in multiple clinical trials across tumour types 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 (C_{max}) and trough concentration (C_{min}) was 1.91, 1.46 and 2.75-fold, respectively.

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

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.

Metabolism: The metabolism of atezolizumab has not been directly studied. Antibodies are cleared principally by catabolism.

Excretion: A population pharmacokinetic analysis indicates that the clearance of atezolizumab is 0.200 L/day and the typical terminal elimination half-life ($t_{1/2}$) is 27 days.

Special Populations and Conditions

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, tumour burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status.

Pediatrics: No studies have been conducted to investigate the pharmacokinetics of atezolizumab in children.

Geriatrics: No dedicated studies of atezolizumab have been conducted in elderly patients. The effect of age on the pharmacokinetics of atezolizumab was assessed in a population

pharmacokinetic analysis. Age was not identified as a significant covariate influencing 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 DOSAGE AND ADMINISTRATION).

Renal Impairment: No dedicated studies of atezolizumab have been conducted in patients with renal impairment. In the population pharmacokinetic analysis, no clinically important differences in the clearance of atezolizumab were found in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n = 208) or moderate (eGFR 30 to 59 mL/min/1.73 m^2; n = 116) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m^2; n = 140) renal function. Only a few patients had severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2; n = 8). The impact of severe renal impairment on the clearance of atezolizumab is unknown (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment: No dedicated studies of atezolizumab have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of atezolizumab between patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin < 1.0 to 1.5 x 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 DOSAGE AND ADMINISTRATION).

STORAGE AND STABILITY

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

TECENTRIQ should be protected from light.

Do not freeze. Do not shake.

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 2-8°C, or 8 hours at ambient temperature (≤ 25°C).

SPECIAL HANDLING INSTRUCTIONS

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

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems", if available in your location.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form / Composition
TECENTRIQ (atezolizumab) is supplied as a single-use vial containing 20 mL preservative-free, colourless to slightly yellow solution, at a concentration of 60 mg/mL for dilution for intravenous infusion. Each vial of TECENTRIQ contains a total of 1200 mg atezolizumab. Non-medicinal ingredients (alphabetical order) include: glacial acetic acid, L-histidine, polysorbate 20, sucrose, and water for injection.

Packaging
Each carton contains one vial of 1200 mg TECENTRIQ.

PART II: SCIENTIFIC INFORMATION

TECENTRIQ® has been issued marketing authorization **with conditions**, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for TECENTRIQ®, please refer to Health Canada's Notice of Compliance with conditions - drug products website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php

TECENTRIQ® is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

TECENTRIQ® has been issued marketing authorization **without conditions** for:

- adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving TECENTRIQ.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	atezolizumab
Structure:	non-glycosylated IgG1 kappa immunoglobulin monoclonal antibody which consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each).
Molecular formula and molecular mass:	$C_{6434}H_{9878}O_{1996}N_{1702}S_{42}$. Atezolizumab has a calculated molecular mass of 144,356 Da.
Physicochemical properties:	colourless to slightly yellow solution

NOC/c CLINICAL TRIALS

Locally Advanced or Metastatic Urothelial Carcinoma

GO29293 (IMvigor210)

Study Demographics and Trial Design

Cohort 2 of study GO29293 (IMvigor210), a phase II, multi-center, international, single-arm clinical trial was conducted in patients (n=310) with locally advanced or metastatic urothelial carcinoma (also known as urothelial bladder cancer) who had disease progression on or following a platinum-based chemotherapy regimen or had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. The study enrolled patients regardless of primary tumour location (bladder, renal pelvis, ureter, urethra). 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 Ventana SP142 immunohistochemistry (IHC) assay was used to prospectively evaluate tumour specimens for baseline PD-L1 expression. Testing was performed at a central laboratory. The test detects the expression of PD-L1 on both tumour cells and immune cells present in the tumour. Evaluation of PD-L1 expression level was determined by the proportion of the tumour area occupied by tumour-infiltrating immune cells with any intensity of PD-L1 staining. Based on the assay described, of the 310 patients treated with TECENTRIQ in Cohort 2, 210 patients had <5% PD-L1 expression and 100 patients had PD-L1 expression ≥5%.

TECENTRIQ was administered by IV infusion as a fixed dose of 1200 mg on Day 1 of a 21-day cycle. Patients in Cohort 2 were treated until loss of clinical benefit as assessed by the investigator. The median duration of survival follow-up was 14.39 months. For patients with PD-L1 <5% and patients with PD-L1 ≥5%, the duration of survival follow-up was 14.03 months and 14.55 months, respectively.

