PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTECENTRIQ®

Atezolizumab for injection

Concentrate for solution for infusion, 60 mg/mL

1200 mg/20 mL and 840 mg/14 mL single use vials

Professed Standard

Antineoplastic agent, monoclonal antibody

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:

- in combination with nab-paclitaxel, for the treatment of adult patients with unresectable, locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1%, and who have not received prior chemotherapy for metastatic disease.
- for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:
  - Have disease progression during or following platinum-containing chemotherapy; or
  - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

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

- in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).
- as monotherapy for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have high PD-L1 expression (PD-L1 stained ≥ 50% of tumour cells [TCs] or PD-L1 stained tumour-infiltrating immune cells [ICs] covering ≥ 10% of the tumour area), as determined by a validated test and who do not have EGFR or ALK genomic tumour aberrations.
- in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic non-squamous NSCLC.
- in combination with nab-paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) who do not have EGFR or ALK genomic tumour aberrations.

- for the treatment of adult patients with locally advanced or metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving TECENTRIQ.
- in combination with bevacizumab, for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who require systemic therapy.

Hoffmann-La Roche Limited
7070 Mississauga Road
Mississauga, Ontario, Canada
L5N 5M8
www.rochecanada.com

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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.

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 5

SUMMARY PRODUCT INFORMATION 6
DESCRIPTION 6
INDICATIONS AND CLINICAL USE 6
CONTRAINDICATIONS 7
WARNINGS AND PRECAUTIONS 7
ADVERSE REACTIONS 14
DRUG INTERACTIONS 55
DOSAGE AND ADMINISTRATION 55
OVERDOSAGE 62
ACTION AND CLINICAL PHARMACOLOGY 62
STORAGE AND STABILITY 64
SPECIAL HANDLING INSTRUCTIONS 64
DOSAGE FORMS, COMPOSITION AND PACKAGING 64

PART II: SCIENTIFIC INFORMATION 65

PHARMACEUTICAL INFORMATION 66
CLINICAL TRIALS 66
TOXICOLOGY 93
REFERENCES 99

PART III: PATIENT MEDICATION INFORMATION 100

PrTECENTRIQ®
Atezolizumab for injection

PART I: HEALTH PROFESSIONAL INFORMATION

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- for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:
  - Have disease progression during or following platinum-containing chemotherapy; or
  - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

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

- in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).
- as monotherapy for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have high PD-L1 expression (PD-L1 stained ≥ 50% of tumour cells [TCs] or PD-L1 stained tumour-infiltrating immune cells [ICs] covering ≥ 10% of the tumour area), as determined by a validated test and who do not have EGFR or ALK genomic tumour aberrations.
- in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic non-squamous NSCLC.
- in combination with nab-paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) who do not have EGFR or ALK genomic tumour aberrations.
- for the treatment of adult patients with locally advanced or metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving TECENTRIQ.
- in combination with bevacizumab, for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who require systemic therapy.

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 and 840 mg atezolizumab / 14 mL (60 mg/mL)	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

TECENTRIQ (atezolizumab for injection) 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

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

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

Non-Small Cell Lung Cancer (NSCLC)

- TECENTRIQ as monotherapy, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have high PD-L1 expression (PD-L1 stained ≥ 50% of tumour cells [TCs] or PD-L1 stained tumour-infiltrating immune cells [ICs] covering ≥ 10% of the tumour area), as determined by a validated test and who do not have EGFR or ALK genomic tumour aberrations.
- TECENTRIQ in combination with bevacizumab, paclitaxel and carboplatin is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic non-squamous NSCLC.
- TECENTRIQ in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous, non-small cell lung cancer (NSCLC) who do not have EGFR or ALK genomic tumour aberrations.
- TECENTRIQ is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving TECENTRIQ.

First-Line Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

TECENTRIQ (atezolizumab for injection), in combination with bevacizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who require systemic therapy.

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

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

Locally Advanced or Metastatic Urothelial Carcinoma

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

- Have disease progression during or following platinum-containing chemotherapy; or
- 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 been established (see Part II: CLINICAL TRIALS).

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 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

General

TECENTRIQ should be administered under the supervision of physicians experienced in the treatment of cancer.

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

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

Use in lung and hepatocellular cancer patients treated with the combination of TECENTRIQ and bevacizumab
Bleeding (including fatal events) is a known adverse reaction with bevacizumab. Serious bleeding events, including fatalities, have occurred in lung and hepatocellular cancer patients treated with the combination of TECENTRIQ and bevacizumab. Lung cancer patients, who had clear tumour infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging, were excluded from the pivotal clinical study GO30081 (IMpower150) after several cases of fatal pulmonary hemorrhage occurred following initiation of treatment with TECENTRIQ in combination with bevacizumab, paclitaxel and carboplatin.

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

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

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

<u>Immune-Mediated Adverse Reactions</u>

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

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-Mediated Hepatitis
TECENTRIQ can cause hepatitis, some leading to fatal outcomes across tumour types. Patients should be monitored for signs and symptoms of hepatitis. Monitor aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin prior to and periodically during treatment with TECENTRIQ. Consider appropriate management of patients with abnormal liver function tests (LFTs) at baseline. Refer to section DOSAGE AND ADMINISTRATION for recommended dose modifications.

Treatment with TECENTRIQ should be withheld if Grade 2 (ALT or AST >3x upper limit of normal (ULN) or blood bilirubin >1.5x ULN) persists for more than 5-7 days, and 1-2 mg/kg prednisone or equivalent per day should be started. If LFTs improve to ≤ Grade 1, taper corticosteroids over ≥ 1 month. Treatment with TECENTRIQ 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-Mediated Colitis
TECENTRIQ can cause diarrhea or colitis. Patients should be monitored for signs and symptoms of colitis. Refer to section DOSAGE AND ADMINISTRATION for recommended dose modifications.

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

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

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. Patients with abnormal thyroid function tests who are asymptomatic may receive TECENTRIQ. Refer to section DOSAGE AND ADMINISTRATION for recommended dose modifications.

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.

Refer to section ADVERSE REACTIONS for additional information.

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). Refer to section DOSAGE AND ADMINISTRATION for recommended dose modifications.

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

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

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

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

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-Mediated Myocarditis
TECENTRIQ can cause myocarditis. Patients should be monitored for signs and symptoms of myocarditis. Refer to section DOSAGE AND ADMINISTRATION for recommended dose modifications.

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-Mediated Myositis
TECENTRIQ can cause myositis, including fatal cases. Cases of rhabdomyolysis were also observed. Patients should be monitored for signs and symptoms of myositis. Refer to section DOSAGE AND ADMINISTRATION for recommended dose modifications.

Treatment with TECENTRIQ should be withheld if Grade 2 or Grade 3 myositis occurs. Treatment with corticosteroid therapy (1-2 mg/kg/day prednisone or equivalent) should be initiated. Treatment with TECENTRIQ may be resumed in patients with complete or partial resolution (Grade 0 to 1) within 12 weeks, and after corticosteroids have been reduced to ≤10 mg/day oral prednisone or equivalent. Treatment with TECENTRIQ should be permanently discontinued for Grade 4, or recurrent Grade 3 myositis.

Immune-Mediated Nephritis
TECENTRIQ can cause nephritis. Patients should be monitored for changes in renal function. Refer to section DOSAGE AND ADMINISTRATION for recommended dose modifications.

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

Immune-Mediated Skin Reactions
TECENTRIQ can cause immune-mediated rash. Severe cutaneous adverse events, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in patients receiving TECENTRIQ monotherapy or in combination with other anti-cancer agents. In most cases, patients received concomitant medications known to be associated with severe cutaneous reactions. Monitor patients for rash and other skin reactions and exclude other causes. Based on the severity of the reaction, withhold or permanently discontinue TECENTRIQ and administer corticosteroids. Refer to the DOSAGE AND ADMINISTRATION section for recommended dose modifications.

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

Ocular Inflammatory Toxicity

TECENTRIQ can cause ocular inflammatory toxicity including optic neuritis, uveitis, keratitis and retinopathy. Withhold TECENTRIQ for moderate and permanently discontinue for severe ocular inflammatory toxicity. Refer to section DOSAGE AND ADMINISTRATION for recommended dose modifications.

Other Immune-Mediated Toxicities

The following additional clinically significant immune-mediated adverse reactions were reported in less than 1% (unless otherwise indicated) in patients treated with TECENTRIQ for various cancers: vasculitis.

Infections

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

Infusion-Related Reactions

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

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

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: For women of childbearing potential, pregnancy status should be established prior to initiating TECENTRIQ. Women 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: There is no information regarding the presence of atezolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

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). Data for patients ≥ 75 years of age are too limited to draw conclusions on this population.

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

Hepatic Impairment: Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild or moderate hepatic impairment. There are no data in patients with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests

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

NOC/c ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

Study GO30081 (IMpower133) – First-Line Combination Therapy

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

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

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

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

The most common adverse reactions (≥10%) in patients receiving TECENTRIQ plus CE were anemia (43.4%), nausea (37.9%), decreased appetite (27.3%), fatigue (27.3%), vomiting (19.7%), thrombocytopenia (16.7%), platelet count decreased (12.6%), hypothyroidism (10.1%), dyspnea (10.1%), and pyrexia (10.1%).

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

Non-Small Cell Lung Cancer (NSCLC)

Study GO29431 (IMpower110) – First Line Monotherapy
The safety of TECENTRIQ was evaluated in Study GO29431. Patients received TECENTRIQ 1200 mg every 3 weeks (n=286) or platinum-based chemotherapy consisting of carboplatin or cisplatin in combination with either pemetrexed or gemcitabine (n=263). The median duration of treatment was 5.3 months in the TECENTRIQ arm 3.5 months for pemetrexed, 2.1 months for cisplatin, 2.3 months for carboplatin, 2.6 months for gemcitabine in the chemotherapy arm.

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

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

Adverse reactions occurring in ≥1% of TECENTRIQ treated patients are shown in Table 2.

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

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

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

events were related to any study treatment; cerebrovascular accident (n = 1), intestinal obstruction (n = 1), febrile neutropenia (n = 3), haemoptysis (n = 3), pulmonary haemorrhage (n = 2) and aortic dissection (n = 1).

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

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

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

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

Study GO29537 (IMpower130) - First-Line Combination Therapy
The safety of TECENTRIQ (atezolizumab) in combination with nab-paclitaxel and carboplatin for the treatment of chemotherapy-naïve patients with metastatic, non-squamous NSCLC in study GO29537 (IMpower130) in the first-line (1L) setting is presented in Table 4. TECENTRIQ at a dose of 1200 mg was administered intravenously every 3 weeks until loss of clinical benefit or unacceptable toxicity (for carboplatin and nab-paclitaxel (CnP) dosage information see CLINICAL TRIALS).

The majority of patients in both treatment arms experienced at least one AE of any grade (TECENTRIQ + CnP 99.6% vs. CnP 99.1%). The incidence of Grade ≥3 AEs was 85.8% in the

TECENTRIQ + CnP arm and 76.3% in the CnP arm. The incidence of Grade 5 AEs was 5.3% in the TECENTRIQ + CnP versus 5.6% in the CnP arm. Overall, 8 of the Grade 5 AEs in the TECENTRIQ + CnP arm and 1 Grade 5 AE in the CnP arm were considered by the investigator as related to any study treatment component. The proportion of patients who experienced SAEs was 50.7% in the TECENTRIQ + CnP arm and 37.9% in the CnP arm. AEs led to withdrawal of any study treatment during the overall study period in 26.4% in the TECENTRIQ + CnP arm and 22.0% in the CnP arm. The proportion of patients experiencing AEs leading to any dose modification/interruption was 85.0% in the TECENTRIQ + CnP arm and 80.2% in the CnP arm. The most common adverse events in patients treated with TECENTRIQ + CnP (reported by ≥10% patients) were: anemia (52.4%), neutropenia (46.1%), nausea (43.8%), fatigue (39.1%), diarrhea (31.7%), alopecia (30.7%), thrombocytopenia (26.8%), decreased appetite (22.6%), platelet count decrease (22.2%), vomiting (20.9%), neutrophil count decrease (19.7%), constipation (15.4%), hypomagnesaemia (13.1%), asthenia (12.9%), white blood cell count decrease (10.8%), dysgeusia (10.8%), peripheral sensory neuropathy (10.6%), neuropathy peripheral (10.4%), hypothyroidism (10.4%) and leukopenia (10.1%).

The most common adverse events in patients treated with TECENTRIQ + CnP leading to dose modification/interruption were neutropenia (38.5%), thrombocytopenia (19.7%), anemia (16.3%), platelet count decrease (15.0%), neutrophil count decrease (14.4%), diarrhea (9.1%), fatigue (7.4%), leukopenia (5.7%), white blood cell count decrease (5.7%), pyrexia (4.9%), nausea (4.4%), pneumonia (3.8%), dyspnea (3.6%), vomiting (3.2%), pneumonitis (2.7%), dehydration (2.5%), blood creatinine increased (2.3%), decreased appetite (2.3%), asthenia (2.1%) and febrile neutropenia (1.5%).

Study GO28915 (OAK) - Second Line Monotherapy

The safety of TECENTRIQ (atezolizumab), as presented in Table 5, is based on use in 1187 patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC), who had progressed during or following a platinum-containing regimen. These patients were enrolled in the phase III pivotal trial study GO28915 (OAK), in which 609 patients received TECENTRIQ 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 (OAK), had at least one adverse event versus 555/578 (96.0%) patients treated with docetaxel. Grade 3-4 events were experienced by 227 (37.3%) patients treated with TECENTRIQ versus 310 (53.6%) patients treated with docetaxel. Serious adverse events occurred in 194 (31.9%) patients treated with TECENTRIQ 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 (POPLAR), two phase II global multi-centered single arm studies GO28754 (BIRCH) and GO28625 (FIR), and phase I multi-centered open-label study PCD4989g with a NSCLC cohort. The total number of locally advanced or metastatic NSCLC patients who were treated with TECENTRIQ in clinical trials was 1636.

Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

Study YO40245 (IMbrave150) -First-Line Combination Therapy

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

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

Serious adverse reactions occurred in 38% of patients in the TECENTRIQ and bevacizumab arm. The most frequent serious adverse reactions (≥ 2%) were hemorrhages (7.3%), infections (7.3%), and pyrexia (2.1%).

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

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

Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 12.2% of patients in the TECENTRIQ and bevacizumab arm.

Table 6 and Table 13 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ and bevacizumab in Study YO40245 (IMbrave150).

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

Study WO29522 (IMpassion130) - First-Line Combination Therapy
The safety of TECENTRIQ in combination with nab-paclitaxel was evaluated in WO29522 (IMpassion130), a multicenter, international, randomized, double-blinded placebo controlled trial in patients with locally advanced or metastatic TNBC who had not received prior chemotherapy for metastatic disease (see Part II: CLINICAL TRIALS). Patients received 840 mg of TECENTRIQ (n=452) or placebo (n=438) intravenously followed by nab-paclitaxel (100 mg/m^2) intravenously. For each 28-day cycle, TECENTRIQ was administered on days 1 and 15 and nab-paclitaxel was administered on days 1, 8, and 15 until radiographic disease progression per RECIST v1.1, or unacceptable toxicity. In the safety-evaluable population, the median duration of exposure to TECENTRIQ was 5.5 months (range: 0-32.0 months) and nab-paclitaxel was 5.1 months (range: 0 – 31.5 months) in the TECENTRIQ plus nab-paclitaxel arm. The median duration of exposure to placebo was 5.1 months (range: 0-25.1 months) and nab-paclitaxel was 5.0 months (range: 0-23.7 months) in the nab-paclitaxel arm. The addition of TECENTRIQ did not compromise the patient's ability to receive nab-paclitaxel. The mean dose intensity was 87.7% in the TECENTRIQ plus nab-paclitaxel arm and 90.4% in the placebo arm.

Overall, 449 (99.3%) patients treated with TECENTRIQ in combination with nab-paclitaxel had at least one adverse event versus 429 (97.9%) patients treated with placebo plus nab-paclitaxel. Grade 3 to 4 adverse events were experienced by 220 (48.7%) patients treated with TECENTRIQ in combination with nab-paclitaxel versus 185 (42.2%) patients treated with placebo plus nab-paclitaxel. Serious adverse events occurred in 103 (22.8%) patients treated with TECENTRIQ in combination with nab-paclitaxel versus 80 (18.3%) patients treated with placebo plus nab-paclitaxel. The most frequent of these serious adverse events (≥ 1%) were pneumonia (2.2%), urinary tract infection (1.1%), dyspnea (1.1%) and pyrexia (1.1%). Grade 5 adverse events occurred in 6 (1.3%) patients treated with TECENTRIQ in combination with nab-paclitaxel versus 3 (0.7%) patients treated with placebo plus nab-paclitaxel. Adverse events leading to TECENTRIQ/placebo discontinuation occurred in 29 (6.4%) patients treated with TECENTRIQ in combination with nab-paclitaxel and 6 (1.4%) patients in the placebo plus nab-paclitaxel arm. Dose reductions of TECENTRIQ/placebo were not permitted by the protocol.

The most common adverse events leading to TECENTRIQ discontinuation were peripheral neuropathies (1.3%). Overall, the most common (≥1% of patients in either arm) adverse events leading to nab-paclitaxel withdrawal were peripheral neuropathies (7.5% TECENTRIQ + nab-paclitaxel vs. 3.9% placebo + nab-paclitaxel), and fatigue (1.3% vs. 1.4%).

Adverse events leading to interruption of TECENTRIQ/placebo occurred in 139 (30.8%) patients treated with TECENTRIQ in combination with nab-paclitaxel and 103 (23.5%) patients in the placebo plus nab-paclitaxel arm. The most common adverse events leading to interruption of TECENTRIQ/placebo (≥ 2%) were neutropenia (3.8% TECENTRIQ + nab-paclitaxel vs. 1.8% placebo + nab-paclitaxel), neutrophil count decreased (2.7% vs. 1.4%), hyperthyroidism (2.0% vs. 0.2%) and pyrexia (2.0% vs. 0.5%). Adverse events leading to dose modification/interruption of nab-paclitaxel occurred in 195 (43.1%) patients treated with TECENTRIQ in combination with nab-paclitaxel and 172 (39.3%) patients in the placebo plus nab-paclitaxel arm.

The common adverse reactions (≥ 10%) in patients receiving TECENTRIQ in combination with nab-paclitaxel were fatigue (46.7%), nausea (46.0%), peripheral neuropathies (42.5%), diarrhea (32.5%), cough (24.8%), neutropenia (20.8%), decreased appetite (19.9%), vomiting (19.5%), pyrexia (18.8%), arthralgia (17.9%), rash (17.3%), dyspnea (15.9%), back pain (15.3%), hypothyroidism (13.7%), pruritus (13.7%), neutrophil count decreased (12.6%), asthenia (12.4%), urinary tract infection (11.7%), ALT increased (10.4%), abdominal pain (10.2%) (see Table 7).

NOC/c Locally Advanced or Metastatic Urothelial Carcinoma

Study GO29293 (IMvigor210) (Cohort 2) - Monotherapy
The safety of TECENTRIQ (atezolizumab), as presented in Table 8, 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 (IMvigor210), 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 (IMvigor210) 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 (IMvigor210) 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.

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.

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

Study GO30081 (IMpower133) - First-Line Combination Therapy

Table 1 summarizes adverse reactions that occurred in ≥1% of patients in the TECENTRIQ in combination with carboplatin and etoposide arm and in the placebo with carboplatin and etoposide arm. Table 9 summarizes selected laboratory abnormalities worsening from baseline that occurred in ≥1% of patients in the TECENTRIQ with carboplatin and etoposide arm and at a higher incidence than in the placebo with carboplatin and etoposide arm.

