

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **TECENTRIQ** safely and effectively. See full prescribing information for **TECENTRIQ**.

**TECENTRIQ** (atezolizumab) injection, for intravenous use  
Initial U.S. Approval: 2016

### RECENT MAJOR CHANGES

Indications and Usage, Urothelial Carcinoma (1.1)	7/2018
Indications and Usage, Non-Small Cell Lung Cancer (1.2)	12/2018
Dosage and Administration (2.3)	7/2018
Warnings and Precautions, Pneumonitis (5.1)	12/2018
Warnings and Precautions, Hepatitis (5.2)	12/2018
Warnings and Precautions, Colitis (5.3)	12/2018
Warnings and Precautions, Endocrinopathies (5.4)	12/2018
Warnings and Precautions, Infections (5.6)	12/2018
Warnings and Precautions, Infusion-Related Reactions (5.7)	12/2018

### INDICATIONS AND USAGE

**TECENTRIQ** is a programmed death-ligand 1 (PD-L1) blocking antibody indicated in:

#### Urothelial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering  $\geq 5\%$  of the tumor area), as determined by an FDA-approved test, or
  - are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or
  - have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy. (1.1)

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.1)

#### Non-Small Cell Lung Cancer (NSCLC)

- in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment, of patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations. (1.2)
- for the treatment of patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving **TECENTRIQ**. (1.2)

### DOSAGE AND ADMINISTRATION

#### Metastatic Urothelial Carcinoma or Previously Treated NSCLC

- **TECENTRIQ** 1200 mg intravenously (IV) over 60 minutes every 3 weeks. First-line Treatment of Non-squamous NSCLC
- **TECENTRIQ** 1200 mg IV over 60 minutes, followed by bevacizumab, paclitaxel and carboplatin, on the same day, every 3 weeks for a maximum

of 4-6 cycles. Following completion of chemotherapy, **TECENTRIQ** 1200 mg IV, following by bevacizumab, every 3 weeks.

If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. (2.2, 2.3)

### DOSAGE FORMS AND STRENGTHS

Injection: 1200 mg/20 mL (60 mg/mL) solution in a single-dose vial (3)

### CONTRAINDICATIONS

None. (4)

### WARNINGS AND PRECAUTIONS

- Immune-Mediated Pneumonitis: Withhold or permanently discontinue based on severity of pneumonitis. (2.4, 5.1)
- Immune-Mediated Hepatitis: Monitor for changes in liver function. Withhold or permanently discontinue based on severity of transaminase or total bilirubin elevation. (2.4, 5.2)
- Immune-Mediated Colitis: Withhold or permanently discontinue based on severity of colitis. (2.4, 5.3)
- Immune-Mediated Endocrinopathies (2.4, 5.4):
  - Hypophysitis: Withhold based on severity of hypophysitis.
  - Thyroid Disorders: Monitor for changes in thyroid function. Withhold based on severity of hyperthyroidism.
  - Adrenal Insufficiency: Withhold based on severity of adrenal insufficiency.
  - Type 1 Diabetes Mellitus: Withhold based on severity of hyperglycemia.
- Infections: Withhold for severe or life-threatening infection. (2.4, 5.6)
- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue based on severity of infusion reactions. (2.4, 5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

### ADVERSE REACTIONS

- Most common adverse reactions (reported in  $\geq 20\%$  of patients) with **TECENTRIQ** as a single agent were fatigue, nausea, constipation, cough, dyspnea, and decreased appetite. (6.1)
- The most common adverse reactions (reported in  $\geq 20\%$  of patients) with **TECENTRIQ** in combination with bevacizumab, paclitaxel, and carboplatin were fatigue/asthenia, alopecia, nausea, diarrhea, constipation, decreased appetite, arthralgia, hypertension, and peripheral neuropathy. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2018

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Locally Advanced or Metastatic Urothelial Carcinoma

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

- are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering  $\geq 5\%$  of the tumor area), as determined by an FDA-approved test, or
- are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or
- have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials [see *Clinical Studies (14.1)*].

#### 1.2 Metastatic Non-Small Cell Lung Cancer

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

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Selection of Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

Select cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial carcinoma for treatment with TECENTRIQ based on the PD-L1 expression on tumor-infiltrating immune cells [see *Clinical Studies (14.1)*].

Information on FDA-approved tests for the determination of PD-L1 expression in locally advanced or metastatic urothelial carcinoma is available at:

<http://www.fda.gov/CompanionDiagnostics>

#### 2.2 Recommended Dosage for TECENTRIQ for Locally Advanced or Metastatic Urothelial Carcinoma or Previously Treated NSCLC

The recommended dosage of TECENTRIQ is 1200 mg intravenously over 60 minutes every 3 weeks until disease progression or unacceptable toxicity. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

#### 2.3 Recommended Dosage for TECENTRIQ for First-line Treatment of Metastatic Non-squamous NSCLC

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.

If the first infusion of TECENTRIQ is tolerated, all subsequent infusions may be delivered over 30 minutes.

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.

Refer to the Prescribing Information for bevacizumab, paclitaxel, and carboplatin for recommended dosing information.

## 2.4 Dosage Modifications for Adverse Reactions

No dose reductions of TECENTRIQ are recommended. Recommendations for dosage modifications are provided in Table 1.

**Table 1: Recommended Dosage Modifications for Adverse Reactions**

<b>Adverse Reaction</b>	<b>Severity of Adverse Reaction<sup>1</sup></b>	<b>Dosage Modifications</b>
Pneumonitis [ <i>see Warnings and Precautions (5.1)</i> ]	Grade 2	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grade 3 or 4	Permanently discontinue
Hepatitis [ <i>see Warnings and Precautions (5.2)</i> ]	AST or ALT more than 3 and up to 8 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	AST or ALT more than 8 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Colitis or diarrhea [ <i>see Warnings and Precautions (5.3)</i> ]	Grade 2 or 3	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grade 4	Permanently discontinue
Endocrinopathies (including but not limited to hypophysitis, adrenal insufficiency, hyperthyroidism, and type 1 diabetes mellitus) [ <i>see Warnings and Precautions (5.4)</i> ]	Grade 2, 3, or 4	Withhold dose until Grade 1 or resolved and clinically stable on hormone replacement therapy.
Other immune-mediated adverse reactions involving a major organ [ <i>see Warnings and Precautions (5.5)</i> ]	Grade 3	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)

<b>Adverse Reaction</b>	<b>Severity of Adverse Reaction<sup>1</sup></b>	<b>Dosage Modifications</b>
	Grade 4	Permanently discontinue
Infections [ <i>see Warnings and Precautions (5.6)</i> ]	Grade 3 or 4	Withhold dose until Grade 1 or resolved
Infusion-Related Reactions [ <i>see Warnings and Precautions (5.7)</i> ]	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 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

<sup>1</sup> National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0

## **2.5 Preparation and Administration**

### Preparation

Visually inspect drug product for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the vial if the solution is cloudy, discolored, or visible particles are observed. Do not shake the vial.

Prepare the solution for infusion as follows:

- Withdraw 20 mL of TECENTRIQ from the vial.
- Dilute into a 250 mL polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% Sodium Chloride Injection, USP.
- Dilute with 0.9% Sodium Chloride Injection only.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard used or empty vials of TECENTRIQ.

### Storage of Infusion Solution

This product does not contain a preservative.

Administer immediately once prepared. If diluted TECENTRIQ infusion solution is not used immediately, store solution either:

- At room temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration of the infusion, or

- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from time of preparation.