The median age of patients was 66 years (range: 32 – 91). The majority of patients were male (78% for Cohort 2), and the majority of patients were white (91%).

Nineteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Forty-one percent 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. Seventy-three percent of patients had prior treatment with cisplatin, 26% had prior carboplatin and no other platinum-based regimen, and < 1% had prior treatment 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.

Response was assessed by an independent review facility (IRF) and was based on RECIST criteria version 1.1. Confirmed objective response rates are tabulated below for all patients

(Cohort 2) and for patients stratified by PD-L1 expression level (<5% vs. ≥5%). Additional efficacy assessments included duration of objective response and overall survival.

Study Results
Key results of the analysis are summarized in Table 6.

Table 6 Summary of Efficacy from Study GO29293 (IMvigor210) Cohort 2

Efficacy Endpoint	PD-L1 Expression of ≥ 5% in IC*	PD-L1 Expression of < 5% in IC*	All Patients
Co-Primary Efficacy Endpoint			
ORR (IRF-Assessed; RECIST v1.1)	n = 100	n = 210	n = 310
No. of Responders (%)	26 (26.0%)	20 (9.5%)	46 (14.8%)
95% CI	17.7, 35.7	5.9, 14.3	11.1, 19.3
Complete Response (CR) (%)	12 (12.0%)	5 (2.4%)	17 (5.5 %)
Partial Response (PR) (%)	14 (14.0%)	15 (7.10%)	29 (9.4%)
Additional Efficacy Endpoints			
DOR (IRF-Assessed; RECIST v1.1)	n = 26	n = 20	n = 46
Patients with event (%)	4 (15.4%)	5 (25.0%)	9 (19.6%)
Median, months (range)	NE (4.2, 13.8+)	12.7 (2.1+, 12.7)	NE (2.1+, 13.8+)
1 year DOR rate (%)	85%	78%	82%

* PD-L1 expression in tumour-infiltrating immune cells (IC)
+ Denotes a censored value
CI=confidence interval; DOR=duration of response; IRF= independent review facility; NE=not estimable; ORR=objective response rate; RECIST=Response Evaluation Criteria in Solid Tumours v1.1.

In 57 patients with disease progression within 12 months of neoadjuvant or adjuvant therapy, the ORR was 22.8% (95% CI: 12.7%, 34.8%). In 251 patients with disease progression during or following chemotherapy in the metastatic setting, the ORR was 13.1% (95% CI: 9.2%, 18.0%).

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

GO28915 (OAK)
Study Demographics and Trial Design
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 tumour-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, HIV, Hepatitis B or Hepatitis C infection, administration of a live, attenuated vaccine within 28 days prior to enrollment,

administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Tumour assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter. Tumour specimens were evaluated prospectively for PD-L1 expression on tumour cells (TC) and IC using the VENTANA PD-L1 (SP142) Assay and the results were used to define the PD-L1 expression subgroups for the analyses described below.

The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 64 years (range: 33 to 85), and 61% of patients were male. The majority of patients were white (70%). Approximately three-fourths of patients had non-squamous disease (74%), 10% had known EGFR mutation, 0.2% had known ALK rearrangements, 10% had 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 unacceptable toxicity or disease progression. However, treatment with TECENTRIQ was permitted until loss of clinical benefit (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Duration of Treatment).

Docetaxel was administered at 75 mg/m^2 by IV infusion on day 1 of each 21-day cycle until unacceptable toxicity or disease progression. For all treated patients, the median duration of treatment was 2.1 months for the docetaxel arm and 3.4 months for the TECENTRIQ arm.

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

Study Results
The key results of this study with a median survival follow-up of 21 months are summarized in Table 7.