Table 1 Adverse Drug Reactions Occurring in ≥ 1% of Patients with First-Line Extensive-Stage Small Cell Lung Cancer (ES-SCLC) treated with TECENTRIQ plus Carboplatin plus Etoposide vs. Carboplatin plus Etoposide in Pivotal Study GO30081 (IMpower133)

System Organ Class ADR (MedDRA v22.0	TECENTRIQ + carboplatin + etoposide (n=198)		Placebo + carboplatin + etoposide (n=196)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Blood and Lymphatic System Disorders				
Anemia	86 (43.4)	31 (15.7)	69 (35.2)	26 (13.3)

System Organ Class ADR (MedDRA v22.0	TECENTRIQ + carboplatin + etoposide (n=198)		Placebo + carboplatin + etoposide (n=196)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Thrombocytopenia[a]	56 (28.3)	27 (13.6)	58 (29.6)	25 (12.8)
Endocrine Disorders				
Hypothyroidism[b]	25 (12.6)	0	1 (0.5)	0
Hyperthyroidism	11 (5.6)	0	5 (2.6)	0
Adrenal insufficiency[c]	0	0	3 (1.5)	0
Gastrointestinal Disorders				
Nausea	75 (37.9)	1 (0.5)	64 (32.7)	1 (0.5)
Vomiting	39 (19.7)	3 (1.5)	33 (16.8)	5 (2.6)
Diarrhea	35 (17.7)	4 (2.0)	31 (15.8)	2 (1.0)
Abdominal pain[d]	14 (7.1)	1 (0.5)	17 (8.7)	0
Oropharyngeal pain	12 (6.1)	0	5 (2.6)	0
Dysphagia	4 (2.0)	0	3 (1.5)	0
Pancreatitis[e]	2 (1.0)	2 (1.0)	2 (1.0)	2 (1.0)
Colitis[f]	3 (1.5)	2 (1.0)	0	0
General Disorders and Administration Site Conditions				
Fatigue[g]	84 (42.4)	10 (5.1)	68 (34.7)	5 (2.6)
Pyrexia	20 (10.1)	0	16 (8.2)	0
Infusion related reaction[h]	12 (6.1)	5 (2.5)	12 (6.1)	1 (0.5)
Influenza like illness	2 (1.0)	0	3 (1.5)	0
Chills	3 (1.5)	0	0	0
Hepatobiliary Disorder				
AST increased	9 (4.5)	0	6 (3.1)	0
ALT increased	7 (3.5)	1 (0.5)	7 (3.6)	0
Infections and infestations				
Urinary Tract Infection[i]	14 (7.1)	2 (1.0)	7 (3.6)	2 (1.0)
Metabolism and Nutrition Disorders				
Decreased Appetite[j]	54 (27.3)	2 (1.0)	37 (18.9)	0
Hypokalaemia	8 (4.0)	0	18 (9.2)	3 (1.5)
Hyponatraemia	11 (5.6)	9 (4.5)	14 (7.1)	13 (6.6)
Hyperglycaemia	11 (5.6)	4 (2.0)	4 (2.0)	1 (0.5)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain[k]	37 (18.7)	1 (0.5)	43 (21.9)	2 (1.0)
Arthralgia	18 (9.1)	0	13 (6.6)	1 (0.5)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough[l]	28 (14.1)	1 (0.5)	31 (15.8)	2 (1.0)
Dyspnea[m]	20 (10.1)	3 (1.5)	21 (10.7)	4 (2.0)
Pneumonitis	4 (2.0)	1 (0.5)	5 (2.6)	2 (1.0)
Nasopharyngitis[n]	6 (3.0)	0	2 (1.0)	0
Hypoxia	2 (1.0)	1 (0.5)	2 (1.0)	0

System Organ Class ADR (MedDRA v22.0	TECENTRIQ + carboplatin + etoposide (n=198)		Placebo + carboplatin + etoposide (n=196)	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Skin and Subcutaneous Tissue Disorders				
Rash[o]	37 (18.7)	4 (2.0)	20 (10.2)	0
Pruritus	12 (6.1)	0	9 (4.6)	0
Vascular Disorders				
Hypotension	8 (4.0)	0	9 (4.6)	0

[a] Includes reports of thrombocytopenia and platelet count decreased
[b] Includes reports of autoimmune hypothyroiditis, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, hypothyroidism, thyroiditis, thyroxine free increased and tri-iodothyronine free increased
[c] Includes reports of adrenal insufficiency and cortisol decreased
[d] Includes reports of abdominal pain, abdominal pain upper and flank pain
[e] Includes reports of lipase increased, pancreatic enzymes increased, pancreatitis and pancreatitis acute
[f] Includes reports of colitis and autoimmune colitis
[g] Includes reports of asthenia, fatigue, lethargy and malaise
[h] Includes reports of anaphylactic reaction, hypersensitivity and infusion related reaction
[i] Includes reports of cystitis, urinary tract infection and urinary tract infection enterococcal
[j] Includes reports of decreased appetite, early satiety and hypophagia
[k] Includes reports of back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia and neck pain
[l] Includes reports of cough, productive cough and upper airway cough syndrome
[m] Includes reports of dyspnea and dyspnea exertional
[n] Includes reports of nasopharyngitis and nasal congestion
[o] Includes reports of dermatitis, dermatitis acneiform, dermatitis bullous, drug eruption, erythema, folliculitis, rash, rash erythematous, rash follicular, rash maculo-papular, rash papular, rash pruritic, rash pustular, skin toxicity, skin ulcer and toxic skin eruption

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

Renal and urinary disorders: tubulointerstitial nephritis
Endocrine disorders: diabetes mellitus, temperature regulation disorder
Nervous system disorders: Guillan Barré Syndrome
Musculoskeletal and connective tissue disorders: myopathy, rhabdomyolysis

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

Study GO29431 (IMpower110) – First Line Monotherapy

The information provided in Table 2 and Listing 2 summarizes the adverse drug reactions observed in patients included in study GO29431 (IMpower110) during treatment with TECENTRIQ 1200 mg every 3 weeks (n=286) or platinum-based chemotherapy consisting of carboplatin or cisplatin in combination with either pemetrexed or gemcitabine (n=263).

Table 2 Adverse Drug Reactions Occurring in ≥ 1% of Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) Treated with TECENTRIQ vs. Platinum Agent in Combination with Pemetrexed or Gemcitabine in the Study GO29431 (IMpower110)

ADR (MedDRA v22.0) System Organ Class Preferred Term	TECENTRIQ (n=286)		Platinum Agent in Combination with Pemetrexed or Gemcitabine (n=263)	
	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)
Gastrointestinal				
Nausea	39 (13.6%)	1 (0.3%)	89 (33.8%)	5 (1.9%)
Constipation	35 (12.2%)	3 (1.0%)	57 (21.7%)	2 (0.8%)
Diarrhoea	32 (11.2%)	0	31 (11.8%)	2 (0.8%)
Vomiting	18 (6.3%)	1 (0.3%)	34 (12.9%)	2 (0.8%)
Stomatitis	8 (2.8%)	0	14 (5.3%)	2 (0.8%)
Dry mouth	12 (4.2%)	0	1 (0.4%)	0
Abdominal pain[a]	12 (4.2%)	0	11 (4.2%)	0
Dyspepsia	6 (2.1%)	0	6 (2.3%)	0
Dysphagia	5 (1.7%)	0	5 (1.9%)	0
Colitis[b]	3 (1.0%)	2 (0.7%)	0	0
Haemorrhoids	3 (1.0%)	0	2 (0.8%)	0
Gastritis	3 (1.0%)	0	1 (0.4%)	0
General				
Fatigue[c]	75 (26.2%)	4 (1.4%)	95 (36.1%)	11 (4.2%)
Pyrexia	39 (13.6%)	0	23 (8.7%)	1 (0.4%)
Oedema[d]	19 (6.6%)	1 (0.3%)	18 (6.8%)	2 (0.8%)
Chest pain	17 (5.9%)	2 (0.7%)	10 (3.8%)	1 (0.4%)
Mucosal inflammation	4 (1.4%)	0	11 (4.2%)	1 (0.4%)
Chills	6 (2.1%)	0	3 (1.1%)	0
Pain	6 (2.1%)	0	2 (0.8%)	0
Influenza like illness	7 (2.4%)	2 (0.7%)	0	0

Blood and lymphatic system disorders				
Anaemia	44 (15.4%)	5 (1.7%)	125 (47.5%)	48 (18.3%)
Neutropenia[e]	4 (1.4%)	2 (0.7%)	90 (34.2%)	55 (20.9%)
Thrombocytopenia	7 (2.4%)	1 (0.3%)	44 (16.7%)	19 (7.2%)
Leukopenia	3 (1.0%)	1 (0.3%)	21 (8.0%)	4 (1.5%)
Lymphopenia	6 (2.1%)	1 (0.3%)	3 (1.1%)	0
Thrombocytosis	3 (1.0%)	0	3 (1.1%)	1 (0.4%)
Metabolism and nutrition disorders				
Decreased appetite	44 (15.4%)	2 (0.7%)	50 (19.0%)	0
Hyponatraemia	17 (5.9%)	6 (2.1%)	12 (4.6%)	6 (2.3%)
Hyperglycaemia	12 (4.2%)	1 (0.3%)	13 (4.9%)	4 (1.5%)
Hyperkalaemia	12 (4.2%)	6 (2.1%)	8 (3.0%)	3 (1.1%)
Hypomagnesaemia	8 (2.8%)	0	11 (4.2%)	1 (0.4%)
Hypokalaemia	4 (1.4%)	0	10 (3.8%)	3 (1.1%)
Hypoalbuminaemia	8 (2.8%)	0	5 (1.9%)	2 (0.8%)
Hypercalcaemia	7 (2.4%)	4 (1.4%)	2 (0.8%)	0
Hypocalcaemia	4 (1.4%)	0	4 (1.5%)	1 (0.4%)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea[f]	41 (14.3%)	3 (1.0%)	30 (11.4%)	0
Cough[g]	38 (13.3%)	1 (0.3%)	26 (9.9%)	0
Haemoptysis	21 (7.3%)	0	12 (4.6%)	2 (0.8%)
Chronic obstructive pulmonary disease	11 (3.8%)	4 (1.4%)	2 (0.8%)	0
Pneumonitis	9 (3.1%)	2 (0.7%)	1 (0.4%)	0
Oropharyngeal pain	8 (2.8%)	0	1 (0.4%)	0
Pleurisy	4 (1.4%)	0	2 (0.8%)	0
Infections and infestations				
Respiratory tract infection[h]	40 (14.0%)	10 (3.5%)	29 (11.0%)	10 (3.8%)
Nasopharyngitis[i]	21 (7.3%)	0	6 (2.3%)	0
Urinary tract infection[j]	8 (2.8%)	1 (0.3%)	12 (4.6%)	3 (1.1%)
Conjunctivitis	3 (1.0%)	0	8 (3.0%)	0
Influenza	7 (2.4%)	0	4 (1.5%)	0
Lower respiratory tract infection	3 (1.0%)	1 (0.3%)	6 (2.3%)	3 (1.1%)
Lung infection	5 (1.7%)	2 (0.7%)	3 (1.1%)	2 (0.8%)
Respiratory tract infection viral	4 (1.4%)	0	4 (1.5%)	0
Pharyngitis	5 (1.7%)	1 (0.3%)	1 (0.4%)	0
Infection	3 (1.0%)	0	0	0
Oral fungal infection[k]	3 (1.0%)	0	3 (1.1%)	0

Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[l]	44 (15.4%)	2 (0.7%)	26 (9.9%)	3 (1.1%)
Arthralgia	18 (6.3%)	2 (0.7%)	6 (2.3%)	0
Pain in extremity	10 (3.5%)	2 (0.7%)	11 (4.2%)	1 (0.4%)
Spinal pain	4 (1.4%)	0	3 (1.1%)	0
Muscular weakness	4 (1.4%)	0	0	0
Nervous system disorders				
Headache	26 (9.1%)	0	18 (6.8%)	0
Neuropathy peripheral[m]	21 (7.3%)	0	13 (4.9%)	1 (0.4%)
Dizziness	9 (3.1%)	0	13 (4.9%)	0
Dysgeusia	6 (2.1%)	0	8 (3.0%)	0
Somnolence	6 (2.1%)	0	2 (0.8%)	1 (0.4%)
Cerebral ischaemia	3 (1.0%)	1 (0.3%)	2 (0.8%)	0
Tremor	4 (1.4%)	0	1 (0.4%)	0
Skin and subcutaneous tissue disorders				
Rash[n]	44 (15.4%)	3 (1.0%)	19 (7.2%)	2 (0.8%)
Pruritus	19 (6.6%)	0	4 (1.5%)	0
Alopecia	3 (1.0%)	0	15 (5.7%)	0
Dry skin	8 (2.8%)	0	4 (1.5%)	0
Hyperhidrosis	4 (1.4%)	0	2 (0.8%)	0
Psychiatric disorders				
Insomnia	20 (7.0%)	0	15 (5.7%)	0
Anxiety	9 (3.1%)	0	2 (0.8%)	0
Depression	8 (2.8%)	0	3 (1.1%)	0
Confusional state	4 (1.4%)	0	0	0
Endocrine disorders				
Hypothyroidism[o]	27 (9.4%)	0	4 (1.5%)	0
Hyperthyroidism[p]	13 (4.5%)	0	2 (0.8%)	0
Renal and urinary disorders				
Renal impairment	3 (1.0%)	0	7 (2.7%)	1 (0.4%)
Dysuria	4 (1.4%)	0	0	0
Haematuria	4 (1.4%)	1 (0.3%)	0	0
Urinary retention	3 (1.0%)	0	1 (0.4%)	0
Vascular disorders				
Hypertension	5 (1.7%)	2 (0.7%)	9 (3.4%)	3 (1.1%)
Embolism[q]	10 (3.5%)	4 (1.4%)	4 (1.5%)	2 (0.8%)
Cardiac disorders				
Atrial fibrillation	3 (1.0%)	0	3 (1.1%)	0
Tachycardia	4 (1.4%)	0	2 (0.8%)	0

Ear and labyrinth disorders				
Vertigo	3 (1.0%)	0	4 (1.5%)	0
Eye disorders				
Vision blurred	3 (1.0%)	0	3 (1.1%)	0
Injury, poisoning and procedural complications				
Infusion related reaction	4 (1.4%)	0	0	0

[a] Includes reports of abdominal pain, abdominal pain lower, abdominal pain upper, flank pain
[b] Includes reports of autoimmune colitis, colitis
[c] Includes reports of asthenia, fatigue, lethargy, malaise
[d] Includes reports of lymphoedema, oedema, oedema peripheral, peripheral swelling, swelling
[e] Includes reports of neutropenia, neutrophil count decreased
[f] Includes reports of dyspnoea, dyspnoea exertional
[g] Includes reports of cough, productive cough, upper-airway cough syndrome
[h] Includes reports of bronchitis, pneumonia, respiratory tract infection, upper respiratory tract infection
[i] Includes reports of nasal congestion, nasopharyngitis
[j] Includes reports of cystitis, urinary tract infection
[k] Includes reports of oral candidiasis, oral fungal infection
[l] Includes reports of back pain, musculoskeletal pain, musculoskeletal chest pain, myalgia, neck pain
[m] Includes reports of herpes zoster, hypoaesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, polyneuropathy
[n] Includes reports of acne, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis exfoliative, drug eruption, eczema, erythema, erythema multiforme, folliculitis, rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin exfoliation, skin ulcer
[o] Includes reports of hypothyroidism, blood thyroid stimulating hormone decreased, myxedema, thyroxine free decreased
[p] Includes reports of exophthalmos, hyperthyroidism
[q] Includes reports of deep vein thrombosis, pulmonary embolism

Listing 2: Less Common Adverse Drug Reactions Occurring in (<1%) Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) Treated with TECENTRIQ in Study GO29431 (IMpower110)

Cardiac disorders: Myocarditis
Endocrine disorders: Adrenal insufficiency
Hepatobiliary disorders: Hepatitis
Immune system disorders: Hypersensitivity
Metabolism and nutrition disorders: Diabetes mellitus
Musculoskeletal and connective tissue disorders: Myositis
Renal and urinary disorders: Nephritis
Vascular disorders: Hypotension

Study GO29436 (IMpower150) (First-Line Combination Therapy)
The information provided in Table 3 and Listing 3 summarizes the adverse drug reactions observed in patients included in study GO29436 (IMpower150) (n=1202) in chemotherapy-naïve patients with metastatic, non-squamous non-small cell lung cancer (NSCLC) in the first-line (1L) setting.

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

Table 3 Adverse Drug Reactions Occurring in ≥ 1% of Patients with NSCLC Treated with TECENTRIQ in Combination with bevacizumab, Paclitaxel and Carboplatin in the Pivotal Study GO29436 (IMpower150)

ADR (MedDRA v20.1) System Organ Class Preferred Term	**Arm B: TECENTRIQ + bevacizumab + paclitaxel + carboplatin (n=393) (Frequency rate %)**		**Arm C: bevacizumab + paclitaxel + carboplatin (n=394) (Frequency rate %)**	
	All Grades	**Grades 3-4**	**All Grades**	**Grades 3-4**
Gastrointestinal disorders				
Diarrhea[a]	127 (32.3)	18 (4.6)	97 (24.6)	2 (0.5)
Vomiting	73 (18.6)	7 (1.8)	69 (17.5)	5 (1.3)
Abdominal Pain[b]	53 (13.5)	7 (1.8)	39 (9.9)	4 (1.0)
Colitis[c]	11 (2.8)	7 (1.8)	2 (0.5)	2 (0.5)
General disorders & administration site conditions				
Fatigue[d]	222 (56.5)	24 (6.1)	192 (48.7)	25 (6.3)
Pyrexia	73 (18.6)	1 (0.3)	34 (8.6)	2 (0.5)
Edema[e]	41 (10.4)	1 (0.3)	26 (6.6)	2 (0.5)
Hepatobiliary disorders				
Liver Function Test Abnormality	35 (8.9)	10 (2.5)	26 (6.6)	2 (0.5)
Alanine Aminotransferase Increased	30 (7.6)	9 (2.3)	20 (5.1)	2 (0.5)
Blood Alkaline Phosphatase Increased	11 (2.8)	2 (0.5)	9 (2.3)	0
Blood Bilirubin Increased	4 (1.0)	1 (0.3)	1 (0.3)	0
Infections & infestations				
Respiratory Tract Infection[f]	107 (27.2)	31 (7.9)	67 (17.0)	18 (4.6)
Urinary Tract Infection[g]	42 (10.7)	5 (1.3)	30 (7.6)	4 (1.0)
Oral Fungal Infection[h]	7 (1.8)	0	5 (1.3)	0
Sepsis[i]	5 (1.3)	5 (1.3)	5 (1.3)	3 (0.8)
Metabolism disorders				
Decreased Appetite[j]	114 (29.0)	14 (3.6)	84 (21.3)	3 (0.8)
Dehydration	34 (8.7)	8 (2.0)	21 (5.3)	7 (1.8)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain[k]	153 (38.9)	8 (2.0)	117 (29.7)	8 (2.0)

ADR (MedDRA v20.1) System Organ Class Preferred Term	Arm B: TECENTRIQ + bevacizumab + paclitaxel + carboplatin (n=393) (Frequency rate %)		Arm C: bevacizumab + paclitaxel + carboplatin (n=394) (Frequency rate %)	
	All Grades	**Grades 3-4**	**All Grades**	**Grades 3-4**
Nervous System Disorders				
Neuropathy Peripheral[l]	224 (57.0)	14 (3.6)	190 (48.2)	13 (3.3)
Psychiatric disorders				
Insomnia	39 (9.9)	0	37 (9.4)	0
Confusional State[m]	9 (2.3)	1 (0.3)	10 (2.5)	4 (1.0)
Renal & urinary disorders				
Blood Creatinine Increased	11 (2.8)	0	9 (2.3)	0
Hematuria	13 (3.3)	0	7 (1.8)	1 (0.3)
Acute Kidney Injury	7 (1.8)	1 (0.3)	6 (1.5)	4 (1.0)
Respiratory, thoracic and mediastinal disorders				
Cough[n]	86 (21.9)	3 (0.8)	79 (20.1)	1 (0.3)
Dyspnea[o]	58 (14.8)	4 (1.0)	64 (16.2)	7 (1.8)
Skin & subcutaneous disorders				
Rash[p]	115 (29.3)	9 (2.3)	53 (13.5)	2 (0.5)
Vascular Disorders				
Embolism[q]	23 (5.9)	10 (2.5)	22 (5.6)	13 (3.3)

[a] Includes reports of diarrhea and frequent bowel movements
[b] Includes reports of abdominal pain, abdominal pain lower, abdominal pain upper and flank pain
[c] Includes reports of colitis, colitis ischemic and immune-mediated enterocolitis
[d] Includes reports of asthenia, fatigue, lethargy and malaise
[e] Includes reports of edema, edema peripheral, localized edema, lymphedema, peripheral swelling and swelling
[f] Includes reports of bronchitis, pneumonia, respiratory tract infection and upper respiratory tract infection
[g] Includes reports of cystitis, emphysematous cystitis, pyelonephritis and urinary tract infection
[h] Includes reports of oral candidiasis and oral fungal infection
[i] Includes reports of bacteremia, sepsis and urosepsis
[j] Includes reports of decreased appetite, early satiety and hypophagia
[k] Includes reports of back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia and neck pain
[l] Includes reports of brachial plexopathy, herpes zoster, hypoaesthesia, neuralgia, neuralgic amyotrophy, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy and toxic neuropathy
[m] Includes reports of confusional state and mental status changes
[n] Includes reports of cough, productive cough and upper airway cough syndrome
[o] Includes reports of dyspnea and dyspnea exertional
[p] Includes reports of acne, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis exfoliative generalized, eczema, eczema infected, erythema, erythema multiforme, exfoliative rash, folliculitis, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, rash pustular, seborrheic dermatitis, skin exfoliation, skin toxicity, skin ulcer and toxic skin eruption
[q] Includes reports of deep vein thrombosis, embolism, embolism venous and pulmonary embolism

Listing 3 **Less Common Adverse Drug Reactions Occurring in (< 1%) Patients with NSCLC Treated with TECENTRIQ in Combination with bevacizumab, Paclitaxel and Carboplatin in the Pivotal Study GO29436 (IMpower150)**

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

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

Study GO29537 (IMpower130) – First-Line Combination Therapy
The information provided in Table 4 and Listing 4 summarizes the adverse drug reactions observed in patients included in study GO29537 (IMpower130) (n=705) in chemotherapy-naïve patients with metastatic, non-squamous non-small cell lung cancer (NSCLC) in the first-line (1L) setting.