Do not freeze.

Do not shake.

### Administration

Administer the initial infusion over 60 minutes through an intravenous line with or without a sterile, non-pyrogenic, low-protein binding in-line filter (pore size of 0.2–0.22 micron). If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

Do not coadminister other drugs through the same intravenous line.

Do not administer as an intravenous push or bolus.

## **3 DOSAGE FORMS AND STRENGTHS**

Injection: 1200 mg/20 mL (60 mg/mL) colorless to slightly yellow solution in a single-dose vial.

## **4 CONTRAINDICATIONS**

None.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Immune-Mediated Pneumonitis**

TECENTRIQ can cause immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids, including fatal cases. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids, prednisone 1–2 mg/kg/day or equivalents, followed by a taper for Grade 2 or higher pneumonitis. Withhold or permanently discontinue TECENTRIQ based on the severity [*see Dosage and Administration (2.4)*].

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single agent [*see Adverse Reactions (6.1)*], pneumonitis occurred in 2.5% of patients, including Grade 3 (0.6%), Grade 4 (0.1%), and Grade 5 (<0.1%) immune-mediated pneumonitis. The median time to onset of pneumonitis was 3.6 months (3 days to 20.5 months) and median duration of pneumonitis was 1.4 months (1 day to 15.1 months). Pneumonitis resolved in 67% of patients. Pneumonitis led to discontinuation of TECENTRIQ in 0.4% of the 2616 patients. Systemic corticosteroids were required in 1.5% of patients, including 0.8% who received high-dose corticosteroids (prednisone  $\geq$  40 mg per day or equivalent) for a median duration of 4 days (1 day to 45 days) followed by a corticosteroid taper.

The incidence of pneumonitis in 793 TECENTRIQ-treated patients in IMpower150 was 4.5%, including Grade 3-4 (1.8%) events. Systemic corticosteroids were required in 4% of patients, including 2.8% who received high-dose corticosteroids (prednisone  $\geq$  40 mg per day or equivalent) for a median duration of 3 days (1 day to 43 days) followed by a corticosteroid taper.

### **5.2 Immune-Mediated Hepatitis**

TECENTRIQ can cause liver test abnormalities and immune-mediated hepatitis, defined as requiring use of corticosteroids. Fatal cases have been reported. Monitor patients for signs and symptoms of hepatitis, during and after discontinuation of TECENTRIQ, including clinical chemistry monitoring. Administer corticosteroids, prednisone 1–2 mg/kg/day or equivalents, followed by a taper for Grade 2 or higher elevations of ALT, AST and/or total bilirubin. Interrupt or permanently discontinue TECENTRIQ based on the severity [*see Dosage and Administration (2.4)*].

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ [see *Adverse Reactions (6.1)*], hepatitis occurred in 9% of patients, including Grade 3 (2.3%), Grade 4 (0.6%), and Grade 5 (< 0.1%). The median time to onset of hepatitis was 1.4 months (1 day to 25.8 months) and median duration was 24 days (1 day to 13 months). Hepatitis resolved in 71% of patients. Hepatitis led to discontinuation of TECENTRIQ in 0.4% of 2616 patients. Systemic corticosteroids were required in 2% of the patients, with 1.3% requiring high-dose corticosteroids for a median duration of 3 days (1 day to 35 days) followed by a corticosteroid taper.

The incidence of hepatitis in 793 TECENTRIQ-treated patients in IMpower150 was 12.1%, including Grade 3-4 (4.0%) events. Systemic corticosteroids were required in 3.8% of the patients, with 2.6% requiring high-dose corticosteroids for a median duration of 7 days (1 day to 68 days) followed by a corticosteroid taper.

### **5.3 Immune-Mediated Colitis**

TECENTRIQ can cause immune-mediated colitis or diarrhea, defined as requiring use of corticosteroids. Monitor patients for signs and symptoms of diarrhea or colitis. Withhold treatment with TECENTRIQ for Grade 2 or 3 diarrhea or colitis. If symptoms persist for longer than 5 days or recur, administer corticosteroids, prednisone 1–2 mg/kg/day or equivalents, followed by a taper for Grade 2 diarrhea or colitis. Interrupt or permanently discontinue TECENTRIQ based on the severity [see *Dosage and Administration (2.4)* and *Adverse Reactions (6.1)*].

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single agent [see *Adverse Reactions (6.1)*], diarrhea or colitis occurred in 20%, including Grade 3 (1.4%) events. The median time to onset of diarrhea or colitis was 1.5 months (1 day to 41 months). Diarrhea and colitis resolved in 85% of the patients. Diarrhea or colitis led to discontinuation of TECENTRIQ in 0.2% of 2616 patients. Systemic corticosteroids were required in 1.1% of patients and high-dose corticosteroids was required in 0.4% patients with a median duration of 3 days (1 day to 11 days) followed by a corticosteroid taper.

The incidence of diarrhea or colitis in 793 TECENTRIQ-treated patients in IMpower150 was 27%, including Grade 3-4 (4.3%) events. Systemic corticosteroids were required in 4.5% of patients and high-dose corticosteroids was required in 3.2% patients with a median duration of 5 days (1 day to 103 days) followed by a corticosteroid taper.

### **5.4 Immune-Mediated Endocrinopathies**

TECENTRIQ can cause immune-mediated endocrinopathies, including thyroid disorders, adrenal insufficiency, and type 1 diabetes mellitus, including diabetic ketoacidosis, and hypophysitis/hypopituitarism.

*Thyroid Disorders:* Monitor thyroid function prior to and periodically during treatment with TECENTRIQ. Initiate hormone replacement therapy or medical management of hyperthyroidism as clinically indicated. Continue TECENTRIQ for hypothyroidism and interrupt for hyperthyroidism based on the severity [see *Dosage and Administration (2.4)*].

In clinical studies enrolling 2616 patients who received TECENTRIQ [see *Adverse Reactions (6.1)*], hypothyroidism occurred in 4.6% of patients, and 3.8% of patients required the use of hormone replacement therapy. Hyperthyroidism occurred in 1.6% of patients. One patient experienced acute thyroiditis.

The incidence of hypothyroidism in 793 TECENTRIQ-treated patients in IMpower150 was 11.3%, and 8.6% of patients required hormone replacement therapy. Hyperthyroidism occurred in 3.4% of patients and 0.1% experienced thyroiditis.

*Adrenal Insufficiency:* Monitor patients for clinical signs and symptoms of adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate prednisone 1 to 2 mg/kg/day or equivalents, followed by a taper and hormone replacement as clinically indicated. Interrupt TECENTRIQ based on the severity [see *Dosage and Administration (2.4)*].

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single agent, adrenal insufficiency occurred in 0.4% of patients, including Grade 3 (< 0.1%) adrenal insufficiency. Median time to onset was 5.7 months (3 days to 19 months). There was insufficient information to adequately characterize the median duration of adrenal insufficiency. Adrenal insufficiency resolved in 27% of patients. Systemic corticosteroids were required in 0.3% of 2616 patients, including 0.1% who required high-dose corticosteroids.

The incidence of adrenal insufficiency in 793 TECENTRIQ-treated patients in Study IMpower150 was 0.8%.

*Type 1 Diabetes Mellitus:* Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Interrupt TECENTRIQ based on the severity [see *Dosage and Administration (2.4)*].