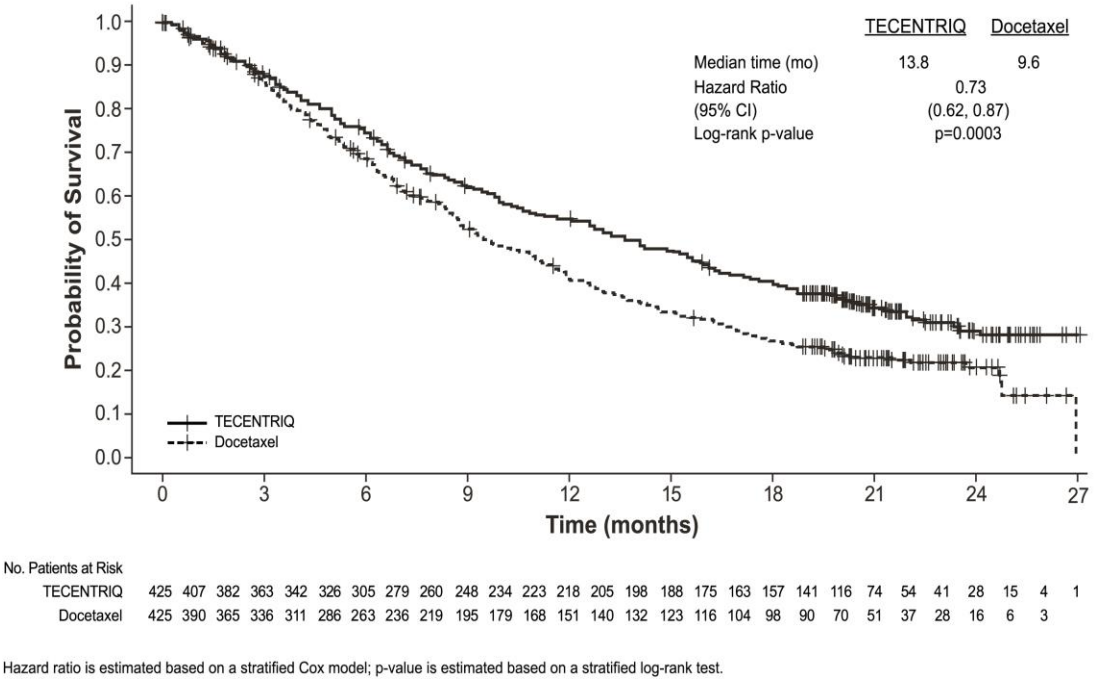
Table 7 Summary of Efficacy from Pivotal Study GO28915 (OAK)

Efficacy Endpoints	TECENTRIQ		Docetaxel
Primary Efficacy Endpoint			
Overall Survival (OS)			
All Patients*	n=425		n=425
No. of deaths (%)	271 (64%)		298 (70%)
Median time to events (months)	13.8		9.6
95% CI	(11.8, 15.7)		(8.6, 11.2)
[a]Stratified hazard ratio (95% CI)		0.73 (0.62, 0.87)	
p-value**		0.0003	
12-month OS (%)	218 (55%)		151 (41%)
18-month OS (%)	157 (40%)		98 (27%)
Secondary Endpoints			
Investigator-assessed PFS (RECIST v1.1)			
All Patients	n=425		n=425
No. of deaths (%)	380 (89%)		375 (88%)
Median time to events (months)	2.8		4.0
95% CI	(2.6, 3.0)		(3.3, 4.2)
Stratified hazard ratio (95% CI)		0.95 (0.82, 1.10)	
Investigator-assessed ORR (RECIST v1.1)			
All Patients	n=425		n=425
No. of responders (%)	58 (14%)		57 (13%)
95% CI	(10.5, 17.3)		(10.3, 17.0)
Complete Response	6 (1%)		1 (<1%)
Partial Response	52 (12%)		56 (13%)
Investigator-assessed DOR (RECIST v1.1)			
All Patients	n=58		n=57
Median in months	16.3		6.2
95% CI	(10.0, NE)		(4.9, 7.6)

CI=confidence interval; DOR=duration of response; IC=tumour-infiltrating immune cells; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1; TC = tumour cells.
*All patients refer to the primary analysis population consisting of the first 850 randomized patients
[a]Stratified by PD-L1 expression in tumour infiltrating immune cells, the number of prior chemotherapy regimens, and histology
** Based on the stratified log-rank test

Kaplan-Meier curves for OS in the intention-to-treat (ITT) population are presented in Figure 1.