Table 4 **Adverse Drug Reactions Occurring in ≥ 1% of Patients with NSCLC Treated with TECENTRIQ in Combination with nab-Paclitaxel and Carboplatin in the Pivotal Study GO29537 (IMpower130)**

ADR (MedDRA v20.1) System Organ Class Preferred Term	**TECENTRIQ + nab-paclitaxel + carboplatin (n=473) (Frequency rate %)**		**nab-paclitaxel + carboplatin (n=232) (Frequency rate %)**	
	All Grades	**Grades 3-4**	**All Grades**	**Grades 3-4**
Gastrointestinal disorders				
Diarrhea[a]	202 (42.7)	25 (5.3)	73 (31.5)	14 (6.0)
Vomiting	128 (27.1)	13 (2.7)	45 (19.4)	5 (2.2)
Abdominal Pain[b]	82 (17.3)	6 (1.3)	28 (12.1)	3 (1.3)
General disorders & administration site conditions				
Fatigue[c]	294 (62.2)	52 (11.0)	140 (60.3)	19 (8.2)
Pyrexia	82 (17.3)	1 (0.2)	23 (9.9)	0
Edema[d]	72 (15.2)	3 (0.6)	33 (14.2)	2 (0.9)
Infections & infestations				
Respiratory Tract Infection[e]	132 (27.9)	47 (9.9)	39 (16.8)	13 (5.6)
Urinary Tract Infection[f]	69 (14.6)	8 (1.7)	24 (10.3)	2 (0.9)
Oral Fungal Infection[g]	10 (2.1)	0	7 (3.0)	0
Sepsis[h]	11 (2.3)	10 (2.1)	3 (1.3)	1 (0.4)
Investigations				
Alanine Aminotransferase Increased	25 (5.3)	6 (1.3)	14 (6.0)	4 (1.7)
Blood Alkaline Phosphatase Increased	20 (4.2)	4 (0.8)	10 (4.3)	0
Metablism disorders				
Decreased Appetite[i]	143 (30.2)	10 (2.1)	60 (25.9)	5 (2.2)
Dehydration	49 (10.4)	6 (1.3)	25 (10.8)	2 (0.9)

ADR (MedDRA v20.1) System Organ Class Preferred Term	TECENTRIQ + nab-paclitaxel + carboplatin (n=473) (Frequency rate %)		nab-paclitaxel + carboplatin (n=232) (Frequency rate %)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Musculoskeletal and Connective Tissue disorders				
Musculoskeletal Pain[j]	158 (33.4)	12 (2.5)	41 (17.7)	1 (0.4)
Nervous System Disorders				
Neuropathy Peripheral[k]	167 (35.3)	14 (3.0)	65 (28.0)	6 (2.6)
Psychiatric disorders				
Insomnia	68 (14.4)	0	31 (13.4)	0
Confusional State[l]	19 (4.0)	8 (1.7)	1 (0.4)	0
Renal & urinary disorders				
Blood Creatinine Increased	26 (5.5)	2 (0.4)	7 (3.0)	0
Hematuria	16 (3.4)	2 (0.4)	5 (2.2)	0
Acute Kidney Injury	9 (1.9)	4 (0.8)	3 (1.3)	1 (0.4)
Respiratory, thoracic and mediastinal disorders				
Cough[m]	149 (31.5)	3 (0.6)	45 (19.4)	0
Dyspnea[n]	148 (31.3)	23 (4.9)	56 (24.1)	3 (1.3)
Skin & subcutaneous disorders				
Rash[o]	114 (24.1)	5 (1.1)	36 (15.5)	2 (0.9)
Vascular disorders				
Embolism[p]	34 (7.2)	19 (4.0)	15 (6.5)	8 (3.4)

[a] Includes reports of diarrhea and frequent bowel movements
[b] Includes reports of abdominal pain, abdominal pain lower, abdominal pain upper and flank pain
[c] Includes reports of asthenia, fatigue, lethargy and malaise
[d] Includes reports of edema, edema peripheral, localized edema, lymphedema, peripheral swelling and swelling
[e] Includes reports of bronchitis, pneumonia, respiratory tract infection and upper respiratory tract infection
[f] Includes reports of cystitis, urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal and urinary tract infection pneumococcal
[g] Includes reports of fungal esophagitis and oral candidiasis
[h] Includes reports of bacteremia, pulmonary sepsis, sepsis and urosepsis
[i] Includes reports of decreased appetite and hypophagia
[j] Includes reports of back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia and neck pain
[k] Includes reports of autoimmune neuropathy, herpes zoster, hypoaesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy and toxic neuropathy
[l] Includes reports of confusional state and mental status changes
[m] Includes reports of cough, productive cough and upper airway cough syndrome
[n] Includes reports of dyspnea and dyspnea exertional
[o] Includes reports of acne, dermatitis, dermatitis acneiform, dermatitis allergic, drug eruption, eczema, erythema, erythema multiforme, folliculitis, furuncle, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, seborrheic dermatitis, skin exfoliation, skin ulcer and toxic skin eruption
[p] Includes reports of deep vein thrombosis, embolism, embolism venous, pulmonary embolism and venous thrombosis

Listing 4 **Less Common Adverse Drug Reactions Occurring in (< 1%) Patients with NSCLC Treated with TECENTRIQ in Combination with nab-Paclitaxel and Carboplatin in the Pivotal Study GO29537 (IMpower130)**

Liver Function Test Abnormalities: Blood Bilirubin Increased
Altered Mentation: Delirium, Hallucination.
Urinary Obstruction: Urinary Tract Obstruction.

Study GO28915 (OAK) – Second Line Monotherapy
The information provided in Table 5 and Listing 5 summarizes the adverse drug reactions observed in patients included in study GO28915 (OAK) (n=1187), during treatment with TECENTRIQ compared to treatment with docetaxel.

Table 5 **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 (OAK)**

Adverse Drug Reaction (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)
Blood and Lymphatic System Disorders				
Thrombocytopenia	8 (1.3)	1 (0.2)	8 (1.4)	1 (0.2)
Endocrine Disorders				
Hypothyroidism[a]	27 (4.4)	0	2 (0.3)	0
Hyperthyroidism[b]	9 (1.5)	0	0	0
Gastrointestinal Disorders				
Nausea	109 (17.9)	4 (0.7)	132 (22.8)	2 (0.3)
Diarrhea	94 (15.4)	4 (0.7)	141 (24.4)	11 (1.9)
Vomiting	74 (12.2)	2 (0.3)	63 (10.9)	5 (0.9)
Abdominal pain[c]	44 (7.2)	3 (0.5)	57 (9.9)	6 (1.0)
Dysphagia	13 (2.1)	2 (0.3)	11 (1.9)	1 (0.2)
General Disorders and Administration				
Fatigue[d]	271 (44.5)	25 (4.1)	329 (56.9)	35 (6.1)
Pyrexia	109 (17.9)	2 (0.3)	77 (13.3)	1 (0.2)
Chills	22 (3.6)	1 (0.2)	9 (1.6)	0
Influenza like illness	32 (5.3)	0	14 (2.4)	0
Hepatobiliary Disorders				
AST increased	38 (6.2)	5 (0.8)	12 (2.1)	2 (0.3)
ALT increased	35 (5.7)	6 (1.0)	14 (2.4)	2 (0.3)
Immune System Disorders				
Hypersensitivity	6 (1.0)	1 (0.2)	11 (1.9)	0

Adverse Drug Reaction (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
Metabolism and Nutrition Disorders				
Decreased appetite[e]	145 (23.8)	2 (0.3)	138 (23.9)	9 (1.6)
Hyponatremia	26 (4.3)	11 (1.8)	18 (3.1)	4 (0.7)
Hypokalemia	25 (4.1)	4 (0.7)	24 (4.2)	6 (1.0)
Hyperglycemia[f]	19 (3.1%)	7 (1.1)	26 (4.5)	5 (0.9)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[g]	170 (27.9)	16 (2.6)	152 (26.3)	9 (1.6)
Arthralgia	73 (12.0)	3 (0.5)	58 (10.0)	1 (0.2)
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea[h]	134 (22.0)	17 (2.8)	123 (21.3)	15 (2.6)
Nasopharyngitis[i]	42 (6.9)	0	26 (4.5)	0
Pneumonitis[j]	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[k]	105 (17.2)	5 (0.8)	86 (14.9)	1 (0.2)
Pruritus	50 (8.2)	3 (0.5)	18 (3.1)	0
Vascular Disorders				
Hypotension	17 (2.8)	2 (0.3)	23 (4.0)	3 (0.5)

[a] Includes reports of blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, hypothyroidism, thyroid function test abnormal and thyroiditis
[b] Includes reports of endocrine opthalmopathy, exophthalmos and hyperthyrodism
[c] Includes reports of abdominal pain, abdominal pain lower, abdominal pain upper and flank pain
[d] Includes reports of asthenia, fatigue, lethargy and malaise
[e] Includes reports of decreased appetite and hypophagia
[f] Includes reports of glucose tolerance impaired and hyperglycemia
[g] Includes reports of back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia and neck pain
[h] Includes reports of dyspnea and dyspnea exertional
[i] Includes reports of nasal congestion and nasopharyngitis
[j] Includes reports of interstitial lung disease, lung infiltration, radiation pneumonitis, pneumonitis and bronchioloitis
[k] Includes reports of acne, dermatitis, dermatitis acneiform, dermatitis bullous, drug eruption, eczema, erythema, erythema multiforme, erythema of eyelid, folliculitis, furuncle, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, rash pustular, seborrheic dermatitis, skin exfoliation, skin toxicity and skin ulcer

Listing 5 Less Common Adverse Drug Reactions Occurring in (< 1%) Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with TECENTRIQ in the Pivotal Study GO28915 (OAK)

Endocrine Disorders: Adrenal insufficiency, type 2 diabetes mellitus and type 1 diabetes mellitus.
Gastrointestinal Disorders: Colitis, pancreatitis.
Hepatobiliary Disorders: Hepatitis
Injury, Poisoning and Procedural Complications: Infusion related reaction

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

Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

Study Y040245 (IMbrave150) - First-Line Combination Therapy
The information provided in Table 6 and Listing 6 summarizes the adverse drug reactions observed in Study YO40245 (IMbrave150) in adult patients who received 1200 mg of TECENTRIQ intravenously, followed by 15 mg/kg bevacizumab (n=329), every 3 weeks until loss of clinical benefit or unacceptable toxicity or 400 mg of sorafenib (n=156) given orally twice daily.

Table 6 Adverse Reactions Occurring in ≥1% of Patients with Unresectable or Metastatic HCC Receiving TECENTRIQ in Combination with Bevacizumab Compared to Sorafenib in YO40245

Adverse Reaction	TECENTRIQ in combination with bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades n (%)	Grades 3–4 n (%)	All Grades n (%)	Grades 3–4 n (%)
Blood and Lymphatic System Disorders				
Anemia	30 (9.1)	9 (2.7)	15 (9.6)	4 (2.6)
Neutropenia[a]	28 (8.5)	6 (1.8)	7 (4.5)	1 (0.6)
Thrombocytopenia	27 (8.2)	6 (1.8)	8 (5.1)	3 (1.9)
Leukopenia	19 (5.8)	3 (0.9)	4 (2.6)	0
Leukocytosis	5 (1.5)	0	1 (0.6)	0
Endocrine Disorders				
Hypothyroidism[b]	36 (10.9)	0	4 (2.6)	0
Hyperthyroidism	15 (4.6)	1 (0.3)	0	0
Eye Disorders				
Cataract	0	0	2 (1.3)	0
Gastrointestinal Disorders				
Diarrhoea[c]	62 (18.8)	6 (1.8)	77 (49.4)	8 (5.1)
Abdominal Pain[d]	57 (17.3)	5 (1.5)	32 (20.5)	5 (3.2)
Constipation	44 (13.4)	0	22 (14.1)	0
Nausea	40 (12.2)	1 (0.3)	25 (16)	1 (0.6)
Vomiting[e]	33 (10)	2 (0.6)	13 (8.3)	1 (0.6)
Ascites	23 (7)	6 (1.8)	9 (5.8)	2 (1.3)
Abdominal distension	23 (7)	1 (0.3)	5 (3.2)	2 (1.3)
Stomatitis	19 (5.8)	3 (0.9)	7 (4.5)	1 (0.6)
Gingival bleeding	9 (2.7)	0	0	0
Pancreatitis[f]	9 (2.7)	3 (0.9)	6 (3.8)	5 (3.2)
Dyspepsia	8 (2.4)	0	3 (1.9)	2 (1.3)

Adverse Reaction	TECENTRIQ in combination with bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades n (%)	Grades 3–4 n (%)	All Grades n (%)	Grades 3–4 n (%)
Gastrointestinal hemorrhage	8 (2.4)	4 (1.2)	3 (1.9)	3 (1.9)
Oesophageal varices haemorrhage	8 (2.4)	6 (1.8)	1 (0.6)	1 (0.6)
Gastrooesophoageal reflux disease	6 (1.8)	1 (0.3)	3 (1.9)	0
Colitis	6 (1.8)	2 (0.6)	1 (0.6)	1 (0.6)
Dysphagia	6 (1.8)	0	1 (0.6)	2 (1.3)
Haemorrhoids	5 (1.5)	0	5 (3.2)	1 (0.6)
Dry mouth	5 (1.5)	0	3 (1.9)	0
Rectal haemorrhage	5 (1.5)	1 (0.3)	3 (1.9)	0
Flatulence	4 (1.2)	0	3 (1.9)	0
Mouth ulceration	4 (1.2)	0	2 (1.3)	0
Upper gastrointestinal haemorrhage	4 (1.2)	2 (0.6)	2 (1.3)	2 (1.3)
General Disorders and Administration Site Conditions				
Fatigue[g]	95 (28.9)	8 (2.4)	55 (35.3)	10 (6.4)
Pyrexia	59 (17.9)	4 (1.2)	15 (9.6)	2 (1.3)
Edema[h]	38 (11.6)	0	6 (3.8)	0
Pain	8 (2.4)	0	1 (0.6)	0
Chills	7 (2.1)	0	2 (1.3)	0
Influenza like illness	7 (2.1)	0	0	0
Mucosal inflammation	5 (1.5)	0	5 (3.2)	0
Chest pain	4 (1.2)	2 (0.6)	3 (1.9)	0
Hepatobiliary Disorders				
Hepatic function abnormal	7 (2.1)	2 (0.6)	5 (3.2)	2 (1.3)
Hyperbilirubinaemia	6 (1.8)	3 (0.9)	3 (1.9)	1 (0.6)
Hepatic pain	5 (1.5)	1 (0.3)	2 (1.3)	0
Cholangitis	5 (1.5)	4 (1.2)	1 (0.6)	1 (0.6)
Infections and Infestations				
Upper Respiratory tract infection[i]	31 (9.4)	7 (2.1)	4 (2.6)	1 (0.6)
Urinary tract infection[j]	17 (5.2)	2 (0.6)	3 (1.9)	0
Periodontitis	7 (2.1)	0	0	0
Gingivitis	5 (1.5)	1 (0.3)	1 (0.6)	0
Oral fungal infection[k]	6 (1.8)	0	1 (0.6)	0
Sepsis[l]	6 (1.8)	4 (1.2)	0	0
Sinusitis	4 (1.2)	0	1 (0.6)	0
Injury, Poisoning and Procedural Complications				
Infusion related reaction	37 (11.2)	8 (2.4)	0	0
Fall	4 (1.2)	0	0	0
Metabolism and Nutrition Disorders				
Decreased Appetite[m]	58 (17.6)	4 (1.2)	38 (24.4)	6 (3.8)
Hypoalbuminaemia	24 (7.3)	1 (0.3)	12 (7.7)	0

Adverse Reaction	TECENTRIQ in combination with bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades n (%)	Grades 3–4 n (%)	All Grades n (%)	Grades 3–4 n (%)
Hyponatraemia	19 (5.8)	9 (2.7)	9 (5.8)	3 (1.9)
Hyperglycemia	16 (4.9)	2 (0.6)	4 (2.6)	2 (1.3)
Hyperkalaemia	11 (3.3)	4 (1.2)	4 (2.6)	0
Hypokalaemia	9 (2.7)	2 (0.6)	10 (6.4)	4 (2.6)
Diabetes mellitus	8 (2.4)	1 (0.3)	0	0
Hypophosphataemia	7 (2.1)	2 (0.6)	11 (7.1)	6 (3.8)
Hypoglycaemia	5 (1.5)	3 (0.9)	3 (1.9)	2 (1.3)
Hypercalcaemia	4 (1.2)	0	0	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[n]	54 (16.4)	2 (0.6)	16 (10.3)	3 (1.9)
Arthralgia	32 (9.7)	0	8 (5.1)	1 (0.6)
Pain in extremity	8 (2.4)	0	6 (3.8)	0
Muscle spasms	7 (2.1)	0	5 (3.2)	0
Muscular weakness	5 (1.5)	1 (0.3)	0	0
Nervous System Disorders				
Headache	27 (8.2)	0	11 (7.1)	1 (0.6)
Dizziness	10 (3.0)	0	1 (0.6)	1 (0.6)
Neuropathy peripheral[o]	8 (2.4)	0	4 (2.6)	0
Dysgeusia	6 (1.8)	0	3 (1.9)	0
Hepatic encephalopathy	5 (1.5)	2 (0.6)	3 (1.9)	2 (1.3)
Tremor	4 (1.2)	0	0	0
Psychiatric Disorders				
Insomnia	28 (8.5)	1 (0.3)	11 (7.1)	0
Confusional state[p]	6 (1.8)	3 (0.9)	0	0
Renal and Urinary Disorders				
Proteinuria	66 (20.1)	10 (3.0)	11 (7.1)	1 (0.6)
Haematuria	10 (3.0)	1 (0.3)	0	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough[q]	45 (13.7)	0	17 (10.9)	1 (0.6)
Epistaxis	34 (10.3)	0	7 (4.5)	1 (0.6)
Dyspnoea[r]	32 (9.7)	4 (1.2)	9 (5.8)	3 (1.9)
Dysphonia	28 (8.5)	0	11 (7.1)	0
Nasopharyngitis[s]	18 (5.5)	0	4 (2.6)	0
Rhinorrhoea	10 (3.0)	0	3 (1.9)	0
Oropharyngeal pain	8 (2.4)	0	4 (2.6)	0
Pleural effusion	7 (2.1)	2 (0.6)	2 (1.3)	1 (0.6)
Productive cough	7 (2.1)	0	2 (1.3)	0

Adverse Reaction	TECENTRIQ in combination with bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades n (%)	Grades 3–4 n (%)	All Grades n (%)	Grades 3–4 n (%)
Skin and Subcutaneous Tissue Disorders				
Pruritus	64 (19.5)	0	15 (9.6)	0
Rash[t]	64 (19.5)	2 (0.6)	96 (61.5)	21 (13.5)
Dry Skin	13 (4.0)	0	4 (2.6)	1 (0.6)
Urticaria	6 (1.8)	0	0	0
Alopecia	4 (1.2)	0	22 (14.1)	0
Vascular Disorders				
Hypertension	98 (29.8)	50 (15.2)	38 (24.4)	19 (12.2)
Embolism[u]	9 (2.7)	5 (1.5)	5 (3.2)	3 (1.9)
Hypotension	7 (2.1)	1 (0.3)	1 (0.6)	1 (0.6)