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single agent, type 1 diabetes mellitus occurred in < 0.1% of patients. Insulin was required in one patient. The incidence of new onset diabetes mellitus in 698 TECENTRIQ-treated patients in Study IMpower150 was 0.1%

*Hypophysitis:* For Grade 2 or higher hypophysitis, initiate prednisone 1–2 mg/kg/day or equivalents, followed by a taper and hormone replacement therapy as clinically indicated. Interrupt TECENTRIQ based on the severity [see *Dosage and Administration (2.4)*].

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single agent, Grade 2 hypophysitis occurred in < 0.1% of patients.

The incidence of hypophysitis in 793 TECENTRIQ-treated patients in IMpower150 was 0.4%, including Grade 2 (0.1%) and Grade 3 (0.1%) events.

## **5.5 Other Immune-Mediated Adverse Reactions**

TECENTRIQ can cause severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system. While immune-mediated reactions usually manifest during treatment with TECENTRIQ, immune-mediated adverse reactions can also manifest after discontinuation of TECENTRIQ.

For suspected Grade 2 immune-mediated adverse reactions, exclude other causes and initiate corticosteroids as clinically indicated. For severe (Grade 3 or 4) adverse reactions, administer corticosteroids, prednisone 1 to 2 mg/kg/day or equivalents, followed by a taper. Interrupt or permanently discontinue TECENTRIQ, based on the severity of the reaction [see *Dosage and Administration (2.4)*].

If uveitis occurs in combination with other immune-mediated adverse reactions, evaluate for Vogt-Koyanagi-Harada syndrome, which has been observed with other products in this class and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of < 1% in 2616 patients who received TECENTRIQ or were reported in other products in this class [see *Adverse Reactions (6.1)*]:

*Cardiac:* myocarditis

*Dermatologic:* bullous dermatitis, pemphigoid, erythema multiforme, Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN).

*Gastrointestinal:* pancreatitis, including increases in serum amylase or lipase levels

*General:* systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis

*Hematological:* autoimmune hemolytic anemia, immune thrombocytopenic purpura.

*Musculoskeletal:* myositis, rhabdomyolysis.

*Neurological:* Guillain-Barre syndrome, myasthenia syndrome/myasthenia gravis, demyelination, immune-related meningoencephalitis, aseptic meningitis, encephalitis, facial and abducens nerve paresis, polymyalgia rheumatica, autoimmune neuropathy, and Vogt-Koyanagi-Harada syndrome.

*Ophthalmological:* uveitis, iritis.

*Renal:* nephrotic syndrome, nephritis.

*Vascular:* vasculitis

## **5.6 Infections**

TECENTRIQ can cause severe infections including fatal cases. Monitor patients for signs and symptoms of infection. For Grade 3 or higher infections, withhold TECENTRIQ and resume once clinically stable [see *Dosage and Administration (2.4)* and *Adverse Reactions (6.1)*].

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ [see *Adverse Reactions (6.1)*], infections occurred in 42% of patients, including Grade 3 (8.7%), Grade 4 (1.5%), and Grade 5 (1%). In patients with urothelial carcinoma, the most common Grade 3 or higher infection was urinary tract infections, occurring in 6.5% of patients. In patients with NSCLC, the most common Grade 3 or higher infection was pneumonia, occurring in 3.8% of patients.

The incidence of infections in 793 TECENTRIQ-treated patients in IMpower150 was 50.1%, including Grade 3 (12%), Grade 4 (1.9%), and Grade 5 (0.4%). The most common Grade 3 or higher infection was pneumonia, occurring in 4.8% of patients.

## **5.7 Infusion-Related Reactions**

TECENTRIQ can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue TECENTRIQ based on the severity [see *Dosage and Administration (2.4)*]. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single agent [see *Adverse Reactions (6.1)*], infusion-related reactions occurred in 1.3% of patients, including Grade 3 (0.2%). The incidence of infusion-related reactions in 793 TECENTRIQ-treated patients in IMpower150 was 3.8%, including Grade 3-4 (0.8%).

## **5.8 Embryo-Fetal Toxicity**

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death.

Verify pregnancy status of females of reproductive potential prior to initiating TECENTRIQ. Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose [see *Use in Specific Populations (8.1, 8.3)*].

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Immune-Mediated Pneumonitis [*see Warnings and Precautions (5.1)*]
- Immune-Mediated Hepatitis [*see Warnings and Precautions (5.2)*]
- Immune-Mediated Colitis [*see Warnings and Precautions (5.3)*]
- Immune-Mediated Endocrinopathies [*see Warnings and Precautions (5.4)*]
- Other Immune-Mediated Adverse Reactions [*see Warnings and Precautions (5.5)*]
- Infections [*see Warnings and Precautions (5.6)*]
- Infusion-Related Reactions [*see Warnings and Precautions (5.7)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in Warnings and Precautions reflect exposure to TECENTRIQ as a single agent in 2616 patients in two randomized, active-controlled studies (POPLAR, OAK) and four open-label, single arm studies (PCD4989g, IMvigor210, BIRCH, FIR) which enrolled 524 patients with metastatic urothelial carcinoma, 1636 patients with metastatic NSCLC, and 456 patients with other tumor types or in combination with paclitaxel and carboplatin with or without bevacizumab in 793 patients with metastatic non-squamous NSCLC from one randomized, open-label, active-controlled trial (IMpower150). TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks in all studies except PCD4989g. Among the 2616 patients who received single-agent TECENTRIQ, 36% were exposed for longer than 6 months and 20% were exposed for longer than 12 months. Among 393 patients who received TECENTRIQ in combination with bevacizumab, paclitaxel, and carboplatin and 400 patients who received TECENTRIQ in combination with paclitaxel and carboplatin in IMpower150, 65% and 54%, respectively, were exposed to TECENTRIQ for longer than 6 months and 36% and 28%, respectively, were exposed to TECENTRIQ for longer than 12 months.

The data described in this section were obtained from one open-label, single arm, multiple cohort study (IMvigor210) and two randomized open-label, active-controlled studies (OAK and IMpower150) in which TECENTRIQ was administered to 429 patients with locally advanced and metastatic urothelial carcinoma and 1002 patients with metastatic NSCLC. In these trials, TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks.

#### Locally Advanced or Metastatic Urothelial Carcinoma

##### *Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma*

The safety of TECENTRIQ was evaluated in IMvigor 210 (Cohort 1), a multicenter, open-label, single-arm trial that included 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy and were either previously untreated or had disease progression at least 12 months after neoadjuvant or adjuvant chemotherapy [*see Clinical Studies (14.1)*]. Patients received TECENTRIQ 1200 mg intravenously every 3 weeks until either unacceptable toxicity or disease progression. The median duration of exposure was 15 weeks (0 to 87 weeks).

The most common adverse reactions ( $\geq 20\%$ ) were fatigue (52%), decreased appetite (24%), diarrhea (24%), and nausea (22%). The most common Grade 3–4 adverse reactions ( $\geq 2\%$ ) were fatigue, urinary tract infection, anemia, diarrhea, blood creatinine increase, intestinal obstruction,

ALT increase, hyponatremia, decreased appetite, sepsis, back/neck pain, renal failure, and hypotension.