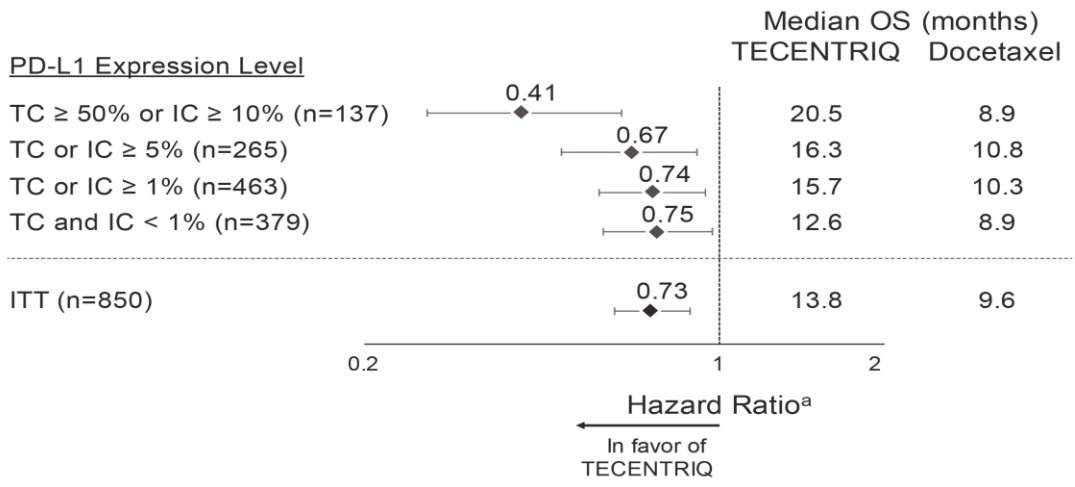
Figure 1 Kaplan-Meier Plot for Overall Survival in the Primary Analysis Population (All Patients, GO28915)



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

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.

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



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

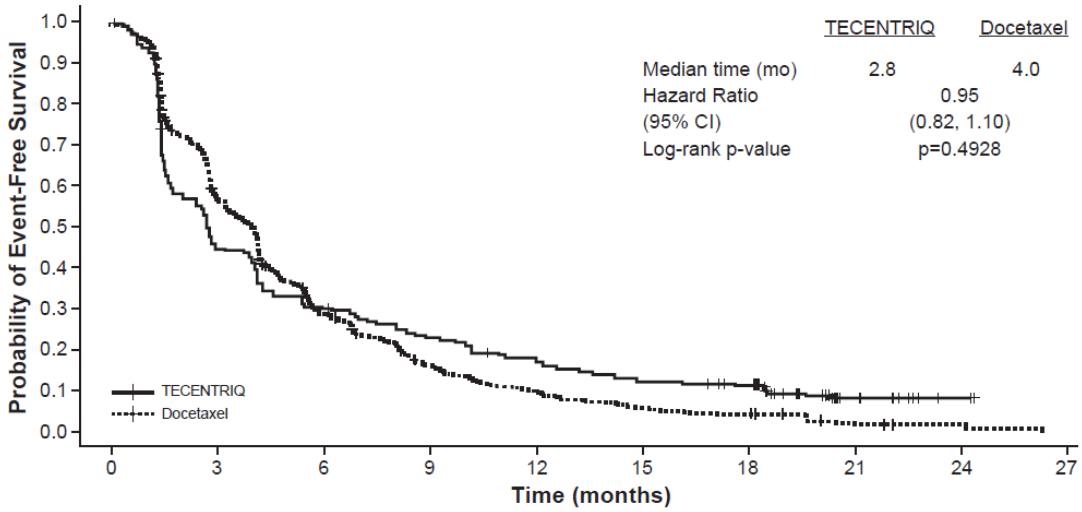
In an exploratory efficacy subgroup analysis based on histology, an improvement in OS was observed with TECENTRIQ compared to docetaxel in both non-squamous NSCLC patients (hazard ratio [HR] of 0.73, 95% CI: 0.60, 0.89; median OS of 15.6 vs. 11.2 months for TECENTRIQ and docetaxel, respectively) and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

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

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

PFS was one of the secondary efficacy endpoints. Delayed crossing of the progression-free survival (PFS) curves on Kaplan-Meier plots was noted. The study was not specifically powered to assess statistical significance of PFS. Per investigator-assessed RECIST v.1.1 in the primary analysis population, the hazard ratio was 0.95 [95% CI: 0.82, 1.10]. See Figure 3.