[a] Includes reports of neutropenia and neutrophil count decreased
[b] Includes reports of blood thyroid stimulating hormone increased, hypothyroidism, thyroid disorder, thyroxine free increased and tri-iodothyronine free increased
[c] Includes reports of diarrhea and frequent bowel movements
[d] Includes reports of abdominal pain, abdominal pain lower, abdominal pain upper and flank pain
[e] Includes reports of retching and vomiting
[f] Includes reports of amylase increased, lipase increased, pancreatic enzymes increased and pancreatitis
[g] Includes reports of asthenia, fatigue, lethargy and malaise
[h] Includes reports of edema, edema peripheral, peripheral swelling and swelling
[i] Includes reports of bronchitis, pneumonia, respiratory tract infection and upper respiratory tract infection
[j] Includes reports of cystitis and urinary tract infection
[k] Includes reports of oral candidiasis and oral fungal infection
[l] Includes reports of pulmonary sepsis and sepsis
[m] Includes reports of decreased appetite and early satiety
[n] Includes reports of back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia and neck pain
[o] Includes reports of hypoaesthesia, neuropathy peripheral, paraesthesia and peripheral sensory neuropathy
[p] Includes reports of confusional state and mental status changes
[q] Includes reports of cough and productive cough
[r] Includes reports of dyspnea and dyspnea exertional
[s] Includes reports of nasal congestion and nasopharyngitis
[t] Includes reports of dermatitis, dermatitis acneiform, dermatitis allergic, drug eruption, erythema, folliculitis, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, skin exfoliation, skin toxicity, skin ulcer and toxic skin eruption
[u] Includes reports of deep vein thrombosis, embolism, embolism venous and pulmonary embolism

Listing 6 Less Common Adverse Drug Reactions Occurring in (< 1%) Patients with Hepatocellular Carcinoma Treated with TECENTRIQ plus Bevacizumab in Study YO40245 (IMbrave150)

Blood and Lymphatic System Disorders: haemolytic anaemia
Cardiac Disorders: acute coronary syndrome, acute myocardial infarction, aortic valve stenosis, atrial fibrillation, cardiac arrest, conduction disorder, myocardial infarction
Congenital, Familial and Genetic Disorders: hydrocele
Ear and Labyrinth Disorders: hypoacusis

Endocrine Disorders: adrenal insufficiency
Eye Disorders: blindness
Gastrointestinal disorders: dental caries, duodenal ulcer, gastric mucosal lesion, gastric ulcer perforation, gastric varices haemorrhage, gastrointestinal necrosis, haematemesis, hiatus hernia, ileus, large intestinal haemorrhage, melaena, mesenteric vein thrombosis, oesophageal haemorrhage, oesophageal stenosis, varices oesophageal
General Disorders and Administration Site Conditions: multiple organ dysfunction syndrome
Hepatobiliary Disorders: autoimmune hepatitis, bile duct stone, hepatic cirrhosis, hepatitis, hepatobiliary disease, hepatorenal failure, immune-mediated hepatitis, jaundice, liver injury
Immune System Disorders: anaphylactic reaction, cytokine release syndrome, hypersensitivity
Infections and infestations: burkholderia pseudomallei infection, cellulitis, empyema, escherichia sepsis, gastroenteritis, haemophilus infection, herpes simplex encephalitis, neutropenic sepsis, peritonitis, post procedural infection, septic shock, skin infection, tooth infection
Injury, Poisoning and Procedural Complications: acetabulum fracture, femur fracture, head injury, hip fracture
Investigations: granulocyte count decreased, liver function test abnormal
Metabolism and Nutrition Disorders: hyperammonaemia, hypoproteinaemia, lactic acidosis, metabolic acidosis, tumour lysis syndrome, type 2 diabetes mellitus
Musculoskeletal and Connective Tissue Disorders: autoimmune arthritis, groin pain, hypercreatinaemia, pathological fracture, tendonitis
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps): chronic myeloid leukaemia, oesophageal squamous cell carcinoma, oropharyngeal neoplasm, tumour haemorrhage
Nervous System Disorders: cerebral infarction, cerebrovascular accident, subarachnoid haemorrhage, subdural hygroma, syncope, VIth nerve disorder, VIth nerve paralysis
Psychiatric Disorders: delirium
Renal and Urinary Disorders: acute kidney injury, ketonuria, nephritis, nephrotic syndrome
Reproductive System and Breast Disorders: pelvic pain
Respiratory, Thoracic and Mediastinal Disorders: asthma, chronic obstructive pulmonary disease, laryngeal pain, pharyngeal inflammation, pneumonitis, pneumothorax, pulmonary haemorrhage, respiratory distress
Skin and Subcutaneous Tissue Disorders: psoriasis
Vascular Disorders: bleeding varicose vein

NOC/c Locally Advanced or Metastatic Triple Negative Breast Cancer (TNBC)

Study WO29522 (IMpassion130) – First-Line Combination Therapy
The information provided in Table 7 and Listing 7 summarizes the adverse drug reactions observed in patients included in study WO29522 (n=890), during treatment with TECENTRIQ + nab-paclitaxel compared to treatment with placebo + nab-paclitaxel.

Table 7 Adverse Drug Reactions Occurring in ≥ 1% of Patients with Triple Negative Breast Cancer (TNBC) Treated with TECENTRIQ + Nab-paclitaxel versus Placebo + Nab-paclitaxel in Study WO29522 (IMpassion130)

Adverse Drug Reaction (MedDRA) System Organ Class (SOC)	TECENTRIQ + Nab-paclitaxel N = 452 n (%)		Placebo + Nab-paclitaxel N = 438 n (%)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Any Adverse Drug Reactions	427 (94.5)	160 (35.4)	400 (91.3)	123 (28.1)
Blood and Lymphatic System Disorders				
Neutropenia[a]	143 (31.6)	56 (12.4)	109 (24.9)	47 (10.7)
Febrile neutropenia	7 (1.5)	7 (1.5)	4 (0.9)	4 (0.9)
Thrombocytopenia	9 (2.0)	2 (0.4)	5 (1.1)	1 (0.2)
Endocrine Disorders				
Hypothyroidism[b]	78 (17.3)	0	19 (4.3)	0
Hyperthyroidism	20 (4.4)	1 (0.2)	6 (1.4)	0
Gastrointestinal Disorders				
Nausea	208 (46.0)	5 (1.1)	167 (38.1)	8 (1.8)
Diarrhea[c]	147 (32.5)	6 (1.3)	150 (34.2)	9 (2.1)
Vomiting[d]	88 (19.5)	4 (0.9)	74 (16.9)	5 (1.1)
Abdominal pain[e]	73 (16.2)	3 (0.7)	75 (17.1)	1 (0.2)
Dysphagia	9 (2.0)	1 (0.2)	5 (1.1)	0 (0)
Colitis[f]	5 (1.1)	1 (0.2)	3 (0.7)	1 (0.2)
General Disorders and Administration				
Fatigue[g]	263 (58.2)	20 (4.4)	244 (55.7)	18 (4.1)
Pyrexia	85 (18.8)	3 (0.7)	47 (10.7)	0 (0)
Chills	40 (8.8)	1 (0.2)	23 (5.3)	0
Influenza-like illness	29 (6.4)	0	11 (2.5)	0
Hepatobiliary Disorders				
ALT increased	47 (10.4)	8 (1.8)	40 (9.1)	5 (1.1)
AST increased	43 (9.5)	9 (2.0)	43 (9.8)	9 (2.1)
Transaminases increased	5 (1.1)	2 (0.4)	2 (0.5)	0
Immune System Disorders				
Hypersensitivity	5 (1.1)	0	4 (0.9)	0
Infections and Infestations				
Urinary tract infection[h]	66 (14.6)	5 (1.1)	54 (12.3)	2 (0.5)
Injury, Poisoning and Procedural Complications				
Infusion-related reaction	5 (1.1)	0	5 (1.1)	0
Metabolism and Nutrition Disorders				
Decreased appetite	90 (19.9)	3 (0.7)	79 (18.0)	3 (0.7)
Hypokalemia	27 (6.0)	10 (2.2)	10 (2.3)	4 (0.9)
Hyponatremia	9 (2.0)	3 (0.7)	15 (3.4)	6 (1.4)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[i]	157 (34.7)	9 (2.0)	149 (34.0)	9 (2.1)

Adverse Drug Reaction (MedDRA) System Organ Class (SOC)	TECENTRIQ + Nab-paclitaxel N = 452 n (%)		Placebo + Nab-paclitaxel N = 438 n (%)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Arthralgia	81 (17.9)	1 (0.2)	70 (16.0)	1 (0.2)
Nervous System Disorder				
Peripheral neuropathy[j]	219 (48.5)	44 (9.7)	206 (47.0)	23 (5.3)
Photophobia	5 (1.1)	0	2 (0.5)	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough[k]	125 (27.7)	0	90 (20.5)	0
Dyspnea[l]	81 (17.9)	4 (0.9)	67 (15.3)	3 (0.7)
Nasopharyngitis[m]	61 (13.5)	0	46 (10.5)	0
Pneumonitis	14 (3.1)	1 (0.2)	0	0
Skin and Subcutaneous Tissue Disorders				
Rash[n]	154 (34.1)	4 (0.9)	114 (26.0)	2 (0.5)
Vascular Disorders				
Hypotension	10 (2.2)	0	7 (1.6)	2 (0.5)

[a] Includes reports of neutropenia and neutrophil count decreased
[b] Includes reports of autoimmune thyroiditis, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, euthyroid sick syndrome, goitre, hypothyroidism, thyroid function test abnormal, thyroiditis, thyroxine decreased and thyroxine free increased
[c] Includes reports of diarrhea and frequent bowel movements
[d] Includes reports of retching and vomiting
[e] Includes reports of abdominal pain, abdominal pain lower, abdominal pain upper and flank pain
[f] Includes reports of colitis and colitis ulcerative
[g] Includes reports of asthenia, fatigue, lethargy and malaise
[h] Includes reports of cystitis, pyelonephritis, pyelonephritis acute and urinary tract infection
[i] Includes reports of back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia and neck pain
[j] Includes reports of herpes zoster, hypoaesthesia, neuralgia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy and toxic neuropathy
[k] Includes reports of cough, productive cough and upper airway cough syndrome
[l] Includes reports of dyspnea and dyspnea exertional
[m] Includes reports of nasal congestion and nasopharyngitis
[n] Includes reports of acne, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalized, dermatitis infected, drug eruption, eczema, erythema, erythema of eyelid, folliculitis, furuncle, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin toxicity and skin ulcer

Listing 7 Less Common Adverse Drug Reactions Occurring in (< 1%) Patients with Triple-Negative Breast Cancer (TNBC) Treated with TECENTRIQ + Nab-paclitaxel in Study WO29522 (IMpassion130) (MedDRA PTs)

Blood and Lymphatic System Disorders: neutropenic sepsis, platelet count decreased
Endocrine Disorders: adrenal insufficiency, Addison's disease, adrenocortical insufficiency acute, diabetes mellitus, diabetic ketoacidosis
Gastrointestinal Disorders: amylase abnormal, amylase increased, lipase increased

Hepatobiliary Disorders: gamma-glutamyltransferase increased, hepatic function abnormal, hepatic pain, liver function test increased, autoimmune hepatitis, hepatitis, hepatoxicity, hepatic failure, hepatitis toxic, immune-mediated hepatitis
Respiratory, Thoracic, and Mediastinal Disorders: hypoxia

NOC/c Locally Advanced or Metastatic Urothelial Carcinoma

Study GO29293 (IMvigor210) (Cohort 2) - Monotherapy
The information provided in Table 8 and Listing 8 summarizes the adverse drug reactions observed in patients included in Cohort 2 of study GO29293 (IMvigor210) (n=310), during treatment with TECENTRIQ and up to 30 days from the last dose received.

Table 8 Adverse Drug Reactions Occurring in ≥ 1% of Patients with Urothelial Carcinoma Treated with TECENTRIQ in Study GO29293 (IMvigor210) Cohort 2

Adverse Drug Reaction (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[a]	11 (3.5)	1 (0.3)
Gastrointestinal Disorders		
Nausea	82 (26.5)	6 (1.9)
Abdominal pain[b]	71 (22.9)	10 (3.2)
Diarrhea[c]	68 (21.9)	3 (1.0)
Vomiting[d]	63 (20.3)	4 (1.3)
Colitis[e]	4 (1.3)	3 (1.0)
General Disorders and Administration		
Fatigue[f]	178 (57.4)	21 (6.8)
Pyrexia	72 (23.2)	3 (1.0)
Chills	34 (11.0)	1 (0.3)
Influenza like illness	16 (5.2)	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[g]	85 (27.4)	4 (1.3)
Hyponatremia	22 (7.1)	12 (3.9)
Hypokalemia	17 (5.5)	4 (1.3)
Hyperglycemia[h]	15 (4.8)	2 (0.6)

Adverse Drug Reaction (MedDRA)	TECENTRIQ N = 310	
System Organ Class	**All Grades (%)**	**Grade 3 - 4 (%)**
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[i]	85 (27.4)	11 (3.5)
Arthralgia	55 (17.7)	3 (1.0)
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea[j]	57 (18.4)	10 (3.2)
Nasopharyngitis[k]	29 (9.4)	0
Pneumonitis	8 (2.6)	3 (0.9)
Hypoxia	5 (1.6)	3 (1.0)
Skin and Subcutaneous Tissue Disorders		
Rash[l]	57 (18.4)	2 (0.6)
Pruritus	46 (14.8)	1 (0.3)
Vascular Disorders		
Hypotension	14 (4.5)	2 (0.6)

[a] Includes reports of blood thyroid stimulating hormone increased and hypothyroidism
[b] Includes reports of abdominal pain, abdominal pain lower, abdominal pain upper and flank pain
[c] Includes reports of diarrhea and frequent bowel movements
[d] Includes reports of vomiting and retching
[e] Includes reports of colitis, colitis ischemic and colitis microscopic
[f] Includes reports of asthenia, fatigue, lethargy and malaise
[g] Includes reports of decreased appetite, early satiety and hypophagia
[h] Includes reports of glucose tolerance impaired and hyperglycemia
[i] Includes reports of back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia and neck pain
[j] Includes reports of dyspnea and dyspnea exertional
[k] Includes reports of nasal congestion and nasopharyngitis
[l] Includes reports of acne, dermatitis allergic, drug eruption, eczema, erythema, erythema multiforme, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, rash pustular, seborrheic dermatitis and skin toxicity

Listing 8 Less Common Adverse Drug Reactions Occurring in (< 1%) Patients with Urothelial Carcinoma Treated with TECENTRIQ in Study GO29293 (IMvigor210) 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

Additional Information on Selected Adverse Reactions

General

- ***Monotherapy***

Clinically significant adverse drug reactions were observed for TECENTRIQ monotherapy and reflect exposure to TECENTRIQ in 3178 patients in three randomized, active-controlled studies

(POPLAR, OAK, IMmotion150) and four open-label, single arm studies (PCD4989g, IMvigor210, IMvigor211, BIRCH, FIR) which provided 983 patients with metastatic urothelial carcinoma, 1636 patients with metastatic NSCLC, 175 patients with renal cell carcinoma (RCC) and 384 patients with other tumour types. Cases of dry skin were also observed in a TECENTRIQ monotherapy study.

- ***Combination Therapy***

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

Immune-Mediated Adverse Reactions

- ***Immune-Mediated Pneumonitis***

Pneumonitis occurred in 2.7% (87/3178) of patients who received TECENTRIQ monotherapy, including Grade 1-2 in 1.9% (59/3178), Grade 3-4 in 0.8% (27/3178), and Grade 5 in 1 (<0.1%) patient. The median time to onset was 3.4 months (range: 0.1 to 24.8 months). The median duration was 1.4 months (range: 0 to 21.2+ months; + denotes a censored value). Pneumonitis resolved in 59 patients. Pneumonitis led to discontinuation of TECENTRIQ in 12 (0.4%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.6% (51/3178) of patients receiving TECENTRIQ.

- ***Immune-Mediated Hepatitis***

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

- ***Immune-Mediated Colitis***

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

Diarrhea occurred in 19.7% (626/3178) patients, including Grade 3-4 diarrhea in 1.1% (36/3178) of patients who received TECENTRIQ.

- ***Immune-Mediated Endocrinopathies***

Hypophysitis

Across clinical trials, hypophysitis occurred in <0.1% (2/3178) of all patients who received TECENTRIQ monotherapy. The median time to onset was 7.2 months (range: 0.8 to 13.7 months). One patient required the use of corticosteroids and treatment with TECENTRIQ was

discontinued.

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

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

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

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

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

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

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

Diabetes Mellitus
Diabetes mellitus occurred in 0.3% (11/3178) of patients who received TECENTRIQ monotherapy, including Grade 1-2 in 0.2% (5/3178) and Grade 3-4 in 0.2% (6/3178) of patients.

The median time to onset was 3.6 months (range: 0.1 to 9.9 months). The median duration was 2.4 months (range: 0.1 to 15.2+ months; + denotes a censored value). Diabetes mellitus resolved in 8 patients.

- ***Immune-Mediated Meningoencephalitis***

Meningoencephalitis occurred in 0.4% (13/3178) of patients who received TECENTRIQ monotherapy, including Grade 1-2 in 0.2% (7/3178) of patients and Grade 3-4 in 0.2% (6/3178) of patients. The median time to onset was 0.5 months (range: 0 to 12.5 months). The median duration was 0.7 months (range: 0.2 to 14.5+ months; + denotes a censored value). Meningoencephalitis requiring the use of corticosteroids occurred in 0.2% (6/3178) of patients receiving TECENTRIQ and led to discontinuation of TECENTRIQ in 4 (0.1%) patients.

- ***Immune-Mediated Neuropathies***

Neuropathies, including Guillain-Barré syndrome and demyelinating polyneuropathy, occurred in 0.2% (5/3178) of patients who received TECENTRIQ monotherapy. Guillain-Barré syndrome Grade 3 occurred in 0.1% (4/3178) patients and demyelinating polyneuropathy Grade 2 occurred in 1 (<0.1%) patient. The median time to onset was 7.0 months (range: 0.6 to 8.1 months). The median duration was 8.0 months (0.6 to 8.3+ months; +denotes a censored value). Guillain-Barré syndrome led to the discontinuation of TECENTRIQ in 1 (<0.1%) patient. Guillain-Barré syndrome requiring the use of corticosteroids occurred in <0.1% (2/3178) of patients.

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

- ***Immune-Mediated Pancreatitis***

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

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

- ***Immune-Mediated Myositis***

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

Myositis requiring the use of corticosteroids occurred in 0.2% (7/3178) of patients receiving TECENTRIQ.

- ***Immune-Mediated Nephritis***

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

- ***Infection***

In 3178 patients who received TECENTRIQ monotherapy, infection occurred in 1351 (42.5%) patients. Grade 1-2 infection occurred in 984 (31.0%) patients and Grade 3 or 4 infection occurred in 336 (10.6%) patients, while 31 (1.0%) patients died due to infection. Pneumonia was the most common type of Grade 3 or higher infection, occurring in 108 (3.4%) patients.

- ***Infusion-Related Reactions***

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

Abnormal Hematologic and Clinical Chemistry Findings

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

Study GO30081 (IMpower133) - First-Line Combination Therapy

The information provided in Table 9 summarizes grade 3-4 laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in pivotal study GO30081 (IMpower133).

Table 9 Grade 3-4 Laboratory Abnormalities in ≥1% of Patients with First-Line Extensive-Stage Small Cell Lung Cancer (ES-SCLC) Treated with TECENTRIQ in Pivotal Study GO30081 (IMpower133)

Laboratory Test	Grade 3-4 (%)
Neutropenia	45
Leukopenia	23
Thrombocytopenia	20
Anemia	17
Hyponatremia	15
Lymphopenia	14
Increased creatinine	4
Hypokalemia	3
Hypomagnesemia	3

Laboratory Test	Grade 3-4 (%)
Increased SGPT/ALT	3
Hypocalcemia	3
Hypophosphatemia	3
Hypermagnesemia	2
Hypercalcemia	2
Increased bilirubin	2
Increased hemoglobin	2
Hypoalbuminemia	1
Increased alkaline phosphatase	1
Hyperkalemia	1
Increased SGOT/AST	1
Hypernatremia	1

Non-Small Cell Lung Cancer (NSCLC)

Study GO29431 (IMpower110) – First Line Monotherapy

The information provided in Table 10 summarizes grade 3-4 laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in study GO29431 (IMpower110).