Five patients (4.2%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, cardiac arrest, myocardial infarction, respiratory failure, or respiratory distress. One additional patient (0.8%) was experiencing herpetic meningoencephalitis and disease progression at the time of death. TECENTRIQ was discontinued for adverse reactions in 4.2% of patients. The adverse reactions leading to discontinuation were diarrhea/colitis (1.7%), fatigue (0.8%), hypersensitivity (0.8%), and dyspnea (0.8%). Adverse reactions leading to interruption occurred in 35% of patients; the most common ( $\geq 1\%$ ) were intestinal obstruction, fatigue, diarrhea, urinary tract infection, infusion-related reaction, cough, abdominal pain, peripheral edema, pyrexia, respiratory tract infection, upper respiratory tract infection, creatinine increase, decreased appetite, hyponatremia, back pain, pruritus, and venous thromboembolism. Serious adverse reactions occurred in 37% of patients. The most frequent serious adverse reactions ( $\geq 2\%$ ) were diarrhea, intestinal obstruction, sepsis, acute kidney injury, and renal failure.

Table 2 summarizes the adverse reactions that occurred in  $\geq 10\%$  of patients and Table 3 summarizes Grade 3–4 selected laboratory abnormalities that occurred in  $\geq 1\%$  of patients treated with TECENTRIQ in IMvigor210 (Cohort 1).

**Table 2: Adverse Reactions in  $\geq 10\%$  of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)**

Adverse Reaction	TECENTRIQ N = 119	
	All Grades (%)	Grades 3–4 (%)
<b>General</b>		
Fatigue <sup>a</sup>	52	8
Peripheral edema <sup>a</sup>	17	2
Pyrexia	14	0.8
<b>Gastrointestinal</b>		
Diarrhea <sup>a</sup>	24	5
Nausea	22	2
Vomiting	16	0.8
Constipation	15	2
Abdominal pain <sup>a</sup>	15	0.8
<b>Metabolism and Nutrition</b>		
Decreased appetite <sup>a</sup>	24	3
<b>Musculoskeletal and Connective Tissue</b>		
Back/Neck pain	18	3
Arthralgia	13	0
<b>Skin and Subcutaneous Tissue</b>		
Pruritus	18	0.8

Adverse Reaction	TECENTRIQ N = 119	
	All Grades (%)	Grades 3–4 (%)
Rash <sup>6</sup>	17	0.8
<b>Infections</b>		
Urinary tract infection <sup>7</sup>	17	5
<b>Respiratory, Thoracic, and Mediastinal</b>		
Cough <sup>8</sup>	14	0
Dyspnea <sup>9</sup>	12	0

<sup>1</sup> Includes fatigue, asthenia, lethargy, and malaise

<sup>2</sup> Includes edema peripheral, scrotal edema, lymphedema, and edema

<sup>3</sup> Includes diarrhea, colitis, frequent bowel movements, autoimmune colitis

<sup>4</sup> Includes abdominal pain, upper abdominal pain, lower abdominal pain, and flank pain

<sup>5</sup> Includes decreased appetite and early satiety

<sup>6</sup> Includes rash, dermatitis, dermatitis acneiform, rash maculo-papular, rash erythematous, rash pruritic, rash macular, and rash papular

<sup>7</sup> Includes urinary tract infection, urinary tract infection bacterial, cystitis, and urosepsis

<sup>8</sup> Includes cough and productive cough

<sup>9</sup> Includes dyspnea and exertional dyspnea

**Table 3: Grade 3–4 Laboratory Abnormalities in ≥ 1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)**

Laboratory Abnormality	Grades 3–4 (%)
<b>Chemistry</b>	
Hyponatremia	15
Hyperglycemia	10
Increased Alkaline Phosphatase	7
Increased Creatinine	5
Hypophosphatemia	4
Increased ALT	4
Increased AST	4
Hyperkalemia	3
Hypermagnesemia	3
Hyperbilirubinemia	3
<b>Hematology</b>	
Lymphopenia	9
Anemia	7

*Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma*

The safety of TECENTRIQ was evaluated in IMvigor210 (Cohort 2), a multicenter, open-label, single-arm trial that included 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following at least one platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a

platinum-containing neoadjuvant or adjuvant chemotherapy regimen [see *Clinical Studies (14.1)*]. Patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. The median duration of exposure was 12.3 weeks (0.1 to 46 weeks).

The most common adverse reactions ( $\geq 20\%$ ) were fatigue (52%), decreased appetite (26%), nausea (25%), urinary tract infection (22%), pyrexia (21%), and constipation (21%). The most common Grade 3–4 adverse reactions ( $\geq 2\%$ ) were urinary tract infection, anemia, fatigue, dehydration, intestinal obstruction, urinary obstruction, hematuria, dyspnea, acute kidney injury, abdominal pain, venous thromboembolism, sepsis, and pneumonia.

Three patients (1%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, pneumonitis, or intestinal obstruction. TECENTRIQ was discontinued for adverse reactions in 3.2% (10/310) of patients. Sepsis led to discontinuation in 0.6% (2/310) of patients. Adverse reactions leading to interruption occurred in 27% of patients; the most common ( $> 1\%$ ) were liver enzyme increase, urinary tract infection, diarrhea, fatigue, confusional state, urinary obstruction, pyrexia, dyspnea, venous thromboembolism, and pneumonitis. Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions ( $> 2\%$ ) were urinary tract infection, hematuria, acute kidney injury, intestinal obstruction, pyrexia, venous thromboembolism, urinary obstruction, pneumonia, dyspnea, abdominal pain, sepsis, and confusional state.

Table 4 summarizes the adverse reactions that occurred in  $\geq 10\%$  of patients and Table 5 summarizes Grade 3–4 selected laboratory abnormalities that occurred in  $\geq 1\%$  of patients treated with TECENTRIQ in IMvigor210 (Cohort 2).

**Table 4: Adverse Reactions in  $\geq 10\%$  of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 2)**

Adverse Reaction	TECENTRIQ N = 310	
	All Grades (%)	Grades 3–4 (%)
<b>Gastrointestinal</b>		
Nausea	25	2
Constipation	21	0.3
Diarrhea	18	1
Abdominal pain	17	4
Vomiting	17	1
<b>General</b>		
Fatigue	52	6
Pyrexia	21	1
Peripheral edema	18	1
<b>Infections</b>		
Urinary tract infection	22	9
<b>Metabolism and Nutrition</b>		
Decreased appetite	26	1
<b>Musculoskeletal and Connective Tissue</b>		

Adverse Reaction	TECENTRIQ N = 310	
	All Grades (%)	Grades 3–4 (%)
Back/Neck pain	15	2
Arthralgia	14	1
<b>Renal and Urinary</b>		
Hematuria	14	3
<b>Respiratory, Thoracic, and Mediastinal</b>		
Dyspnea	16	4
Cough	14	0.3
<b>Skin and Subcutaneous Tissue</b>		
Rash	15	0.3
Pruritus	13	0.3

**Table 5: Grade 3–4 Laboratory Abnormalities in  $\geq 1\%$  of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 2)**

Laboratory Abnormality	Grades 3–4 (%)
<b>Chemistry</b>	
Hyponatremia	10
Hyperglycemia	5
Increased Alkaline Phosphatase	4
Increased Creatinine	3
Increased ALT	2
Increased AST	2
Hypoalbuminemia	1
<b>Hematology</b>	
Lymphopenia	10
Anemia	8

#### Metastatic Non-small Cell Lung Cancer (NSCLC)

##### *Metastatic Non-Squamous NSCLC*

The safety of TECENTRIQ with bevacizumab, paclitaxel and carboplatin was evaluated in IMpower150, a multicenter, international, randomized, open-label trial in which 393 chemotherapy-naïve patients with metastatic non-squamous NSCLC received TECENTRIQ 1200 mg with bevacizumab 15 mg/kg, paclitaxel 175 mg/m<sup>2</sup> or 200 mg/m<sup>2</sup>, and carboplatin AUC 6 mg/mL/min every 3 weeks for a maximum of 4 or 6 cycles, followed by TECENTRIQ 1200 mg with bevacizumab 15 mg/kg every 3 weeks until disease progression or unacceptable toxicity [see Clinical Studies (14.2)].