Figure 3 Kaplan-Meier Plot for Progression-Free Survival in the Primary Analysis Population (All Patients, GO28915)



No. Patients at Risk

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

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

GO28753 (POPLAR)

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. At the time of the primary analysis with 173 events (deaths), OS was observed for patients assigned to atezolizumab in the all-comer (ITT) population compared with docetaxel (HR = 0.73; 95% CI: [0.53, 0.99]; p= 0.0404; median OS 9.7 months in the docetaxel arm versus 12.6 months in the atezolizumab arm. Results of an updated post-hoc analysis with a total of 200 deaths observed and a median survival follow-up of 22 months showed a median OS of 12.6 months in patients treated with TECENTRIQ, 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.

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 anti-atezolizumab antibodies rate was 30.4%. Overall, anti-atezolizumab antibody (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.

No data are currently available to allow conclusions to be drawn on any possible effect of neutralizing antibodies.

TOXICOLOGY

Repeat-Dose Toxicity

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

Cynomolgus Monkeys:

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

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

C57BL/6 and CD-1 mice:

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

For further details on the repeat-dose toxicity studies with TECENTRIQ, see Table 8.

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. Based on this observation, TECENTRIQ may impair fertility in females with reproductive potential. There was no effect on the male reproductive organs.

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

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

Carcinogenicity
No carcinogenicity studies have been conducted with TECENTRIQ.

Mutagenicity
No mutagenicity studies have been conducted with TECENTRIQ.

Table 8 Summary of Toxicology Studies

Study Type	Treatment Duration and Dosing Schedule	Species/ Test System	Gender and No. per group	Doses (mg/kg)	Findings/Conclusions
Non-GLP Repeat Dose Study	Once weekly for 2 weeks (3 total doses); IV	C57BL/6 and CD-1 mice	Female (total of n=32/ group); n=8/group for toxicity assessment; n=15/ group for immune assessment; n=9/group toxicokinetic assessment	C57BL/6 0 mg/kg 10 mg/kg 50 mg/kg CD-1 0 mg/kg 50 mg/kg	• Spleen weight and spleen to brain weight ratios from both C57BL/6 and CD-1 animals dosed 50 mg/kg of atezolizumab were greater (approximately 20%) compared to controls animals. There was no histology correlated to these changes. • Minimal neuropathy was noted in only C57BL/6 mice on Days 17 and 43 in both dose groups (10 and 50 mg/kg). No clinical observations were noted with this finding. • No changes in serum cytokine levels or activation status of peripheral lymphocytes. • Atezolizumab serum concentrations dropped rapidly after Day 15 (the third dose) consistent with the detection of anti-atezolizumab antibodies in all animals.
Repeat Dose Study	Once weekly for 8 consecutive weeks (9 total doses)	Cynomolgus monkeys	n=5/sex/group for each main study dose group (IV or SC); n=3/sex/group for cardiovascular safety pharmacology via implanted telemetry (IV)	0 mg/kg (IV/SC) 5 mg/kg (IV) 15 mg/kg (IV) 50 mg/kg (IV) 15 mg/kg (SC) 50 mg/kg (SC)	• No atezolizumab-related changes in clinical observations, body weight, food consumption, central nervous system, cardiovascular, respiratory safety pharmacology parameters, or clinical pathology endpoints were observed. Atezolizumab administration had no effect on immunologic endpoints, including immunophenotyping via flow cytometry and serum cytokines. • Atezolizumab-related minimal to mild arteritis/periarteritis within the interstitium of parenchymal organs (heart, kidney, liver, pancreas, and epididymis), or within the submucosa or muscularis of tubular organs, such as the gastrointestinal and female reproductive tracts, was observed in 1 of 6 animals in the 15 mg/kg SC, and 50 mg/kg IV dose groups and in 2 of 6 animals in the 50 mg/kg SC dose group. These findings were not present following the 12-week recovery periods, indicating either resolution during the recovery period or lack of occurrence in the recovery cohorts. • The NOAEL was determined to be 5 mg/kg.
Repeat Dose Study	Once weekly for 26 consecutive	Cynomolgus monkeys	5/sex/ group	0 mg/kg (IV) 5 mg/kg (IV) 15 mg/kg (IV) 50 mg/kg (IV)	• Atezolizumab-related anatomic pathology findings were limited to microscopic, minimal to slight, chronic-active, and multifocal arteritis/periarteritis in multiple organs of two animals at the terminal phase necropsy. One female at 15 mg/kg had arteritis/periarteritis in the heart, stomach, and vagina. Another female at 50 mg/kg had