Table 10 Grade 3-4 Laboratory Abnormalities in ≥1% of Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC) Treated with TECENTRIQ vs. Platinum Agent in Combination with Pemetrexed or Gemcitabine in Study GO29431 (IMpower110)

Laboratory Test	TECENTRIQ (n=286)	Platinum Agent in Combination with Pemetrexed or Gemcitabine (n=263)
	Grade 3–4 (%)	Grade 3–4 (%)
Lymphopenia	9	17
Hyponatremia	9	7
Hypermagnesemia	5	2
Hypophosphatemia	4	2
Hypercalcemia	4	0
Hyperkalemia	4	3
Increased Bilirubin	3	0
Increased AST	3	1
Increased ALT	3	1
Increased Alkaline Phosphatase	3	1
Hypocalcemia	1	3
Anemia	2	20
Neutropenia	1	27
Thrombocytopenia	1	13
Hypokalemia	1	2
Increased Creatinine	1	2
Hypoalbuminemia	0	2
Hypomagnesemia	0	1
Leukopenia	0	15

Study GO29436 (IMpower150) - First-Line Combination Therapy

The information provided in Table 11 summarizes grade 3-4 laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in pivotal study GO29436 (IMpower150).

Table 11 Grade 3-4 Laboratory Abnormalities in ≥ 1% Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with TECENTRIQ in Combination with Bevacizumab, Paclitaxel and Carboplatin, in Pivotal Study GO29436 (IMpower150)

Laboratory Test	Arm B: TECENTRIQ + bevacizumab + paclitaxel + carboplatin (n=393)	Arm C: bevacizumab + paclitaxel + carboplatin (n=394)
	Grade 3-4 (%)	Grade 3-4 (%)
Neutropenia	31	26
Lymphopenia	17	13
Thrombocytopenia	11	9
Anemia	10	9
Hyperkalemia	7	4
Increased ALT,	6	1
Hypophosphatemia	4	4
Increased AST,	4	1
Hypocalcemia	3	3
Hypoalbuminemia	3	2
Hypomagnesemia	2	1
Increased Alkaline Phosphatase,	2	1
Hypoglycemia	2	0
Increased Creatinine,	1	2
Increased Bilirubin	1	0

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

Study GO29537 (IMpower130) – First-Line Combination Therapy

The information provided in Table 12 summarizes grade 3-4 laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in combination with nab-paclitaxel and carboplatin in pivotal study GO29537 (IMpower130).

Table 12 Grade 3-4 Laboratory Abnormalities in ≥ 1% Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with TECENTRIQ in combination with nab-Paclitaxel and Carboplatin in Pivotal Study GO29537 (IMpower130)

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

Unresectable or Metastatic Hepatocellular Carcinoma

Study YO40245 (IMbrave150) - First-Line Combination Therapy

The following table summarizes grade 3-4 laboratory abnormalities in ≥ 1% adult patients with unresectable or unresectable hepatocellular carcinoma treated with TECENTRIQ in combination with bevacizumab in pivotal study YO40245.

Table 13 Grade 3-4 Laboratory Abnormalities in ≥ 1% Patients with Unresectable or Metastatic Hepatocellular Carcinoma Treated with TECENTRIQ in combination with Bevacizumab in Pivotal Study YO40245 (IMbrave150)

Laboratory Abnormality	Grades 3–4 (%)
Chemistry	
Increased AST	16
Decreased Sodium	13

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

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

Study GO28915 (OAK) - Second Line Monotherapy
The information provided in Table 14 summarizes grade 3-4 laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in pivotal study GO28915 (OAK).

Table 14 Grade 3-4 Laboratory Abnormalities in ≥ 1% Patients with Non-Small Cell Lung Cancer (NSCLC) Treated with TECENTRIQ in Pivotal Study GO28915 (OAK)

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

Laboratory Test	Grade 3-4 (%)
Thrombocytopenia	2
Hypercalcemia	2
Leukopenia	2
Hypoglycemia	1
INR increased	2
Neutropenia	2
Hypomagnesemia	1

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

Study WO29522 (IMpassion130) – First-Line Combination Therapy

The information provided in Table 15 summarizes grade 3-4 laboratory shifts from baseline (defined as shifts from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post baseline) that occurred in ≥ 1% of patients treated with TECENTRIQ in pivotal study WO29522.

Table 15 Grade 3-4 Laboratory Shifts from Baseline in ≥ 1% Patients with (TNBC) Treated with TECENTRIQ in Pivotal Study WO29522 (IMpassion130)

Laboratory Test	Grade 3-4 (%)
Decreased lymphocytes	14
Decreased leukocytes	14
Decreased neutrophils	14
Decreased sodium	6
Increased ALT	6
Increased AST	5
Decreased hemoglobin	4
Decreased potassium	4
Decreased phosphorus	4
Increased alkaline phosphatase	4
Increased magnesium	2
Increased lymphocytes	2
Decreased albumin	2
Decreased calcium	2
Increased potassium	2
Increased hemoglobin	2
Increased bilirubin	2
Decreased platelets	2
Increased calcium	1

NOC/c Locally Advanced or Metastatic Urothelial Carcinoma

Study GO29293 (IMvigor210) (Cohort 2) - Monotherapy
The information provided in Table 16 summarizes grade 3-4 laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in Cohort 2 of study GO29293 (n=310).

Table 16 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

Immunogenicity

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

Across pooled datasets for patients treated with atezolizumab monotherapy (N=2972) and with combination therapies (N=2285), the following rates of adverse events (AEs) have been observed for the ADA-positive population compared to the ADA-negative population, respectively: Grade 3-4 AEs 48.6% vs. 42.6%, Serious Adverse Events (SAEs) 42.2% vs. 36.0%, AEs leading to treatment withdrawal 6.2% vs 6.5% (for monotherapy); Grade 3-4 AEs 63.9% vs. 60.9%, SAEs 43.9% vs. 35.6%, AEs leading to treatment withdrawal 22.8% vs 18.4% (for

combination therapy). Available data do not allow conclusions to be drawn on possible patterns of adverse drug reactions or their causal relationship with ADAs.

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

Post-Market Adverse Reactions
No new adverse drug reactions have been identified from post-marketing experience.

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.

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

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 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.

TECENTRIQ Combination Therapy

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

- *TECENTRIQ in combination with carboplatin and etoposide (First-Line)*

During the induction phase, the recommended dose of TECENTRIQ is 1200 mg administered by IV infusion followed by carboplatin, and then etoposide administered by IV infusion on day 1. Etoposide is administered by IV infusion on days 2 and 3. This regimen is administered every 3 weeks for four cycles (see Part II: CLINICAL TRIALS).

The induction phase is followed by a maintenance phase without chemotherapy in which 1200 mg TECENTRIQ is administered by IV infusion every 3 weeks. Patients are treated with TECENTRIQ until loss of clinical benefit or unacceptable toxicity.

Non-Small Cell Lung Cancer (NSCLC)

- *TECENTRIQ in Combination with bevacizumab, Paclitaxel and Carboplatin (First-Line)*

The recommended dosage of TECENTRIQ is 1200 mg intravenously over 60 minutes followed by bevacizumab, paclitaxel, and carboplatin, on Day 1 of each 21-day cycle for a maximum of 4 to 6 cycles of chemotherapy.

After completion of chemotherapy, administer TECENTRIQ 1200 mg intravenously, followed by bevacizumab on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity.

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

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

- *TECENTRIQ in Combination with nab-Paclitaxel and Carboplatin (First-Line)*

During the induction phase, the recommended dose of TECENTRIQ is 1200 mg administered by IV infusion, followed by nab-paclitaxel and carboplatin every 3 weeks for four or six cycles. For each 21-day cycle, TECENTRIQ, nab-paclitaxel and carboplatin is administered on day 1. In addition, nab-paclitaxel is administered on days 8 and 15.

The induction phase is followed by a maintenance phase without chemotherapy in which 1200 mg TECENTRIQ is administered by IV infusion every 3 weeks.

Unresectable or Metastatic Hepatocellular Carcinoma (HCC)

- *TECENTRIQ in Combination with Bevacizumab (First-Line)*

The recommended dosage of TECENTRIQ is 1200 mg administered as an intravenous infusion over 60 minutes, followed by 15 mg/kg of bevacizumab, every 3 weeks until loss of clinical benefit or unacceptable toxicity.

Refer to the Product Monograph for bevacizumab prior to initiation.

Triple-Negative Breast Cancer (TNBC)

- *TECENTRIQ in Combination with nab-Paclitaxel (First-Line)*

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

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

TECENTRIQ Monotherapy

Metastatic NSCLC (First Line)

The recommended dose is either:

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

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

Patients should be treated until loss of clinical benefit or unacceptable toxicity.

Locally Advanced or Metastatic NSCLC (Second Line)

The recommended dose is either:

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

Urothelial Carcinoma

The recommended dose is 1200 mg administered by IV infusion every 3 weeks until disease progression or unacceptable toxicity.

Duration of Treatment

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

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

TNBC

Patients are treated with TECENTRIQ until disease progression or unacceptable toxicity.

Delayed or Missed Doses

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

Dose Modifications for Immune-Mediated Adverse Reactions

No dose reductions of TECENTRIQ are recommended.

TECENTRIQ dose modifications for specific adverse drug reactions (see WARNINGS AND PRECAUTIONS) are presented in Table 17**.**

Table 17 Recommended TECENTRIQ Dose Modifications for Specific Adverse Drug Reactions

Adverse Reaction	Severity	TECENTRIQ dose modification
Immune-Mediated Pneumonitis	Grade 2	Withhold[1]
	Grade 3 or 4	Permanently discontinue
Immune-Mediated Hepatitis in patients without HCC	Grade 2 (ALT or AST >3x ULN or blood bilirubin >1.5x ULN for more than 5-7 days)	Withhold[1]

Adverse Reaction	Severity	TECENTRIQ dose modification
	Grade 3 or 4 (ALT or AST >5.0x ULN or blood bilirubin >3x ULN)	Permanently discontinue
Immune-Mediated Hepatitis in patients with HCC	If AST/ALT is within normal limits at baseline and increases to >3x to ≤10x ULN If AST/ALT is >1 to ≤3x ULN at baseline and increases to >5x to ≤10x ULN If AST/ALT is >3x to ≤5x ULN at baseline and increases to >8x to ≤10x ULN	Withhold[1] Permanently discontinue for events lasting > 5 days of duration following withholding of TECENTRIQ
	If AST/ALT increases to >10x ULN or total bilirubin increases to >3x ULN	Permanently discontinue
Immune-Mediated Colitis	Grade 2 diarrhea or colitis	Withhold[1]
	Grade 3 diarrhea or colitis	Withhold[1] Initiate IV corticosteroids and convert to oral corticosteroids after improvement
	Grade 4 diarrhea or colitis	Permanently discontinue
Immune-Mediated Hypothyroidism	Symptomatic	Withhold[2] Initiate thyroid hormone replacement therapy
Immune-Mediated Hyperthyroidism	Symptomatic	Withhold[2] Initiate anti-thyroid therapy as needed
Immune-Mediated Adrenal Insufficiency	Symptomatic	Withhold[1]
Immune-Mediated Hypophysitis	Grade 2 or 3	Withhold[1]
	Grade 4	Permanently discontinue
Immune-Mediated Type 1 Diabetes	For ≥ Grade 3 hyperglycemia (fasting glucose >13.9 mmol/L)	Withhold[2] Initiate insulin
Immune-Mediated Meningitis, Encephalitis, Myasthenic Syndrome / Myasthenia Gravis, Guillain-Barré syndrome	All grades	Permanently discontinue
Immune-Mediated Pancreatitis	Grade 2 or 3 ≥ Grade 3 serum amylase or lipase levels increased (> 2.0 ULN)	Withhold[1]

Adverse Reaction	Severity	TECENTRIQ dose modification
	Grade 4 or any grade recurrent pancreatitis	Permanently discontinue
Immune-Mediated Myocarditis	Grade 2	Withhold[1]
	Grade 3 or 4	Permanently discontinue
Immune-Mediated Myositis	Grade 2 or 3	Withhold[1]
	Grade 4 or grade 3 recurrent myositis	Permanently discontinue
Immune-Mediated Nephritis	Grade 2 (creatinine level >1.5 - 3.0x baseline or >1.5 - 3.0x ULN)	Withhold[1]
	Grade 3 (creatinine level >3.0x baseline or >3.0 - 6.0x ULN) or 4 (creatinine level >6.0x ULN)	Permanently discontinue
Infusion Related Reactions	Grade 1 or 2	Reduce rate of infusion or withhold treatment Premedication with antipyretic and antihistamines may be considered for subsequent doses
	Grade 3 or 4	Permanently discontinue
Immune-Mediated Skin Reactions	Grade 3	Withhold[1]
	Grade 4	Permanently discontinue
Persistent Grade 2 or 3 adverse reaction (excluding endocrinopathies)	Grade 2 or 3 adverse reaction that does not recover to Grade 0 or 1 within 12 weeks after last TECENTRIQ dose	Permanently discontinue
Inability to taper corticosteroid	Inability to reduce to less than or equal to prednisone 10 mg per day (or equivalent) within 12 weeks after last TECENTRIQ dose	Permanently discontinue
Recurrent Grade 3 or 4 adverse reaction	Recurrent Grade 3 or 4 (severe or life-threatening) adverse reaction	Permanently discontinue

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

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

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

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

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

Geriatrics:
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 mild or moderate renal impairment. There is insufficient data in patients with severe 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 or moderate hepatic impairment. There are no data in patients with 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. Use a sterile needle and syringe to prepare TECENTRIQ. Withdraw the required volume of TECENTRIQ liquid concentrate from the vial. Dilute into a 250 mL polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE), or polypropylene (PP) infusion bag containing 0.9% Sodium Chloride Injection, USP. Dilute with 0.9% Sodium Chloride Injection only. After dilution, the final concentration of the diluted solution should be between 3.2 mg/mL and 16.8 mg/mL. Mix diluted solution by gentle inversion. Do not shake.

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

TECENTRIQ must not be mixed with other medicinal products. Discard any unused portion.

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

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 have 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 of 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. The pharmacokinetic properties of atezolizumab 840 mg administered every 2 weeks and 1200 mg administered every 3 weeks, are comparable. A

population pharmacokinetic analysis suggests that steady-state is obtained after 6 to 9 weeks after multiple doses. The systemic accumulation ratio across dosing regimens is 3.3.

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, mild or moderate renal impairment, mild or moderate 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, or moderate hepatic impairment (bilirubin >1.5 to 3x ULN and any AST). No data are available in

patients with severe (bilirubin > 3.0 × ULN and any AST hepatic impairment. Hepatic impairment was defined by the National Cancer Institute (NCI) criteria of hepatic dysfunction (see 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

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

Dosage Form / Composition
TECENTRIQ (atezolizumab) is supplied as a single-use vial containing either 840 mg atezolizumab/14 mL or 1200 mg atezolizumab/20 mL preservative-free, colourless to slightly yellow solution, at a concentration of 60 mg/mL for dilution for intravenous infusion. 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 either 840 mg or 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:

- in combination with nab-paclitaxel, for the treatment of adult patients with unresectable, locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1%, and who have not received prior chemotherapy for metastatic disease.
- for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:
    - Have disease progression during or following platinum-containing chemotherapy; or
    - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

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

- in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).
- as monotherapy for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have high PD-L1 expression (PD-L1 stained ≥ 50% of tumour cells [TC] or PD-L1 stained tumour-infiltrating immune cells [IC] covering ≥ 10% of the tumour area), as determined by a validated test and who do not have EGFR or ALK genomic tumour aberrations.
- in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic non-squamous NSCLC.
- for the first-line treatment of adult patients with metastatic non-squamous (NSCLC) who do not have EGFR or ALK genomic tumour aberrations, in combination with nab-paclitaxel and carboplatin.
- for the treatment of adult patients with locally advanced or metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving TECENTRIQ.
- in combination with bevacizumab, for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who require systemic therapy.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	atezolizumab for injection
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

CLINICAL TRIALS

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

Study GO30081 (IMpower133) – First-Line Combination Therapy

Study Demographics and Trial Design

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

Randomization was stratified by sex, ECOG performance status, and presence of brain metastases. A total of 403 patients were randomized (1:1) to receive one of the treatment regimens described in Table 18. Administration of TECENTRIQ was permitted beyond RECIST-defined disease progression. Prophylactic cranial irradiation (PCI) was permitted during the maintenance phase in accordance with local standards of care.

Table 18 Intravenous Treatment Regimen in Study GO30081 (IMpower133)

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

[a] TECENTRIQ is administered until loss of clinical benefit as assessed by investigator; administer TECENTRIQ prior to chemotherapy when given on the same day.
[b] AUC5 was calculated using Calvert formula; carboplatin and etoposide is administered until completion of 4 cycles, or progressive disease or unacceptable toxicity whichever occurs first.
[c] Etoposide is administered on day 1, 2 and 3 of each cycle.

Tumour assessments performed by the investigator according to RECIST v.1.1 were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Patients treated beyond disease progression had tumour assessment conducted every 6 weeks until treatment discontinuation.

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

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

Study Results
At the time of the primary analysis, patients had a median survival follow up time of 13.9 months (range: 0.0 to 21.4 months). The key results are summarized in Table 19 Kaplan-Meier curves for OS and PFS are presented in Figure 1 and Figure 2, respectively.

Table 19 Summary of Efficacy from Study GO30081 (IMpower133)

Key efficacy endpoints	Arm A (TECENTRIQ + carboplatin + etoposide)	Arm B (Placebo + carboplatin + etoposide)
Co-primary endpoints		
OS analysis	n = 201	n = 202
No. of deaths (%)	104 (51.7%)	134 (66.3%)
Median time to events (months)	12.3	10.3
95% CI	(10.8, 15.9)	(9.3, 11.3)
Stratified hazard ratio[1] (95% CI)	0.70 (0.54, 0.91)	
p-value[2]	0.0069	
12-month OS (%)	51.7	38.2
Investigator-assessed PFS (RECIST v1.1)	n = 201	n = 202
No. of events (%)	171 (85.1%)	189 (93.6%)
Median duration of PFS (months)	5.2	4.3
95% CI	(4.4, 5.6)	(4.2, 4.5)
Stratified hazard ratio[1] (95% CI)	0.77 (0.62, 0.96)	
p-value[3]	0.0170	
6-month PFS (%)	30.9	22.4
12-month PFS (%)	12.6	5.4
Secondary endpoints		
Investigator-assessed ORR (RECIST 1.1)	n = 201	n = 202
No. of responders (%)	121 (60.2%)	130 (64.4%)
95% CI	(53.1, 67.0)	(57.3, 71.0.)
No. of complete response (%)	5 (2.5%)	2 (1.0%)
No. of partial response (%)	116 (57.7%)	128 (63.4%)
Investigator-assessed DOR (RECIST 1.1)	n = 121	n = 130
Median in months	4.2	3.9
95% CI	(4.1, 4.5)	(3.1, 4.2)