The median duration of exposure to TECENTRIQ was 8.3 months in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin.

The most common adverse reactions ( $\geq 20\%$ ) in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin were fatigue/asthenia (50%), alopecia (48%), nausea (39%), diarrhea (32%), constipation (30%), decreased appetite (29%), arthralgia (26%), hypertension (25%), and peripheral neuropathy (24%). The most common Grade 3–4 adverse reactions ( $\geq 2\%$ ) in patients receiving TECENTRIQ were fatigue/asthenia, hypertension, febrile neutropenia, diarrhea, pneumonia, nausea, decreased appetite, dehydration, and pulmonary embolism.

TECENTRIQ was discontinued due to adverse reactions in 15% of patients; the most common adverse reaction leading to discontinuation was pneumonitis (1.8%). Adverse reactions leading to interruption of TECENTRIQ occurred in 48%; the most common ( $>1\%$ ) were neutropenia, thrombocytopenia, fatigue/asthenia, diarrhea, hypothyroidism, anemia, pneumonia, pyrexia, hyperthyroidism, febrile neutropenia, increased ALT, dyspnea, dehydration and proteinuria. Serious adverse reactions occurred in 44%. The most frequent serious adverse reactions ( $>2\%$ ) were febrile neutropenia, pneumonia, diarrhea, and hemoptysis. Fatal adverse reactions occurred in 6% of patients receiving TECENTRIQ; these included hemoptysis, febrile neutropenia, pulmonary embolism, pulmonary hemorrhage, death, cardiac arrest, cerebrovascular accident, pneumonia, aspiration pneumonia, chronic obstructive pulmonary disease, intracranial hemorrhage, intestinal angina, intestinal ischemia, intestinal obstruction and aortic dissection.

Table 6 summarizes adverse reactions that occurred in  $\geq 15\%$  of patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin. Table 7 summarizes laboratory abnormalities worsening from baseline that occurred in  $\geq 20\%$  of patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin. Study IMpower150 was not designed to demonstrate a statistically significant reduction in adverse reaction rates for TECENTRIQ, as compared to the control arm, for any specified adverse reaction or laboratory abnormality listed in Tables 6 and 7.

**Table 6: Adverse Reactions Occurring in  $\geq 15\%$  of Patients Receiving TECENTRIQ in IMpower150**

Adverse Reaction	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin N = 393		Bevacizumab, Paclitaxel and Carboplatin N = 394	
	All grades* (%)	Grade 3–4* (%)	All grades* (%)	Grade 3–4* (%)
<b>Nervous System</b>				
Neuropathy <sup>a</sup>	56	3	47	3
Headache	16	0.8	13	0
<b>General</b>				
Fatigue/Asthenia	50	6	46	6
Pyrexia	19	0.3	9	0.5
<b>Skin and Subcutaneous Tissue</b>				
Alopecia	48	0	46	0
Rash <sup>c</sup>	23	2	10	0.3
<b>Musculoskeletal and Connective Tissue</b>				
Myalgia/Pain <sup>b</sup>	42	3	34	2
Arthralgia	26	1	22	1

	<b>TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin N = 393</b>		<b>Bevacizumab, Paclitaxel and Carboplatin N = 394</b>	
<b>Adverse Reaction</b>	<b>All grades* (%)</b>	<b>Grade 3–4* (%)</b>	<b>All grades* (%)</b>	<b>Grade 3–4* (%)</b>
<b>Gastrointestinal</b>				
Nausea	39	4	32	2
Diarrhea <sup>1</sup>	33	6	25	0.5
Constipation	30	0.3	23	0.3
Vomiting	19	2	18	1
<b>Metabolism and Nutrition</b>				
Decreased appetite	29	4	21	0.8
<b>Vascular</b>				
Hypertension	25	9	22	8
<b>Respiratory</b>				
Cough	20	0.8	19	0.3
Epistaxis	17	1	22	0.3
<b>Renal</b>				
Proteinuria <sup>2</sup>	16	3	15	3

\* Graded per NCI CTCAE v4.0

<sup>1</sup> includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy.

<sup>2</sup> includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, contact dermatitis, rash erythematous, rash macular, pruritic rash, seborrheic dermatitis, dermatitis psoriasiform.

<sup>3</sup> includes pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain, backpain, myalgia, and bone pain.

<sup>4</sup> includes diarrhea, gastroenteritis, colitis, enterocolitis.

<sup>5</sup> Data based on Preferred Terms since laboratory data for proteinuria were not systematically collected.

**Table 7: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving TECENTRIQ in IMpower150**

<b>Laboratory Abnormality</b>	<b>Percentage of Patients with Worsening</b>			
	<b>Laboratory Test from Baseline</b>			
	<b>TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin</b>		<b>Bevacizumab, Paclitaxel and Carboplatin</b>	
	<b>All grades %</b>	<b>Grade 3–4 %</b>	<b>All grades %</b>	<b>Grade 3–4 %</b>
<b>Chemistry</b>				
Hyperglycemia	61	0	60	0
Increased BUN	52	NA	44	NA
Hypomagnesemia	42	2	36	1
Hypoalbuminemia	40	3	31	2
Increased AST	40	4	28	0.8
Hyponatremia	38	10	36	9
Increased Alkaline Phosphatase	37	2	32	1
Increased ALT	37	6	28	0.5

Laboratory Abnormality	Percentage of Patients with Worsening Laboratory Test from Baseline			
	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin		Bevacizumab, Paclitaxel and Carboplatin	
	All grades %	Grade 3–4 %	All grades %	Grade 3–4 %
Increased TSH	30	NA	20	NA
Hyperkalemia	28	3	25	2
Increased Creatinine	28	1	19	2
Hypocalcemia	26	3	21	3
Hypophosphatemia	25	4	18	4
Hypokalemia	23	7	14	4
Hyperphosphatemia	25	N/A	19	N/A
<b>Hematology</b>				
Anemia	83	10	83	9
Neutropenia	52	31	45	26
Lymphopenia	48	17	38	13

NA = Not applicable. NCI CTCAE does not provide a Grade 3-4 definition for these laboratory abnormalities

#### Previously Treated Metastatic NSCLC

The safety of TECENTRIQ was evaluated in OAK, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression [see *Clinical Studies (14.2)*]. A total of 609 patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel (n=578) 75 mg/m<sup>2</sup> intravenously every 3 weeks until unacceptable toxicity or disease progression. The study excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids. The study population characteristics were: median age of 63 years (25 to 85 years), 46% age 65 years or older, 62% male, 71% White, 20% Asian, 68% former smoker, 16% current smoker, and 63% had ECOG performance status of 1. The median duration of exposure was 3.4 months (0 to 26 months) in TECENTRIQ-treated patients and 2.1 months (0 to 23 months) in docetaxel-treated patients.

The most common adverse reactions ( $\geq 20\%$ ) in patients receiving TECENTRIQ were fatigue (44%), decreased appetite (24%), dyspnea (22%), and cough (26%). The most common Grade 3–4 adverse reactions ( $\geq 2\%$ ) were dyspnea, pneumonia, fatigue, and pulmonary embolism.