	weeks (27 total doses)				arteritis/periarteritis in the heart, pancreas, kidney, vagina, urinary bladder, stomach, gallbladder, colon, rectum, duodenum, jejunum, ileum, mandibular salivary gland, skin/subcutis, sternum/marrow, femur/marrow, uterus, larynx, and cervix.). These findings were not present following the 13-week recovery periods, indicating either resolution during the recovery period or lack of occurrence in the recovery cohorts. • Atezolizumab-related effect on menstrual cycles was noted in all females in the 50 mg/kg dose group during the dosing phase. This finding was characterized by an irregular cycle pattern with disturbed cycles and correlated with an absence of fresh corpora lutea in the ovaries at the time of the terminal phase necropsy. This effect showed reversibility during the recovery period. • There was no effect of atezolizumab on semen assessments, testicular evaluations, and serum testosterone level measurements in male cynomolgus monkeys. • The NOAEL was determined to be 5 mg/kg.
In vitro cytokine release assay	24 and 48 hrs	In vitro; isolated human peripheral blood mononuclear cells	3 donors	0, 0.25, 2.5, 25, and 250 μg/ml	• No apparent atezolizumab-dependent cytokine release was detected following 24- and 48-hour incubations with human PBMCs.
Tissue cross reactivity study	NA	In vitro; human and cynomolgus monkey tissues	3 donors each	0.25 or 1.25 μg/ml	• In human tissues, biotin-atezolizumab-specific staining was detected in the placenta, lymph node, tonsil, and thymus. Frequent, moderate, apical cytoplasmic and membranous staining was observed in syncytiotrophoblasts of the placenta. Very rare, minimal to mild, cytoplasmic staining was observed in sinusoidal cells of lymph nodes and tonsil. Rare to frequent, mild to moderate, cytoplasmic staining was observed in thymic cortical and medullary cells. • In cynomolgus monkey tissues, biotin-atezolizumab-specific specific staining was detected only in the lymph node. Rare to frequent, minimal to moderate, cytoplasmic staining was observed in sinusoidal cells of lymph nodes.

NA= not applicable

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrTECENTRIQ® (te-SEN-trik)
atezolizumab, concentrate for solution for infusion

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

What is TECENTRIQ used for?

Bladder Cancer

- TECENTRIQ is used to treat a type of bladder cancer called urothelial carcinoma that cannot be removed by surgery or has spread to other parts of the body. TECENTRIQ is used after you have tried chemotherapy and it did not work or is no longer working.

Lung Cancer

- TECENTRIQ is used to treat a type of lung cancer called Non-Small Cell Lung Cancer (NSCLC) that cannot be removed by surgery or has spread to other parts of the body. TECENTRIQ is used after you have tried platinum-based chemotherapy, and it did not work or is no longer working.

For the following indication, TECENTRIQ has been approved **with conditions** (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

TECENTRIQ is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

For the following indication, TECENTRIQ® has been issued marketing authorization **without conditions** for the treatment of:

- adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving TECENTRIQ.

What is a Notice of Compliance with Conditions (NOC/c)?
A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does TECENTRIQ work?
TECENTRIQ works by attaching to a specific protein in your body called "PD-L1". This protein makes the immune system in your body not work as well. By attaching to the protein, TECENTRIQ helps your immune system to fight your cancer.

What are the ingredients in TECENTRIQ?
Medicinal ingredient: atezolizumab
Non-medicinal ingredients: glacial acetic acid, L-histidine, polysorbate 20, sucrose, and water for injection.

TECENTRIQ comes in the following dosage forms:
Concentrate for solution for infusion. Each vial contains 1200 mg (in 20 mL) of atezolizumab. Each mL contains 60 mg of atezolizumab.

Do not use TECENTRIQ if:
- you are allergic to atezolizumab or any of the other ingredients in TECENTRIQ

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TECENTRIQ. Talk about any health conditions or problems you may have, including if you:
- have immune system problems such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have breathing or lung problems such as inflammation of the lungs (pneumonitis)
- have liver problems
- have heart problems
- have kidney problems
- have problems with your hormone producing glands including your thyroid, pituitary, adrenal glands, and pancreas
- have diabetes
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré Syndrome
- are taking medicine(s) that affect the immune system such as a steroid
- have been given a live, attenuated vaccine
- are taking medicine to treat an infection

- have any other medical conditions
- are pregnant or plan to become pregnant
    - TECENTRIQ can harm your unborn baby.
    - If you are able to become pregnant, you should use an effective method of birth control during your treatment with TECENTRIQ and for at least 5 months after your last dose of TECENTRIQ. Talk to your healthcare provider about birth control methods that you can use during this time.
    - Tell your healthcare provider right away if you become pregnant during treatment with TECENTRIQ.
- are breastfeeding or plan to breastfeed
    - TECENTRIQ may pass into your breast milk.
    - You and your doctor should decide whether you will breast-feed or take TECENTRIQ. You should not do both.