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

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

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

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

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

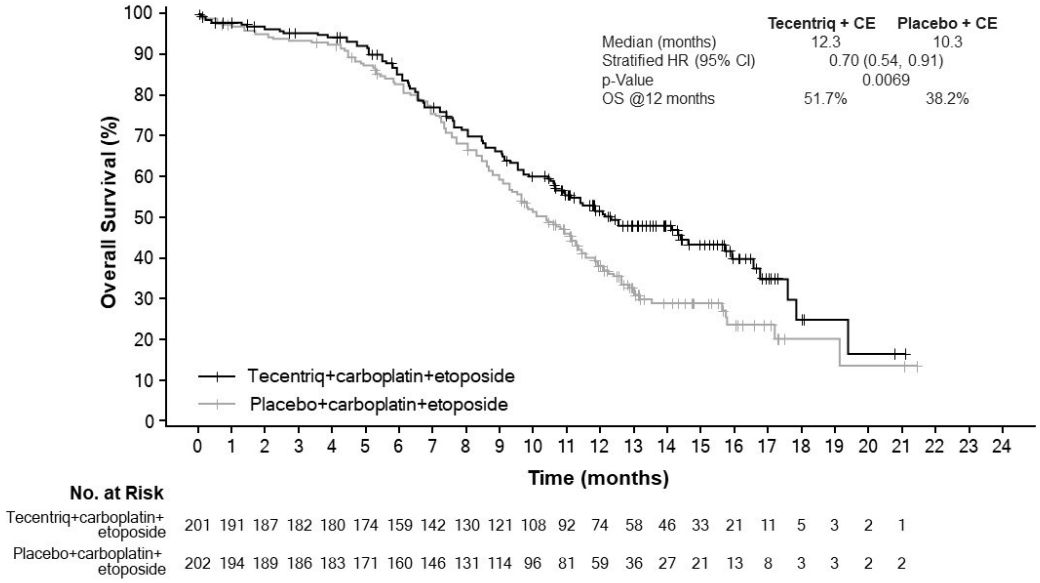
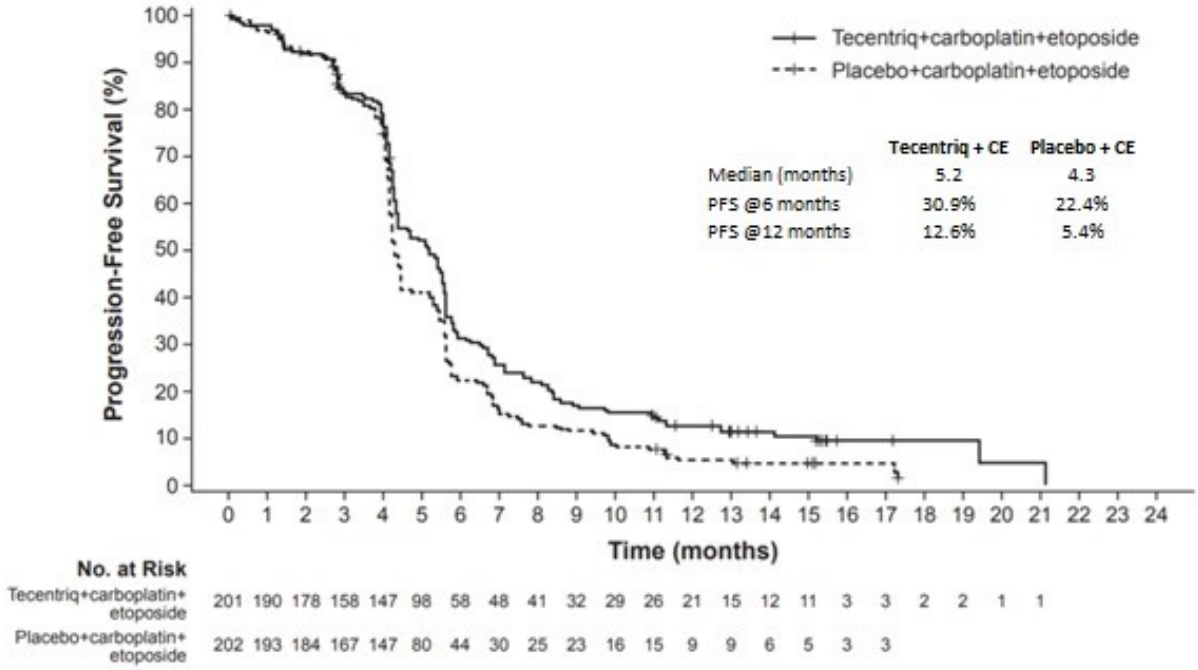


Figure 2 **Kaplan-Meier Plot of Progression-Free Survival in Study GO30081 (IMpower133)**



Non-Small Cell Lung Cancer (NSCLC)

Study GO29431 (IMpower110) – First Line Monotherapy

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

A total of 572 non-squamous or squamous patients were randomized in a 1:1 ratio to receive TECENTRIQ (Arm A) or chemotherapy (Arm B). The wild-type population (n=554) was defined as all randomized patients excluding patients with a sensitizing EGFR mutation or ALK translocation. TECENTRIQ was administered as a fixed dose of 1200 mg by IV infusion every 3 weeks until loss of clinical benefit as assessed by the investigator or unacceptable toxicity. The chemotherapy regimens are described in Table 20. Randomization was stratified by sex, ECOG performance status, histology (non-squamous vs. squamous), and PD-L1 tumour expression on TCs and ICs (TCs ≥ 1% and any ICs vs. TCs < 1% and ICs ≥ 1%). Patients were excluded if they had history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; active or untreated CNS metastases. Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter.

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

Table 20 Chemotherapy Intravenous Treatment Regimens in Study GO29431 (IMpower110)

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

[a] Cisplatin, carboplatin, pemetrexed and gemcitabine are administered until completion of 4 or 6 cycles, or progressive disease or unacceptable toxicity

[b] Pemetrexed is administered as maintenance regimen every 21 days until progressive disease or unacceptable toxicity

[c] Gemcitabine is administered on days 1 and 8 of each cycle

[d] No crossover was allowed from the control arm (platinum-based chemotherapy) to the TECENTRIQ arm (Arm A)

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

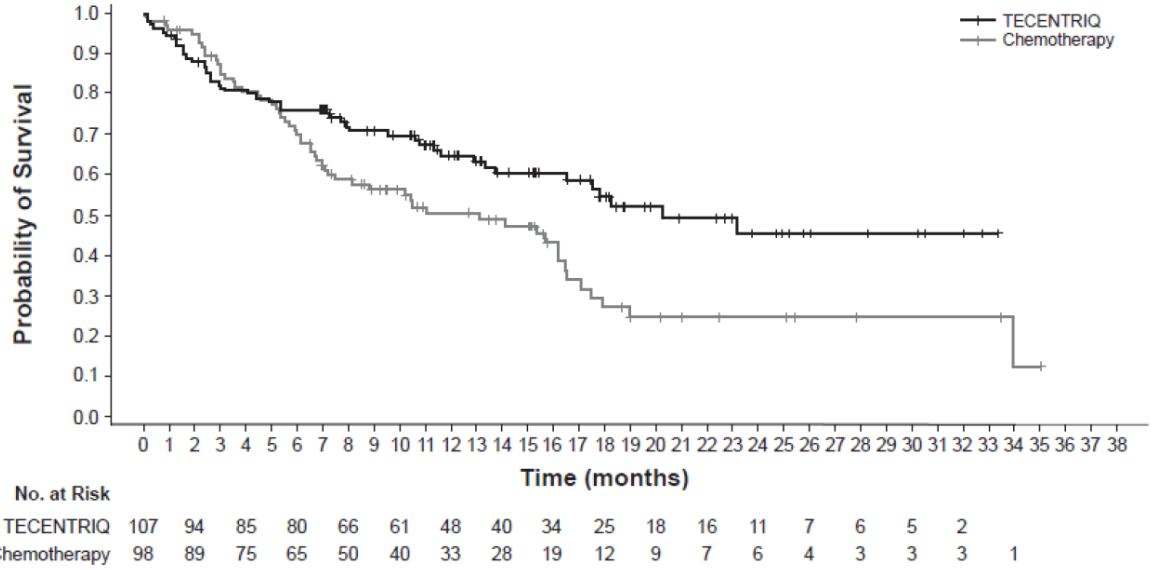
OS results for high PD-L1 subgroup (TCs ≥ 50% or ICs ≥ 10%) are presented in Table 21 and Figure 3. Statistically significant OS benefit was not observed for the TCs ≥ 5% or ICs ≥ 5% and TCs ≥ 1% or ICs ≥ 1% subgroups at prespecified analyses.

Table 21 Summary of Efficacy from Study GO29431 (IMpower110) in Patients with High PD-L1 Expression (TCs ≥ 50% or ICs ≥ 10%) by the VENTANA PD-L1 [SP142] Assay)

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

‡ Stratified by sex and ECOG performance status (0 vs 1)
CI=confidence interval; OS=overall survival; NE=not estimable.
The p-value (two-sided) was compared with the allocated alpha of 0.0413 at the interim analysis.

Figure 3 **Kaplan-Meier Plot of Overall Survival in Patients with high PD-L1 Expression (TCs ≥ 50% or ICs ≥ 10%)**



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

Study GO29436 (IMpower150) - First-Line Combination Therapy

Study Demographics and Trial Design

A phase III, open-label, multicentre, international randomized study, GO29436 (IMpower150), was conducted to evaluate the efficacy and safety of TECENTRIQ in combination with paclitaxel and carboplatin, with or without bevacizumab, in chemotherapy-naïve patients with metastatic non-squamous NSCLC. A total of 1202 patients were enrolled and were randomized in a 1:1:1 ratio to receive one of the treatment regimens. For this indication, only the comparison for Arm B versus Arm C has been reviewed and included in this product monograph.

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

- Arm A: TECENTRIQ 1200 mg, paclitaxel 175 mg/m^2 or 200 mg/m^2 and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles

- Arm B: TECENTRIQ 1200 mg, bevacizumab 15 mg/kg, paclitaxel 175 mg/m^2 or 200 mg/m^2, and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles

- Arm C: bevacizumab 15 mg/kg, paclitaxel 175 mg/m^2 or 200 mg/m^2, and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles

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

- Arm A: TECENTRIQ 1200 mg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity

- Arm B: TECENTRIQ 1200 mg and bevacizumab 15 mg/kg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity

- Arm C: bevacizumab 15 mg/kg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity

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

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

The PFS and OS results are based on the ITT-WT population, defined as the ITT population excluding EGFR mutations or ALK rearrangements.
Patients were excluded if they had history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; active or untreated brain metastases; clear tumour infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging. Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter.

The demographics and baseline disease characteristics of the study population were well balanced between the treatment arms. In this study, the median age was 63 years (range: 31 to 90), and 60% of patients were male. The majority of patients were white (82.2%), 12.5% of patients were Asian, and 2.0% of patients were Black or African American. Hispanic or Latino patients represents 9.6% of the enrolled patients. Patients of Asian race/ethnicity received paclitaxel at a dose of 175 mg/m^2 while the remaining patients received paclitaxel at a dose of 200 mg/m^2. Approximately 10% of patients had known EGFR mutations, 4% had known ALK rearrangements, 14% had liver metastases at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%). PD-L1 was TC3 and any IC in 12%, TC0/1/2 and IC2/3 in 12.8% and TC0/1/2 and IC0/1 in 75.2%.

The median duration of exposure to TECENTRIQ was 8.3 months in patients receiving

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

Study Results
The results of the primary analysis demonstrated a statistically significant PFS improvement in Arm B as compared to Arm C (HR: 0.62 [95% CI: 0.52, 0.74] median PFS 8.3 vs. 6.8 months). The improvement was maintained at the next PFS update which was conducted at the next OS interim analysis (HR: 0.59 [95% CI: 0.50, 0.70] median PFS 8.3 vs. 6.8 months); the results from this analysis are summarized in Table 22. Kaplan-Meier curves for PFS are presented in Figure 4.

The interim analysis of the co-primary endpoint OS was performed when all patients had a median follow up time of 19.6 months (Arm B) and 19.7 months (Arm C); the results of the analysis demonstrated a statistically significant OS improvement in Arm B as compared to Arm C (HR: 0.78 [95% CI: 0.64, 0.96] median OS 19.2 vs. 14.7 months); the results from this analysis are summarized in Table 22. Kaplan-Meier curves for OS are presented in Figure 5.

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

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

[1]Stratified by sex, presence of liver metastases and PD-L1 tumour expression on TC and IC
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1.; CI=confidence interval; OS=overall survival
[2] Based on the stratified log-rank test. The overall two-sided type I error of 0.05 was controlled by splitting it to 0.012 and 0.038, and allocated to the co-primary endpoints of PFS and OS, respectively. For the testing of OS, the statistically boundary for interim analysis was further accounted for following group sequential design using Lan-Demets approximation to the O'Brien-Fleming boundary

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

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

Figure 4 **Kaplan-Meier Curves for Progression Free Survival (PFS) in the ITT-WT Population in GO29436 (IMpower150)**

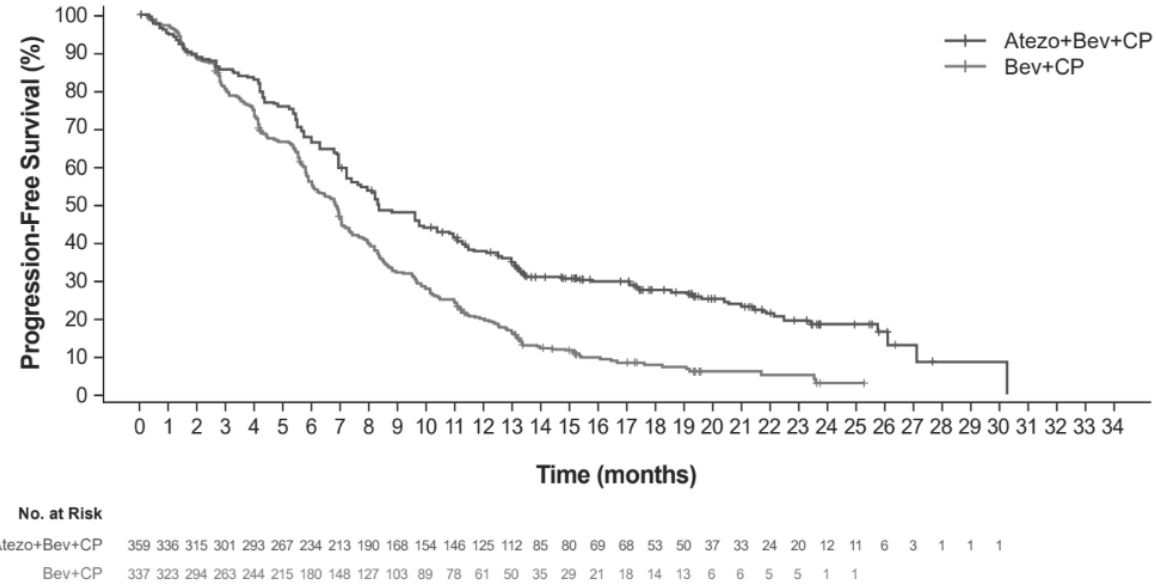
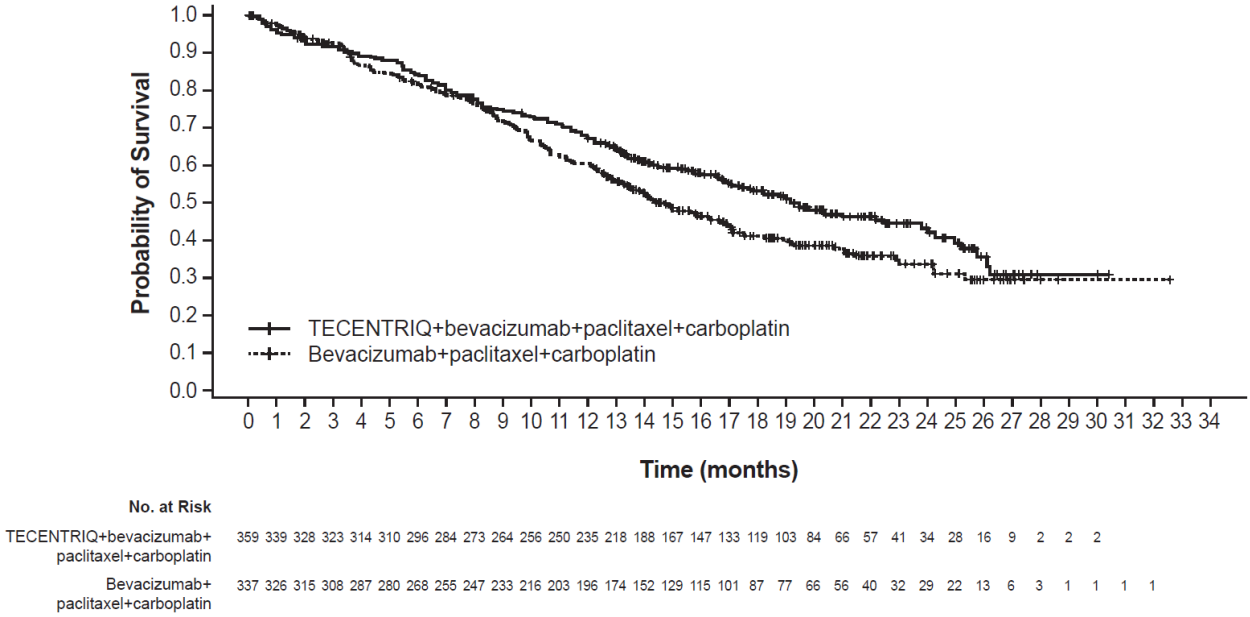


Figure 5 **Kaplan-Meier Curves for Overall Survival (OS) the ITT-WT Population in GO29436 (IMpower150)**



Study GO29537 (IMpower130) – First-Line Combination Therapy

Study Demographics and Trial Design

A Phase III, open-label, randomized study, GO29537 (IMpower130) was conducted to evaluate the efficacy and safety of TECENTRIQ in combination with nab-paclitaxel and carboplatin, in chemotherapy-naïve patients with metastatic non-squamous NSCLC. Patients including those with EGFR or ALK genomic tumour aberrations, were enrolled and were randomized in a 2:1 ratio to receive one of the treatment regimens described in Table 23. Randomization was stratified by sex, presence of liver metastases and PD-L1 tumour expression on tumour cells (TC) and tumour infiltrating cells (IC). Patients in treatment regimen B (Nab-paclitaxel ($100mg/m^2$)[b] + Carboplatin (AUC 6)[c]) were able to crossover and receive TECENTRIQ monotherapy following disease progression.

Table 23 Intravenous treatment regimens in GO29537 (IMpower130)

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

[a] Tecentriq is administered until loss of clinical benefit as assessed by investigator
[b] Nab-paclitaxel is administered on days 1, 8, and 15 of each cycle
[c] Nab-paclitaxel and carboplatin is administered until completion of 4-6 cycles, or progressive disease or unacceptable toxicity whichever occurs first

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

The demographics and baseline disease characteristics of the study population (n = 723) were well balanced between the treatment arms. The median age was 64 years (range 18 to 86). The majority of the patients were, male (57%), white (90%). 14.8% of patients had liver metastases at baseline, and most patients were current or previous smokers (88%). The majority of patients had baseline ECOG performance status of 1 (58.7%).

Study Results

The primary analysis was conducted in all patients, excluding those with EGFR or ALK genomic tumour aberrations (n = 679). Patients had a median survival follow up time of 18.6 months. Improvements in OS and PFS were demonstrated with TECENTRIQ + nab-paclitaxel + carboplatin compared to the control. The key results are summarized in Table 24 and Kaplan-Meier curves for OS and PFS are presented in Figure 6 and Figure 8, respectively.

All PD-L1 subgroups, regardless of expression, derived benefit in terms of OS and PFS; the results are summarized in Figure 7 and Figure 9. Consistent OS and PFS benefit was

demonstrated in all other pre-specified subgroups, with the exception of patients with liver metastases who did not show improved OS with TECENTRIQ, nab-paclitaxel and carboplatin, compared to nab-paclitaxel and carboplatin (HR of 1.04, 95% CI: 0.63,1.72).