TECENTRIQ was discontinued due to adverse reactions in 8% of patients. The most common adverse reactions leading to TECENTRIQ discontinuation were fatigue, infections and dyspnea. Fatal adverse reactions occurred in 1.6% of patients; these included pneumonia, sepsis, septic shock, dyspnea, pulmonary hemorrhage, sudden death, myocardial ischemia or renal failure. Adverse reactions leading to interruption of TECENTRIQ occurred in 25% of patients; the most common ( $> 1\%$ ) were pneumonia, liver function test abnormality, dyspnea, fatigue, pyrexia, and back pain. Serious adverse reactions occurred in 33.5% of patients. The most frequent serious adverse reactions ( $> 1\%$ ) were pneumonia, sepsis, dyspnea, pleural effusion, pulmonary embolism, pyrexia and respiratory tract infection.

Table 8 summarizes adverse reactions that occurred in at least 10% of patients treated with TECENTRIQ. Table 9 summarizes laboratory abnormalities worsening from baseline that occurred in  $\geq 20\%$  of patients treated with TECENTRIQ.

**Table 8: Adverse Reactions Occurring in ≥ 10% of Patients with NSCLC Receiving TECENTRIQ in OAK**

Adverse Reaction <sup>1</sup>	TECENTRIQ 1200 mg every 3 weeks N = 609		Docetaxel 75 mg/m <sup>2</sup> every 3 weeks N = 578	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
<b>General</b>				
Fatigue/Asthenia <sup>2</sup>	44	4	53	6
Pyrexia	18	<1	13	<1
<b>Respiratory</b>				
Cough <sup>3</sup>	26	<1	21	<1
Dyspnea	22	2.8	21	2.6
<b>Musculoskeletal</b>				
Myalgia/pain <sup>4</sup>	20	1.3	20	<1
Arthralgia	12	0.5	10	0.2
<b>Metabolism and Nutrition</b>				
Decreased appetite	23	<1	24	1.6
<b>Gastrointestinal</b>				
Nausea	18	<1	23	<1
Constipation	18	<1	14	<1
Diarrhea	16	<1	24	2
<b>Skin</b>				
Rash <sup>5</sup>	12	<1	10	0

<sup>1</sup> Graded per NCI CTCAE v4.0

<sup>2</sup> Includes fatigue and asthenia

<sup>3</sup> Includes cough and exertional cough

<sup>4</sup> Includes musculoskeletal pain, musculoskeletal stiffness, musculoskeletal chest pain, myalgia

<sup>5</sup> Includes rash, erythematous rash, generalized rash, maculopapular rash, papular rash, pruritic rash, pustular rash, pemphigoid

**Table 9: Laboratory Abnormalities Worsening From Baseline Occurring in ≥ 20% of NSCLC Patients Receiving TECENTRIQ in OAK**

Laboratory Abnormality	TECENTRIQ 1200 mg every 3 weeks		Docetaxel 75 mg/m <sup>2</sup> every 3 weeks	
	All Grades (%) <sup>1</sup>	Grade 3-4 (%)	All Grades (%) <sup>1</sup>	Grade 3-4 (%)
<b>Chemistry</b>				
Hypoalbuminemia	48	4	50	3
Hyponatremia	42	7	31	6
Increased Alkaline Phosphatase	39	2	25	1
Increased AST	31	3	16	0.5
Increased ALT	27	3	14	0.5
Hypophosphatemia	27	5	23	4
Hypomagnesemia	26	1	21	1

	TECENTRIQ 1200 mg every 3 weeks		Docetaxel 75 mg/m <sup>2</sup> every 3 weeks	
	All Grades (%) <sup>1</sup>	Grade 3-4 (%)	All Grades (%) <sup>1</sup>	Grade 3-4 (%)
Laboratory Abnormality				
Increased Creatinine	23	2	16	1
<b>Hematology</b>				
Anemia	67	3	82	7
Lymphocytopenia	49	14	60	21

<sup>1</sup> Graded according to NCI CTCAE version 4.0

<sup>2</sup> Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ (range: 546–585) and docetaxel (range: 532–560)

## 6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

Among 565 patients with NSCLC in OAK, 30% tested positive for treatment-emergent anti-drug antibodies (ADA) at one or more post-dose time points. The median onset time to ADA formation was 3 weeks. The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA also had decreased systemic atezolizumab exposure [see *Clinical Pharmacology (12.3)*]. Exploratory analyses showed that the subset of patients who were ADA positive by week 4 (21%; 118/560) appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 [see *Clinical Studies (14.2)*]. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 275 patients with urothelial carcinoma in IMvigor210 (Cohort 2), 42% tested positive for treatment-emergent ADA at one or more post-dose time points. Among 111 patients in IMvigor210 (Cohort 1), 48% tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA also had decreased systemic atezolizumab exposures. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 364 ADA-evaluable patients with NSCLC who received TECENTRIQ with bevacizumab, paclitaxel and carboplatin in IMpower150, (36% (n=132) tested positive for treatment-emergent ADA at one or more post-dose time points and 83% of these 132 patients tested ADA positive prior to receiving the second dose of atezolizumab. The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA had lower systemic atezolizumab exposure as compared to patients who were ADA negative [see *Clinical Pharmacology (12.3)*]. The presence of ADA did not increase the incidence or severity of adverse reactions [see *Clinical Studies (14.2)*].

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to atezolizumab in the studies described above with the incidence of antibodies in other studies or to other products may be misleading.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on its mechanism of action [*see Clinical Pharmacology (12.1)*], TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women.

Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death (*see Data*). Advise females of reproductive potential of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

#### Data

##### *Animal Data*

Animal reproduction studies have not been conducted with TECENTRIQ to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-L1/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus. Blockage of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to a fetus and to result in an increase in fetal loss; therefore, potential risks of administering TECENTRIQ during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to atezolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

### 8.2 Lactation

#### Risk Summary

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

### 8.3 Females and Males of Reproductive Potential

#### Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TECENTRIQ [*see Use in Specific Populations (8.1)*].

#### Contraception

##### *Females*

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months following the last dose.

## Infertility

### *Females*

Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment [see *Nonclinical Toxicology (13.1)*].

### **8.4 Pediatric Use**

The safety and effectiveness of TECENTRIQ have not been established in pediatric patients.

### **8.5 Geriatric Use**

Of the 919 patients treated with TECENTRIQ as a single-agent in IMvigor210 (Cohort 2) and OAK, 50% were 65 years or older. Of the 400 patients randomized to TECENTRIQ in combination with bevacizumab, paclitaxel, and carboplatin in IMpower150, 46% were 65 years or older and 9% were 75 years or older. No overall differences in safety or efficacy were observed between patients 65 years or older and younger patients in IMvigor210 (Cohort 2), OAK, and IMpower150.