Other warnings you should know about:
- **Children and adolescents**: TECENTRIQ should not be given to children or adolescents. This is because the effects of TECENTRIQ in people younger than 18 years of age are not known.
- **Driving and using machines**: It is not known whether TECENTRIQ affects your ability to drive or use tools or machines. However, if you feel tired, do not drive or use tools or machines until you feel better.

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

How to take TECENTRIQ:
- TECENTRIQ is given through an intravenous infusion (IV). A method of putting the medicine directly into the bloodstream through a vein.
- Your first infusion will be given over 60 minutes.
    - Your healthcare professional will monitor you carefully during the first infusion.
    - If you do not have an infusion reaction during the first infusion, the next infusions will be given to you over a period of 30 minutes.
- Your healthcare professional will decide how many treatments you need.

Usual dose:
- The recommended dose of TECENTRIQ is 1200 milligrams (mg) every three weeks.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

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

What are possible side effects from using TECENTRIQ?
These are not all the possible side effects you may feel when taking TECENTRIQ. If you experience any side effects not listed here, contact your healthcare professional. Please also see the warnings above.

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

Very common (may affect more than 1 in 10 people):
- feeling very tired with no energy (fatigue)
- loss of appetite
- nausea
- fever
- chills
- diarrhea
- vomiting
- rash
- shortness of breath
- itching of the skin
- stomach pain
- joint pain

Common (may affect up to 1 in 10 people):
- lack of energy (asthenia)
- elevated liver enzymes - may be a sign of an inflamed liver (shown in blood tests)
- low blood sugar, potassium or sodium levels in the blood (shown in blood tests)
- flu-like illness
- low blood pressure
- pain in the muscles and bones
- low platelet count, which my make you more likely to bruise or bleed
- underactive thyroid gland (hypothyroidism)
- nasal congestion
- low oxygen levels which may cause shortness of breath
- inflammation of the lungs

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

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
COMMON Inflammation of the lung (pneumonitis): symptoms may include new or worsening cough, shortness of breath, and chest pain		✓

Inflammation of the intestines (colitis): symptoms may include diarrhea (watery, loose or soft stools), blood in stools, and stomach pain		✓
Inflammation of the thyroid and adrenal glands (hypothyroidism, hyperthyroidism, or adrenal insufficiency): symptoms may include tiredness, weight loss, weight gain, change in mood, hair loss, constipation, and dizziness		✓
Severe reactions associated with infusion (events occurring during or within one day of having the infusion): symptoms may include fever, chills, shortness of breath, and flushing		✓
Severe infections: symptoms may include fever, cough, frequent urination, flu-like symptoms, and pain when urinating		✓
UNCOMMON Inflammation of the liver (hepatitis): symptoms may include yellowing of skin or eyes, nausea, vomiting, bleeding or bruising more easily than normal, dark urine, and stomach pain		✓
Inflammation of the pancreas (pancreatitis): symptoms may include abdominal pain, nausea and vomiting		✓
Type 1 diabetes mellitus, including acid in the blood produced from diabetes (diabetic ketoacidosis): symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, weight loss, and feeling tired		✓
RARE Inflammation or problems of the nerves (neuropathy): symptoms may include muscle weakness and numbness, tingling in hands and feet		✓
Inflammation of the brain (encephalitis) or inflammation of the membrane around the spinal cord and brain (meningitis): symptoms may include neck stiffness, headache, fever, chills, vomiting, eye sensitivity to light, confusion and sleepiness		✓
Inflammation of the eyes: symptoms may include blurry vision, double vision, or other vision problems, and eye pain or redness		✓
Inflammation of the heart muscles (myocarditis): symptoms may include chest pain, shortness of breath, irregular heartbeat, decreased exercise tolerance, ankle swelling		✓
Inflammation of the kidneys (nephritis): symptoms may include changes in urine output and color, pain in pelvis, and swelling of the body		✓

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

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect™ (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect™ (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

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

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

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

If you want more information about TECENTRIQ:

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

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