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

Table 24 Summary of efficacy from GO29537 (IMpower130) in the Primary Analysis Population

Key efficacy endpoints	TECENTRIQ + nab-paclitaxel + carboplatin	nab-paclitaxel + carboplatin
Co-primary Endpoints		
OS	n = 451	n = 228
No. of deaths (%)	226 (50.1%)	131 (57.5%)
Median time to events (months)	18.6	13.9
95% CI	(16.0, 21.2)	(12.0, 18.7)
Stratified hazard ratio‡ (95% CI)	0.79 (0.64, 0.98)	
p-value	0.033	
12-month OS (%)	63	56
Investigator-assessed PFS (RECIST v1.1)	n = 451	n = 228
No. of events (%)	347 (76.9)	198 (86.8)
Median duration of PFS (months)	7.0	5.5
95% CI	(6.2, 7.3)	(4.4, 5.9)
Stratified hazard ratio‡ (95% CI)	0.64 (0.54, 0.77)	
p-value	< 0.0001	
12-month PFS (%)	29	14
Secondary Endpoints		
Investigator-assessed ORR (RECIST 1.1)	n = 447	n = 226
No. of confirmed responders (%)	220 (49.2%)	72 (31.9%)
95% CI	(44.5, 54.0)	(25.8, 38.4)
No. of complete response (%)	11 (2.5%)	3 (1.3%)
No. of partial response (%)	209 (46.8%)	69 (30.5%)
Investigator-assessed confirmed DOR (RECIST 1.1)	n = 220	n = 72
Median in months	8.4	6.1
95% CI	(6.9, 11.8)	(5.5, 7.9)

‡ Stratified by sex and PD-L1 tumour expression on TC and IC
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1.; CI=confidence interval; ORR=objective response rate; DOR=duration of response; OS=overall survival

Figure 6 **Kaplan-Meier Plot for Overall Survival GO29537 (IMpower130)**

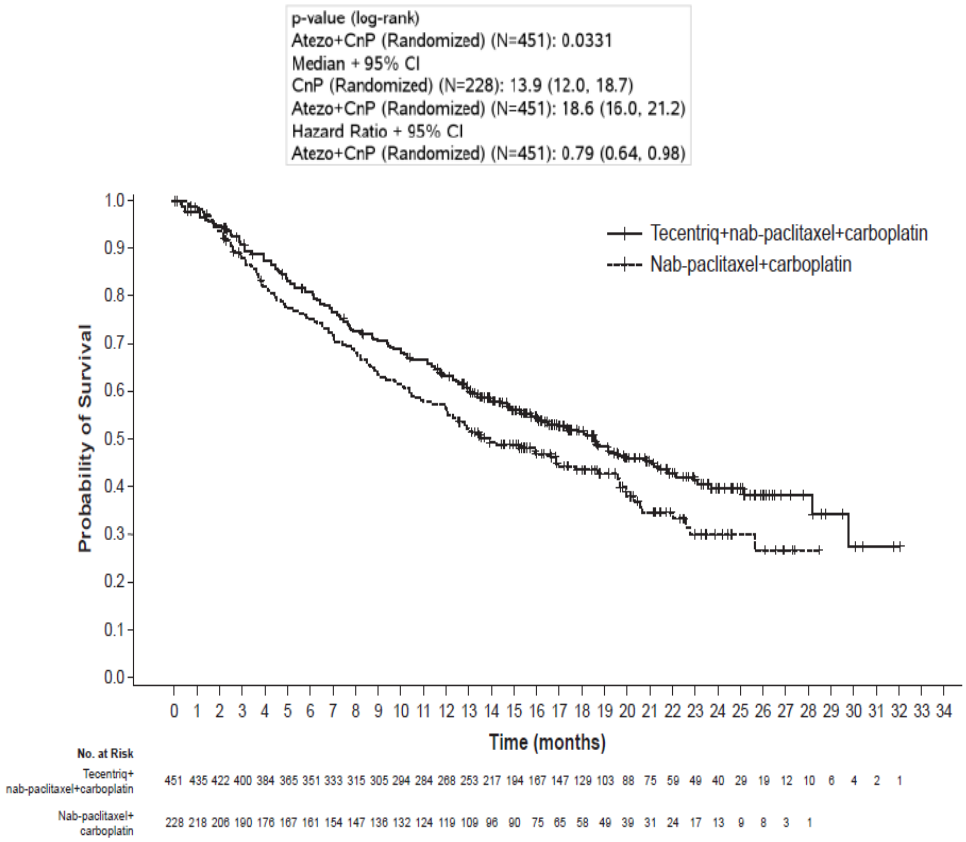


Figure 7 **Forest Plot of Overall Survival by PD-L1 expression GO29537 (IMpower130)**

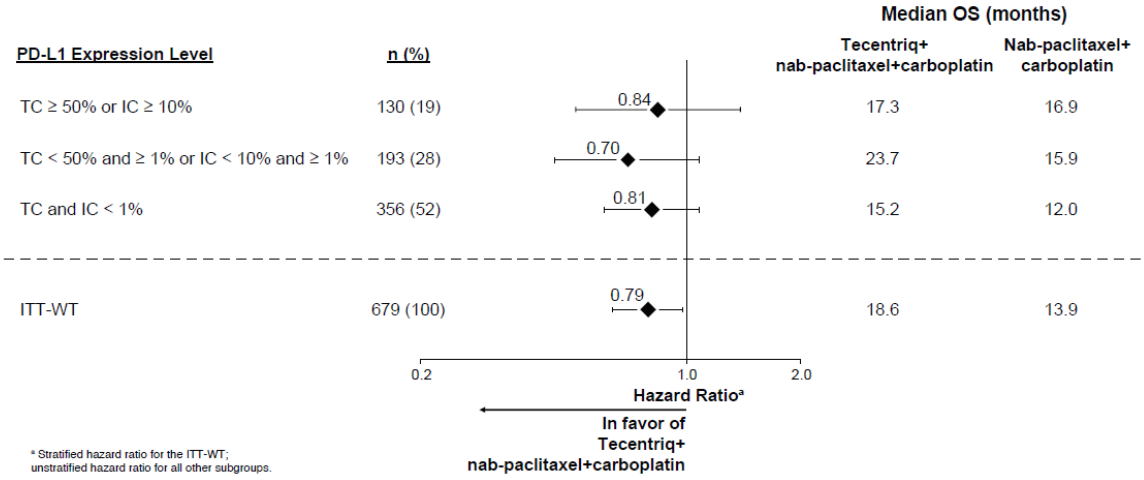


Figure 8 **Kaplan-Meier Plot for Progression Free Survival (PFS) GO29537 (IMpower130)**

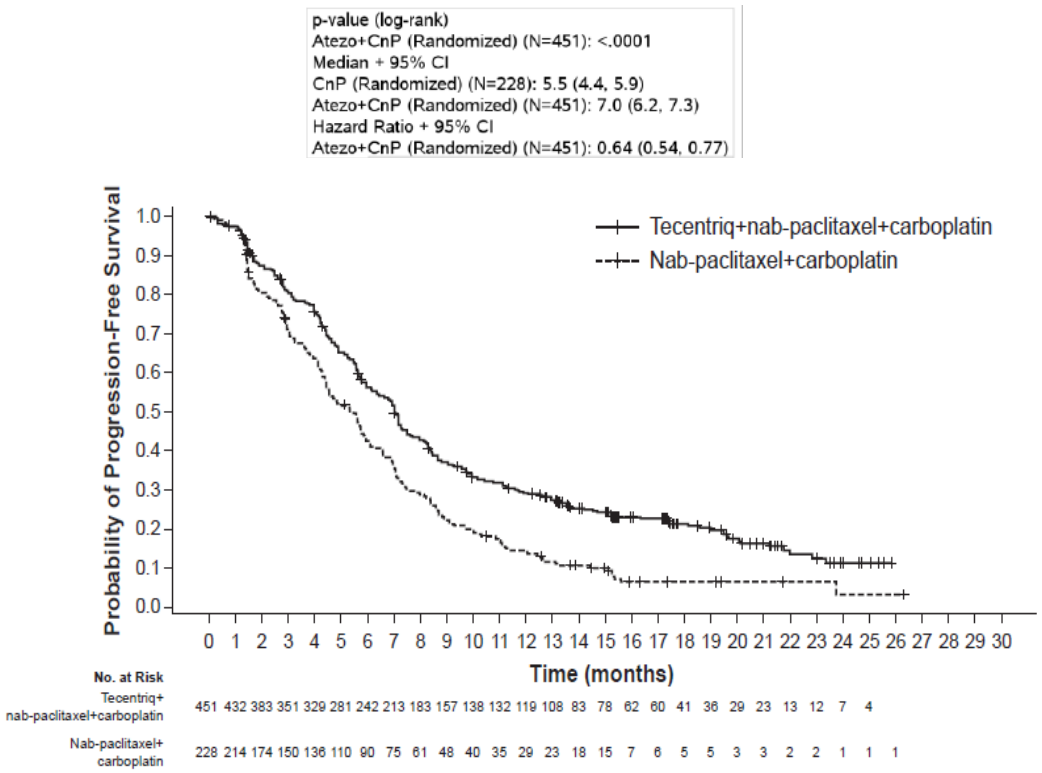
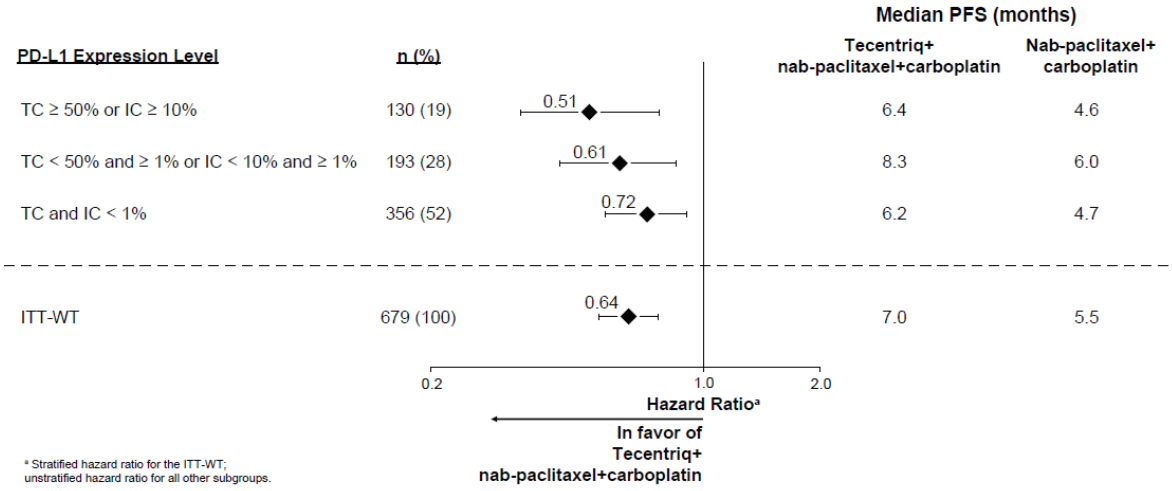


Figure 9 **Forest Plot of Progression Free Survival (PFS) by PD-L1 expression GO29537 (IMpower130)**



Study GO28915 (OAK) – Second Line Monotherapy

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 brain metastases at baseline, and most patients were current or previous smokers (82%). Baseline ECOG performance status was 0 (37%) or 1 (63%). Seventy-five percent of patients received only one prior platinum-based therapeutic regimen.

TECENTRIQ 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 25.

Table 25 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.

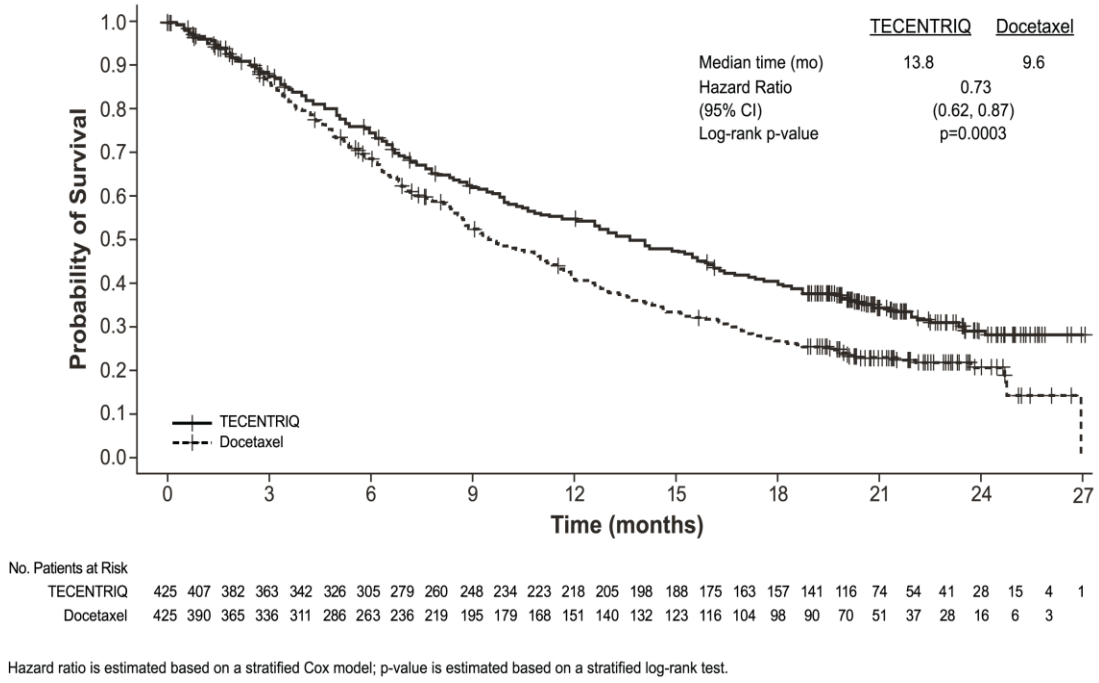
*All patients refer to the primary analysis population consisting of the first 850 randomized patients

[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 10.

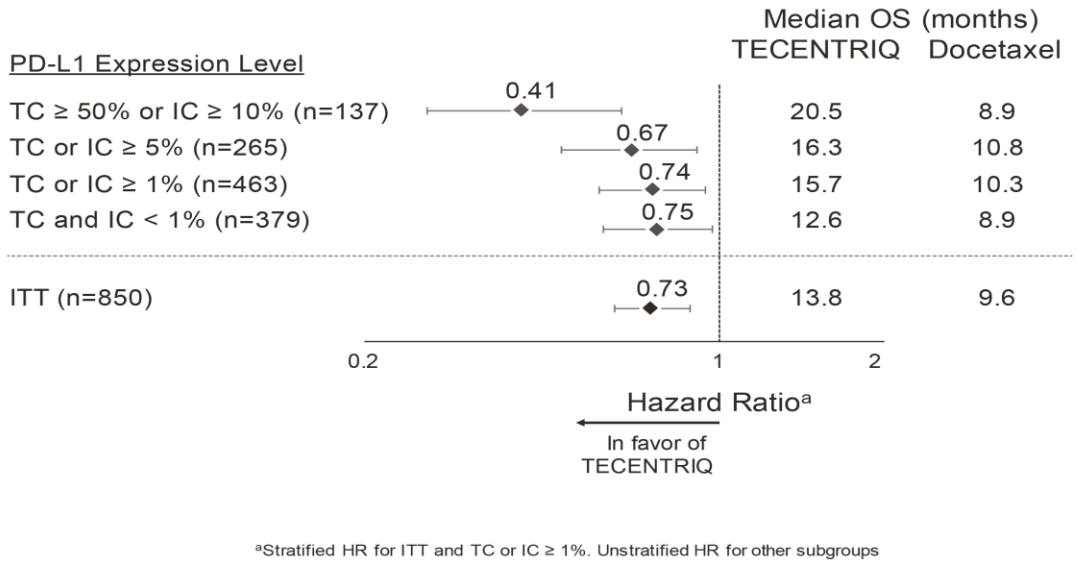
Figure 10 Kaplan-Meier Plot for Overall Survival in the Primary Analysis Population (All Patients, GO28915)



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

Figure 11 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 11 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).

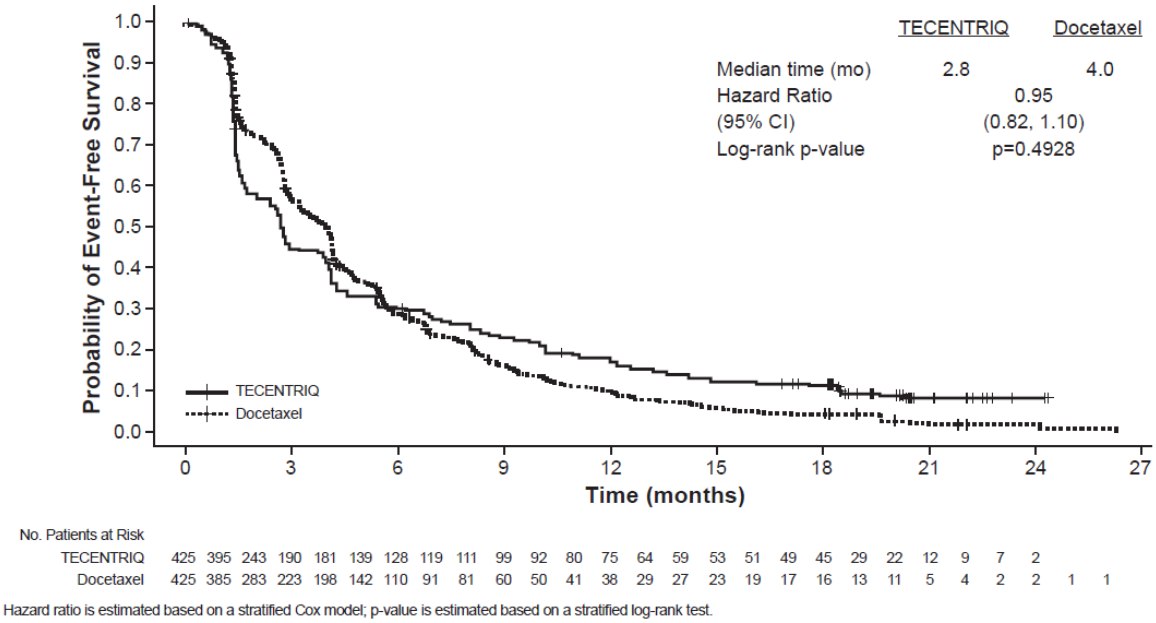
Tumour specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define the PD-L1 expression subgroups for pre-specified analyses. Of the 850 patients constituting the primary analysis population, 16% were classified as having the 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 12.

Figure 12 Kaplan-Meier Plot for Progression-Free 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.

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.

Unresectable or Metastatic Hepatocellular Carcinoma

Study YO40245 (IMbrave150) – First-Line Combination Therapy

Study Demographics and Trial Design

A global phase III, randomized, multi-centre, open-label study, YO40245 (IMbrave150), was conducted to evaluate the efficacy and safety of TECENTRIQ in combination with bevacizumab, compared to sorafenib, as first-line systemic treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC). A total of 501 patients were randomized (2:1) to receive either TECENTRIQ 1200 mg and 15 mg/kg of bevacizumab every 3 weeks administered via IV infusion (n = 336), or sorafenib 400 mg orally twice per day (n = 165). Randomization was stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion, extrahepatic spread (presence vs. absence), baseline alpha-fetoprotein (AFP) (<400 vs. ≥400 ng/mL) and ECOG performance status (0 vs. 1). Patients in both arms received treatment until loss of clinical benefit or unacceptable toxicity. Patients could discontinue either TECENTRIQ or bevacizumab (e.g., due to adverse events) and continue on single-agent therapy until loss of clinical benefit or unacceptable toxicity associated with the single-agent.

The study enrolled adults who were Child-Pugh A, ECOG 0 or1 and who had not received prior systemic treatment for HCC. Patients who were Child-Pugh B were excluded from the study and no information on the safety and efficacy of TECENTRIQ plus bevacizumab is available from YO40245 in these patients. Bleeding (including fatal events) is a known adverse reaction with bevacizumab and upper gastrointestinal bleeding is a common and life threatening complication in patients with HCC. Hence, patients were required to be evaluated for the presence of varices within 6 months prior to treatment and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding or high risk of bleeding.

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

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

Study Results

The primary efficacy endpoints were overall survival (OS) and independent review facility (IRF)-assessed progression free survival (PFS) according to RECIST v1.1. Tumour assessments were performed every 6 weeks for the first 54 weeks following Cycle 1, Day 1, and then every 9 weeks thereafter. The key efficacy results are summarized in Table 26. Kaplan-Meier curves for OS and PFS are presented in Figure 13 and Figure 14, respectively.