Of the 119 cisplatin-ineligible patients with urothelial carcinoma treated with TECENTRIQ as a single-agent in IMvigor210 (Cohort 1), 83% were 65 years or older and 41% were 75 years or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

## **11 DESCRIPTION**

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

TECENTRIQ Injection for intravenous use is a sterile, preservative-free, colorless to slightly yellow solution in single-dose vials. Each mL of TECENTRIQ contains 60 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), sucrose (821.6 mg), polysorbate 20 (8 mg), pH 5.8.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

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

Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody-dependent cellular cytotoxicity. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

### **12.3 Pharmacokinetics**

Patients' exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including a dose of 1200 mg administered every 3 weeks. The clearance (CV%) was 0.20 L/day (29%), the volume of distribution at steady state was 6.9 L, and the terminal half-life was 27 days. Steady state is achieved after 6 to 9 weeks (2 to 3 cycles). The systemic accumulation ratio for area under the curve (AUC), maximum concentration (C<sub>max</sub>) and trough concentration (C<sub>min</sub>) was 1.9, 1.5 and 2.8-fold, respectively. Atezolizumab clearance was found to decrease over time, with a mean maximal reduction (CV%) from baseline value of

approximately 17% (41%); however, the decrease in clearance was not considered clinically relevant.

### Specific Populations

Age (21 to 89 years), body weight, sex, albumin levels, tumor burden, region or race, mild or moderate renal impairment [estimated glomerular filtration rate (eGFR) 30 to 89 mL/min/1.73 m<sup>2</sup>], mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1 to 1.5 × ULN and any AST), level of PD-L1 expression, or performance status had no clinically significant effect on the systemic exposure of atezolizumab. In OAK and IMpower150 (TECENTRIQ, bevacizumab, paclitaxel, carboplatin arm only), atezolizumab clearance in patients who tested positive for treatment-emergent anti-drug antibodies (ADA) was 25% and 18% higher, respectively, as compared to clearance in patients who tested negative for treatment-emergent ADA.

The effect of severe renal impairment or moderate or severe hepatic impairment on the pharmacokinetics of atezolizumab is unknown.

### Drug Interaction Studies

The drug interaction potential of atezolizumab is unknown.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No studies have been performed to test the potential of atezolizumab for carcinogenicity or genotoxicity.

Animal fertility studies have not been conducted with atezolizumab; however, an assessment of the male and female reproductive organs was included in a 26-week, repeat-dose toxicity study in cynomolgus monkeys. Weekly administration of atezolizumab to female monkeys at the highest dose tested caused an irregular menstrual cycle pattern and a lack of newly formed corpora lutea in the ovaries. This effect occurred at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose and was reversible. There was no effect on the male monkey reproductive organs.

### **13.2 Animal Toxicology and/or Pharmacology**

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.

## **14 CLINICAL STUDIES**

### **14.1 Locally Advanced or Metastatic Urothelial Carcinoma**

#### Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The efficacy of TECENTRIQ was investigated in IMvigor210 (Cohort 1) (NCT02951767), a multicenter, open-label, single-arm trial that included 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy and were either previously untreated or had disease progression at least 12 months after neoadjuvant or adjuvant chemotherapy. Patients were considered cisplatin-ineligible if they met any one of the following criteria at study entry: impaired renal function [creatinine clearance (CL<sub>cr</sub>) of 30 to 59 mL/min], Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2,

hearing loss of  $\geq 25$  decibels (dB) at two contiguous frequencies, or Grade 2-4 peripheral neuropathy. This study excluded patients who had: a history of autoimmune disease; active or corticosteroid-dependent brain metastases; administration of a live, attenuated vaccine within 28 days prior to enrollment; or administration of systemic immunostimulatory agents within 6 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Patients received TECENTRIQ 1200 mg as an intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Tumor response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed overall response rate (ORR) as assessed by independent review facility (IRF) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1), duration of response (DoR) and overall survival (OS).

In this study, the median age was 73 years, 81% were male, and 91% were White. Thirty-five percent of patients had non-bladder urothelial carcinoma and 66% had visceral metastases. Eighty percent of patients had an ECOG PS of 0 or 1. Reasons for ineligibility for cisplatin-containing chemotherapy were: 70% had impaired renal function, 20% had an ECOG PS of 2, 14% had a hearing loss of  $\geq 25$  dB, and 6% had Grade 2-4 peripheral neuropathy at baseline. Twenty percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy.

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory, and the results were used to define subgroups for pre-specified analyses. Of the 119 patients, 27% were classified as having PD-L1 expression of  $\geq 5\%$  (defined as PD-L1 stained tumor-infiltrating immune cells [IC] covering  $\geq 5\%$  of the tumor area). The remaining 73% of patients were classified as having PD-L1 expression of  $< 5\%$  (PD-L1 stained tumor-infiltrating IC covering  $< 5\%$  of the tumor area).

Among the 32 patients with PD-L1 expression of  $\geq 5\%$ , median age was 67 years, 81% were male, 19% female, and 88% were White. Twenty-eight percent of patients had non-bladder urothelial carcinoma and 56% had visceral metastases. Seventy-two percent of patients had an ECOG PS of 0 or 1. Reasons for ineligibility for cisplatin-containing chemotherapy were: 66% had impaired renal function, 28% had an ECOG PS of 2, 16% had a hearing loss  $\geq 25$  dB, and 9% had Grade 2-4 peripheral neuropathy at baseline. Thirty-one percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy.

Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 10. The median follow-up time for this study was 14.4 months. In 24 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 33% (95% CI: 16%, 55%).

**Table 10: Efficacy Results in IMvigor210 (Cohort 1)**

	All Patients	PD-L1 Expression Subgroups	
	N = 119	PD-L1 Expression of $< 5\%$ in ICs <sup>a</sup> N = 87	PD-L1 Expression of $\geq 5\%$ in ICs <sup>a</sup> N = 32
<b>Number of IRF-assessed Confirmed Responders</b>	28	19	9
<b>ORR % (95% CI)</b>	23.5% (16.2, 32.2)	21.8% (13.7, 32)	28.1% (13.8, 46.8)
Complete Response (CR) (%)	6.7%	6.9%	6.3%
Partial Response (PR) (%)	16.8%	14.9%	21.9%

	All Patients	PD-L1 Expression Subgroups	
	N = 119	PD-L1 Expression of < 5% in ICs <sup>†</sup> N = 87	PD-L1 Expression of ≥ 5% in ICs <sup>†</sup> N = 32
<b>Median DoR, months</b> <b>(range)</b>	NR (3.7, 16.6+)	NR (3.7, 16.6+)	NR (8.1, 15.6+)
NR = Not reached + Denotes a censored value † PD-L1 expression in tumor-infiltrating immune cells (ICs)			

IMvigor130 (NCT02807636) is an ongoing multicenter, randomized study in previously untreated patients with metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy. The study contains three arms: TECENTRIQ monotherapy, TECENTRIQ with platinum-based chemotherapy (i.e., cisplatin or carboplatin with gemcitabine), and platinum-based chemotherapy alone (comparator). Both cisplatin-eligible and cisplatin-ineligible patients are included in the study. Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory. The independent Data Monitoring Committee (iDMC) for the study conducted a review of early data and found that patients classified as having PD-L1 expression of <5% when treated with TECENTRIQ monotherapy had decreased survival compared to those who received platinum-based chemotherapy. The iDMC recommended closure of the monotherapy arm to further accrual of patients with low PD-L1 expression, however, no other changes were recommended for the study, including any change of therapy for patients who had already been randomized to and were receiving treatment in the monotherapy arm.

#### Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

The efficacy of TECENTRIQ was investigated in IMvigor210 (Cohort 2) (NCT02108652), a multicenter, open-label, single-arm trial that included 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following a platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. This study excluded patients who had: a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, or administration of systemic immunostimulatory agents within 6 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed ORR as assessed by IRF using RECIST v1.1 and DoR.