Table 26 Summary of Efficacy – YO40245 (IMbrave150)

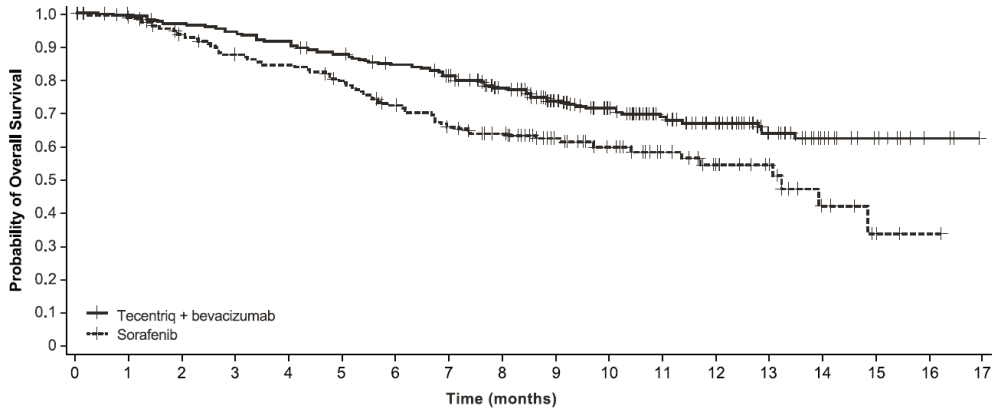
	TECENTRIQ in combination with Bevacizumab (N= 336)	**Sorafenib (N=165)**
Overall Survival		
Number of deaths (%)	96 (28.6%)	65 (39.4%)
Median time to event (months) 95% CI	NE (NE, NE)	13.2 (10.4, NE)
Stratified hazard ratio‡ (95% CI)	0.58 (0.42, 0.79)	
p-value[1]	0.0006	
IRF-assessed PFS, RECIST 1.1		
Number of events (%)	197 (58.6%)	109 (66.1%)
Median duration of PFS (months) (95% CI)	6.8 (5.8, 8.3)	4.3 (4.0, 5.6)
Stratified hazard ratio‡ 95% CI	0.59 (0.47, 0.76)	
p-value[1]	<0.0001	
IRF-assessed ORR, RECIST 1.1	**n=326**	**n=159**
Number of confirmed responders (%)	89 (27.3%)	19 (11.9%)
95% CI	(22.5, 32.5)	(7.4, 18.0)
Number of complete responses (%)	18 (5.5%)	0
Number of partial responses (%)	71 (21.8%)	19 (11.9%)
IRF-assessed ORR, HCC mRECIST	**n=325**	**n=158**
Number of responders (%)	108 (33.2%)	21 (13.3%)
(95% CI)	(28.1, 38.6)	(8.4, 19.6)
Number of complete responses (%)	33 (10.2%)	3 (1.9%)
Number of partial responses (%)	75 (23.1%)	18 (11.4%)

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

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

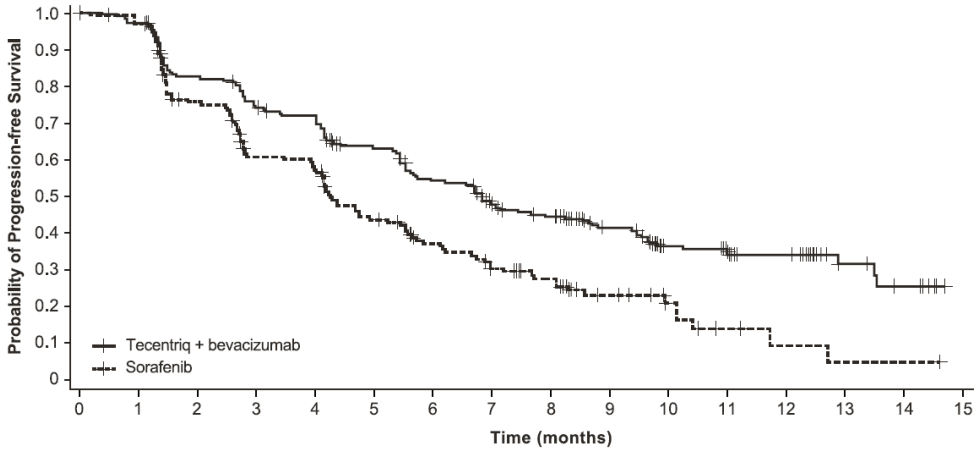
PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1; HCC mRECIST = Modified RECIST Assessment for Hepatocellular Carcinoma ; CI=confidence interval; ORR=objective response rate; OS=overall survival; NE=not estimable; N/A=not applicable

Figure 13 Kaplan-Meier Plot for Overall Survival YO40245 (IMbrave150)



No. of Patients at Risk																	
Tecentriq + bevacizumab	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE

Figure 14 Kaplan-Meier Plot for Progression-Free Survival per RECIST v1.1 YO40245 (IMbrave150)



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

NOC/c **<u>Locally Advanced or Metastatic Triple-Negative Breast Cancer (TNBC)</u>**

Study WO29522 (IMpassion130) - First-Line Combination Therapy

Study Demographics and Trial Design

Designed as a phase III, double-blind, two-arm, randomized, placebo-controlled study, WO29522 (IMpassion130), was conducted to evaluate the efficacy and safety of TECENTRIQ

in combination with nab-paclitaxel compared to placebo plus nab-paclitaxel, in patients with unresectable locally advanced or metastatic TNBC who had not received prior chemotherapy for metastatic disease. A total of 902 patients were enrolled and stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumour-infiltrating immune cells (IC) by the VENTANA PD-L1 (SP142) Assay. Patients were randomized to receive TECENTRIQ (840 mg) or placebo IV infusions on Days 1 and 15 of every 28-day cycle, plus nab-paclitaxel (100 mg/m^2) administered via IV infusion on Days 1, 8 and 15 of every 28-day cycle. Patients received treatment until radiographic disease progression per RECIST v1.1, or unacceptable toxicity. Tumour assessments were performed every 8 weeks (± 1 week) for the first 12 months after Cycle 1, day 1 and every 12 weeks (± 1 week) thereafter.

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

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

The major efficacy outcomes were investigator-assessed progression free survival (PFS) in the ITT and PD-L1 expressing patient population per RECIST v1.1 and overall survival (OS) in the ITT population. OS in the PD-L1 expressing patient population was an additional outcome dependent upon OS results in the ITT population. At the time of the first interim analysis, OS data were immature with 43% deaths in the ITT population.

Study Results
The key results of this study summarized in Table 27 and Figure 15, are described for patients with PD-L1 expression ≥1% with a median survival follow up of 13 months.

Table 27 Summary of Efficacy in Patients with PD-L1 Expression ≥1% (IMpassion130)

Efficacy endpoint	Tecentriq + nab-paclitaxel	Placebo + nab-paclitaxel
Primary endpoint		
Investigator-assessed PFS (RECIST v1.1)*	n=185	n=184
No. of events (%)	138 (74.6%)	157 (85.3%)
Median duration of PFS (months)	7.5	5.0
95% CI	(6.7, 9.2)	(3.8, 5.6)
Stratified hazard ratio‡ (95% CI)	0.62 (0.49, 0.78)	
p-value[1]	<0.0001	
Secondary endpoints		
Investigator-assessed ORR (RECIST 1.1)*	n=185	n=183
No. of responders (%)	109 (58.9%)	78 (42.6%)
95% CI	(51.5, 66.1)	(35.4, 50.1)
No. of complete response (%)	19 (10.3%)	2 (1.1%)
No. of partial response (%)	90 (48.6%)	76 (41.5%)
Investigator-assessed DOR*	n=109	n=78
Median in months	8.5	5.5
95% CI	(7.3, 9.7)	(3.7, 7.1)

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

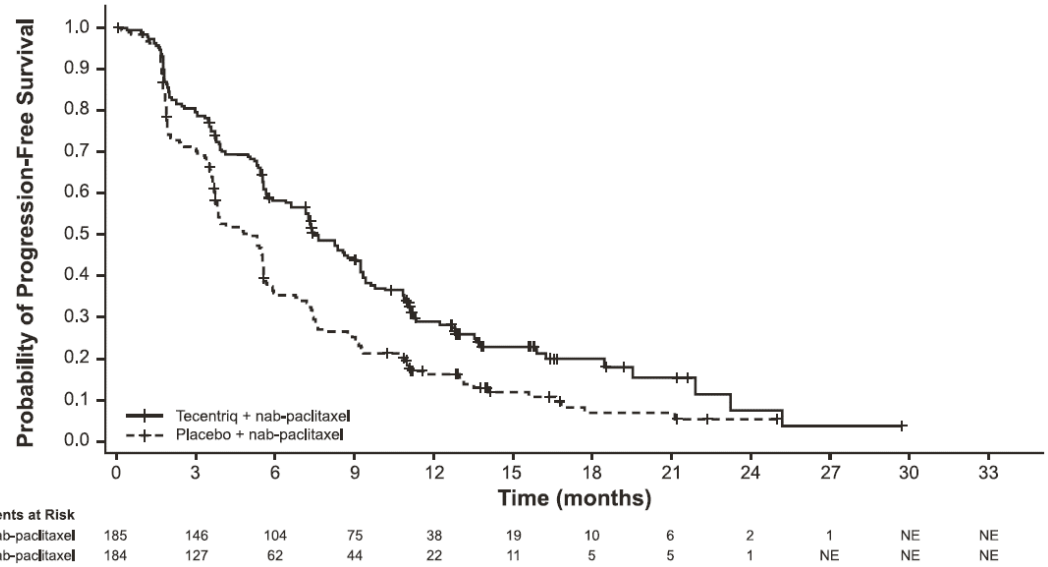
[1] Based on the stratified log-rank test at significance level 0.005 as per the pre-specified type I error control rate

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

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

The estimated HR of OS in patients with PD-L1 expression ≥ 1% at the time of the first interim analysis was HR 0.62 [95% CI: 0.45, 0.86]. This was not formally tested as per the pre-defined statistical analysis hierarchy; OS data were immature in the ITT population at the time of this analysis.

Figure 15 **Kaplan-Meier Plot for Progression Free Survival in Patients with PD-L1 Expression ≥1% (IMpassion130)**



NOC/c **Locally Advanced or Metastatic Urothelial Carcinoma**

Study GO29293 (IMvigor210) - Monotherapy

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 28.

Table 28 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	11.2, 19.3
Complete Response (CR) (%)	12 (12.0%)	5 (2.4%)	17 (5.5 %)
Partial Response (PR) (%)	14 (14.0%)	15 (7.1%)	29 (9.4%)
Additional Efficacy Endpoints			
DOR (IRF-Assessed; RECIST v1.1)			
Median, months (range)	29.7 (4.2, 31.2+)	20.9 (2.1+, 33.4+)	27.7 (2.1+, 33.4+)
95% CI	21.2, NE	8.3, 30.5	18.6, 30.5

* 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; NE=Not Evaluable.

In 59 patients with disease progression within 12 months of neoadjuvant or adjuvant therapy, the ORR was 22.0% (95% CI: 12.3%, 34.7%).

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 29.

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

Special Toxicology 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 29 Summary of Toxicology Studies

Study Type	Treatment Duration and Dosing Schedule	Species/ Test System	Gender and No. per group	Doses (mg/kg)	Findings/Conclusions
Non-GLP Repeat Dose Study	Once weekly for 2 weeks (3 total doses); IV	C57BL/6 and CD-1 mice	Female (total of n=32/ group); n=8/group for toxicity assessment; n=15/ group for immune assessment; n=9/group toxicokinetic assessment	<u>C57BL/6</u> 0 mg/kg 10 mg/kg 50 mg/kg <u>CD-1</u> 0 mg/kg 50 mg/kg	• 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.

Study Type	Treatment Duration and Dosing Schedule	Species/ Test System	Gender and No. per group	Doses (mg/kg)	Findings/Conclusions
Repeat Dose Study	Once weekly for 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.

Study Type	Treatment Duration and Dosing Schedule	Species/ Test System	Gender and No. per group	Doses (mg/kg)	Findings/Conclusions
Repeat Dose Study	Once weekly for 26 consecutive weeks (27 total doses)	Cynomolgus monkeys	5/sex/ group	0 mg/kg (IV) 5 mg/kg (IV) 15 mg/kg (IV) 50 mg/kg (IV)	• Atezolizumab-related anatomic pathology findings were limited to microscopic, minimal to slight, chronic-active, and multifocal arteritis/periarteritis in multiple organs of two animals at the terminal phase necropsy. One female at 15 mg/kg had arteritis/periarteritis in the heart, stomach, and vagina. Another female at 50 mg/kg had arteritis/periarteritis in the heart, pancreas, kidney, vagina, urinary bladder, stomach, gallbladder, colon, rectum, duodenum, jejunum, ileum, mandibular salivary gland, skin/subcutis, sternum/marrow, femur/marrow, uterus, larynx, and cervix.). These findings were not present following the 13-week recovery periods, indicating either resolution during the recovery period or lack of occurrence in the recovery cohorts. • Atezolizumab-related effect on menstrual cycles was noted in all females in the 50 mg/kg dose group during the dosing phase. This finding was characterized by an irregular cycle pattern with disturbed cycles and correlated with an absence of fresh corpora lutea in the ovaries at the time of the terminal phase necropsy. This effect showed reversibility during the recovery period. • There was no effect of atezolizumab on semen assessments, testicular evaluations, and serum testosterone level measurements in male cynomolgus monkeys. • The NOAEL was determined to be 5 mg/kg.
In vitro cytokine release assay	24 and 48 hrs	In vitro; isolated human peripheral blood mononuclear cells	3 donors	0, 0.25, 2.5, 25, and 250 µg/ml	• No apparent atezolizumab-dependent cytokine release was detected following 24- and 48-hour incubations with human PBMCs.

Study Type	Treatment Duration and Dosing Schedule	Species/ Test System	Gender and No. per group	Doses (mg/kg)	Findings/Conclusions
Tissue cross reactivity study	NA	In vitro; human and cynomolgus monkey tissues	3 donors each	0.25 or 1.25 µg/ml	• 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

For the following indications, 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:

- in combination with nab-paclitaxel, for the treatment of adult patients with unresectable, locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1%, and who have not received prior chemotherapy for metastatic disease.
- for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:
    - Have disease progression during or following platinum-containing chemotherapy; or
    - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

For the following indications, TECENTRIQ® has been issued marketing authorization **without conditions**:

- in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).
- as monotherapy for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have high PD-L1 expression (PD-L1 stained ≥ 50% of tumour cells [TCs] or PD-L1 stained tumour-infiltrating immune cells [ICs] covering ≥ 10% of the tumour area), as determined by a validated test and who do not have EGFR or ALK genomic tumour aberrations.
- in combination with bevacizumab, paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic non-squamous NSCLC.
- in combination with nab-paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) who do not have EGFR or ALK genomic tumour aberrations
- for the treatment of adult patients with locally advanced or metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving TECENTRIQ.
- in combination with bevacizumab, for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who require prior systemic therapy.

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.

PrTECENTRIQ® (te-SEN-trik)
Atezolizumab for injection

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?

Lung Cancer

- TECENTRIQ is used to treat a type of lung cancer called extensive-stage small cell lung cancer (ES-SCLC). TECENTRIQ is used if you have not received any prior chemotherapy for ES-SCLC. TECENTRIQ will be given to you in combination with carboplatin and etoposide.
- TECENTRIQ is used to treat a type of lung cancer called Non-Small Cell Lung Cancer (NSCLC).
    - TECENTRIQ may be used alone as your first treatment when your lung cancer:
        - has spread or grown, and
        - your tumour expresses high PD-L1, and
        - your tumour does not have an abnormal EGFR or ALK gene
    - TECENTRIQ may be used with bevacizumab and the chemotherapy medicines carboplatin and paclitaxel as your first treatment when your lung cancer:
        - has spread or grown, and
        - is a type of lung cancer called "non-squamous non-small cell lung cancer", and
        - your tumour does not have an abnormal EGFR or ALK gene
    - TECENTRIQ may be used when your lung cancer:
        - has spread or grown, and

- you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
- If your tumour has an abnormal EGFR or ALK gene, you should have also tried a therapy for tumours with these abnormal genes, and it did not work or is no longer working.

Breast Cancer

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

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.

Liver Cancer

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

How does TECENTRIQ 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 either 840 mg (in 14 mL) or 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 muscle weakness and muscle pain;
- have problems with your hormone producing glands including your thyroid, pituitary, adrenal glands, and pancreas;
- have diabetes;
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré Syndrome;
- have or have had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV);
- have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS);
- are taking medicine(s) that affect the immune system such as a steroid;
- have been given a live, attenuated vaccine;
- are taking medicine to treat an infection; or
- have any other medical conditions.

Pregnancy

- are pregnant or plan to become pregnant
    - TECENTRIQ can harm your unborn baby. Your healthcare provider should do a pregnancy test before you start treatment with TECENTRIQ.
    - 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.

Breast-feeding

- are breastfeeding or plan to breastfeed
    - TECENTRIQ may pass into your breast milk. You should not breast-feed for at least 5 months after the last dose.
    - You and your doctor should decide whether you will breast-feed or take TECENTRIQ. 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.
- **Females of Childbearing Potential:** TECENTRIQ may cause fertility problems, which may affect the ability to have children. Talk to your healthcare provider if you have concerns about fertility.
- **Driving and using machines**: It is not known whether TECENTRIQ 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:

- For bladder and lung cancer (first-line small cell lung cancer), the recommended dose of TECENTRIQ is 1200 milligrams (mg) every 3 weeks.
- For lung cancer (first-line and second-line non-small cell lung cancer), the recommended dose of TECENTRIQ is 840 mg every 2 weeks, 1200 every 3 weeks or 1680 mg every 4 weeks.
- For breast cancer, the recommended dose of TECENTRIQ is 840 mg every 2 weeks.
- For liver cancer, the recommended dose of TECENTRIQ is 1200 milligrams 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);
- lack of energy (asthenia);
- loss of appetite;
- nausea;
- fever;
- chills;
- diarrhea;
- vomiting;
- rash;
- shortness of breath;
- cough;
- lung infection;
- itching of the skin;
- stomach pain;
- joint pain;
- nerve pain;
- back pain;
- urinary tract infection;
- leg swelling caused by the retention of fluid in leg tissues (peripheral edema);
- underactive thyroid gland (hypothyroidism);
- elevated liver enzymes - may be a sign of an inflamed liver (shown in blood tests);
- low neutrophil (a white blood cell) levels in the blood (shown in blood tests); and
- difficulty sleeping (insomnia);

Common (may affect up to 1 in 10 people):
- low blood sugar, magnesium, potassium or sodium levels in the blood (shown in blood tests);
- flu-like illness;
- low blood pressure;
- high blood pressure;
- pain in the muscles and bones;
- low platelet count, which my make you more likely to bruise or bleed;
- nasal congestion;
- low oxygen levels which may cause shortness of breath;
- inflammation of the lungs;
- change in your sense of taste (dysgeusia);
- kidney pain;

- coughing up blood;
- overactive thyroid gland (hyperthyroidism);
- difficulty swallowing;
- sensitivity to light;
- acne-like skin problems; and
- shingles.

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

Very common (may affect more than 1 in 10 people):
- bleeding
- high blood pressure
- low number of red blood cells - which can cause tiredness and shortness of breath;
- low white blood cell count with and without fever – which can increase the risk of infection;
- constipation;
- mouth blisters or sores;
- low levels of magnesium – which can cause weakness and muscle cramping; and numbness and pain in the arms and legs.

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

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
VERY COMMON Inflammation or problems of the nerves (neuropathy): symptoms may include muscle weakness and numbness, tingling in hands and feet		✓
COMMON Inflammation of the lung (pneumonia, pneumonitis): symptoms may include new or worsening cough, shortness of breath, and chest pain		✓
Inflammation of the intestines (colitis): symptoms may include diarrhea (watery, loose or soft stools), blood in stools, or dark, tarry, sticky stools, and stomach pain		✓
Inflammation of the thyroid and adrenal glands (hypothyroidism, hyperthyroidism, or adrenal insufficiency): symptoms may include tiredness, weight loss, weight gain,		✓

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
change in mood, hair loss, constipation, dizziness, and sweating		
Severe reactions associated with infusion (events occurring during or within one day of having the infusion): symptoms may include fever, chills, shortness of breath, or wheezing, swelling of face or lips, itching or rash, and flushing		✓
Severe infections: symptoms may include fever, cough, frequent urination, flu-like symptoms, and pain when urinating		✓
Skin problems which can cause rash, itching, redness, skin blistering, sores, peeling		✓
Inflammation of the bladder (cystitis): symptoms may include persistent urge to urinate, cloudy or bloody urine, burning feeling when urinating, small amounts of urine frequently		✓
UNCOMMON Inflammation of the liver (hepatitis): symptoms may include yellowing of skin or eyes, nausea, vomiting, bleeding or bruising more easily than normal, dark urine, and stomach pain		✓
Inflammation of the pancreas (pancreatitis): symptoms may include abdominal pain, nausea and vomiting		✓
Type 1 diabetes mellitus, including acid in the blood produced from diabetes (diabetic ketoacidosis): symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, weight loss, and feeling tired		✓
Inflammation of the pituitary gland (symptoms may include issues with regulating body temperature)		✓
Severe skin reactions: very severe blistering skin condition, may appear with ulcers of the skin and digestive tract, and may lead to the loss of a large portion of skin		✓
RARE Inflammation of the brain (encephalitis) or inflammation of the membrane around the spinal cord and brain (meningitis): symptoms may include neck stiffness, headache, fever, chills, vomiting, eye sensitivity to light, confusion and sleepiness		✓
Inflammation of the eyes: symptoms may include blurry vision, double vision, or other vision problems, and eye pain or redness		✓
Inflammation of the heart muscles (myocarditis): symptoms may include chest pain, shortness of breath, irregular heartbeat, decreased exercise tolerance, ankle swelling		✓

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
Inflammation of the muscles (myositis): symptoms may include muscle weakness and muscle pain that may lead to difficulty moving, breathing, swallowing, and/or dark brown or red color urine		✓
Inflammation of the kidneys (nephritis): symptoms may include changes in urine output and color, pain in pelvis, and swelling of the body		✓
Inflammation of the pituitary gland (hypophysitis): symptoms may include fatigue and headaches that will not go away, increased thirst, increased urination, and changes in vision		✓

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

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:
TECENTRIQ 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 (2-8ºC). 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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Roche Hoffmann-La Roche Limited
Mississauga, ON L5N 5M8