In this study, the median age was 66 years, 78% were male, 91% of patients were White. Twenty-six percent had non-bladder urothelial carcinoma and 78% of patients had visceral metastases. Sixty-two percent of patients had an ECOG PS of 1 and 35% of patients had a baseline CLcr < 60 mL/min. Nineteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Forty-one percent of patients had received 2 or more prior systemic regimens in the metastatic setting. Seventy-three percent of patients received prior cisplatin, 26% had prior carboplatin, and 1% were treated with other platinum-based regimens.

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 310 patients, 32% were classified as having PD-L1 expression of  $\geq 5\%$ . The remaining 68% of patients were classified as having PD-L1 expression of  $< 5\%$ .

Confirmed ORR and median DOR in all patients and the two PD-L1 subgroups are summarized in Table 11. The median follow-up time for this study was 32.9 months. In 59 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 22.0% (95% CI: 12.3%, 34.7%).

**Table 11: Efficacy Results in IMvigor210 (Cohort 2)**

	All Patients	PD-L1 Expression Subgroups	
	N = 310	PD-L1 Expression of $< 5\%$ in IC <sup>1</sup> N = 210	PD-L1 Expression of $\geq 5\%$ in IC <sup>1</sup> N = 100
<b>Number of IRF-assessed Confirmed Responders</b>	46	20	26
<b>ORR % (95% CI)</b>	14.8% (11.2, 19.3)	9.5% (5.9, 14.3)	26% (17.7, 35.7)
Complete Response (CR) (%)	5.5%	2.4%	12.0%
Partial Response (PR) (%)	9.4%	7.1%	14.0%
<b>Median DOR, months (range)</b>	27.7 (2.1+, 33.4+)	20.9 (2.1+, 33.4+)	29.7 (4.2, 31.2+)
+ Denotes a censored value <sup>1</sup> PD-L1 expression in tumor-infiltrating immune cells (IC)			

## 14.2 Metastatic Non-Small Cell Lung Cancer

### Metastatic Chemotherapy-Naive Non-Squamous NSCLC

The efficacy of TECENTRIQ with bevacizumab, paclitaxel, and carboplatin was evaluated in IMpower150 (NCT02366143), a multicenter, international, randomized (1:1:1), open-label trial in 1202 patients with metastatic non-squamous NSCLC. IMpower150 enrolled patients with stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease, but could have received prior EGFR or ALK kinase inhibitor if appropriate, regardless of PD-L1 or T-effector gene (tGE) status and ECOG performance status 0 or 1. The trial excluded patients with a history of autoimmune disease, administration of a live attenuated vaccine within 28 days prior to randomization, active or untreated CNS metastases, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization, or clear tumor infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions as seen on imaging.

Randomization was stratified by sex, presence of liver metastases, and PD-L1 expression status on tumor cells (TC) and tumor-infiltrating immune cells (IC) as follows: TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1. Patients were randomized to one of the following three treatment arms.

- Arm A: TECENTRIQ 1200 mg, paclitaxel 175 mg/m<sup>2</sup> or 200 mg/m<sup>2</sup> and carboplatin AUC 6 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<sup>2</sup> or 200 mg/m<sup>2</sup>, and carboplatin AUC 6 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<sup>2</sup> or 200 mg/m<sup>2</sup>, and carboplatin AUC 6 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

Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumor specimens were evaluated prior to randomization for PD-L1 tumor expression using the VENTANA PD-L1 (SP142) assay at a central laboratory. Tumor tissue was collected at baseline for expression of tGE signature and evaluation was performed using a clinical trial assay in a central laboratory prior to the analysis of efficacy outcome measures.

The major efficacy outcome measures for comparison of Arms B and C were progression free survival (PFS) by RECIST v1.1 in the tGE-WT (patients with high expression of T-effector gene signature [tGE], excluding those with EGFR- and ALK-positive NSCLC [WT]) and in the ITT-WT subpopulations and overall survival (OS) in the ITT-WT subpopulation. Additional efficacy outcome measures for comparison of Arms B and C or Arms A and C were PFS and OS in the ITT population, OS in the tGE-WT subpopulation, and ORR/DoR in the tGE-WT and ITT-WT subpopulations.

A total of 1202 patients were enrolled across the three arms of whom 1045 were in the ITT-WT subpopulation and 447 were in the tGE-WT subpopulation. The demographic information is limited to the 800 patients enrolled in Arms B and C where efficacy has been demonstrated. The median age was 63 years (range: 31 to 90), and 60% of patients were male. The majority of patients were White (82%), 13% of patients were Asian, 10% were Hispanic, and 2% of patients were Black. Clinical sites in Asia (enrolling 13% of the study population) received paclitaxel at a dose of 175 mg/m<sup>2</sup> while the remaining 87% received paclitaxel at a dose of 200 mg/m<sup>2</sup>.

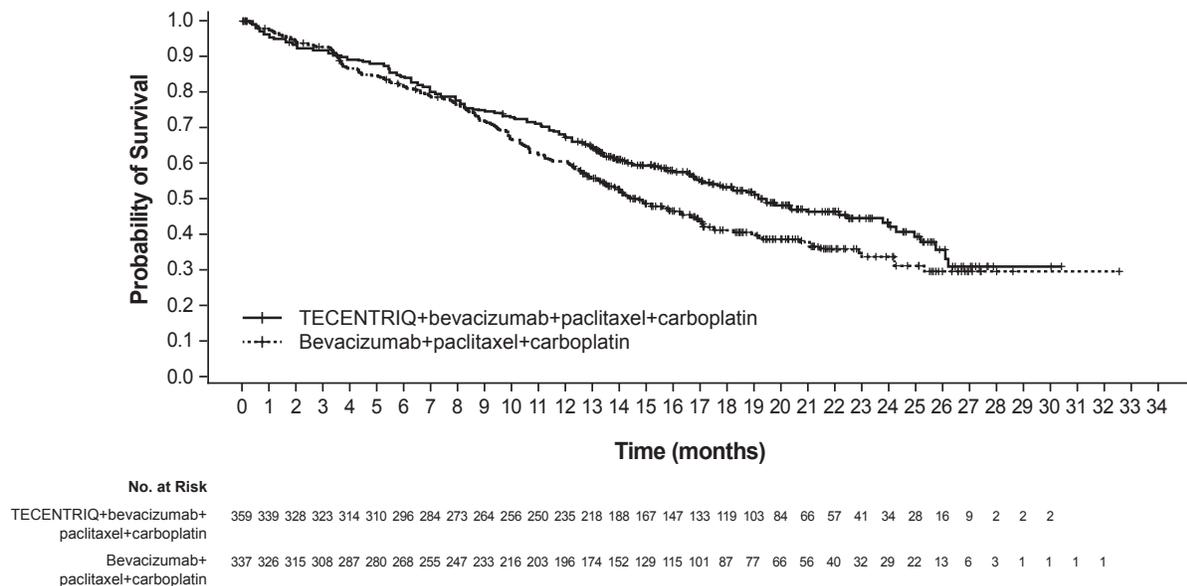
Approximately 14% of patients had liver metastases at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%). PD-L1 was TC3 and any IC in 12%, TC0/1/2 and IC2/3 in 13%, and TC0/1/2 and IC0/1 in 75%. The demographics for the 696 patients in the ITT-WT subpopulation were similar to the ITT population except for the absence of patients with EGFR- or ALK-positive NSCLC.

The trial demonstrated a statistically significant improvement in PFS between Arms B and C in both the tGE-WT and ITT-WT subpopulations, but did not demonstrate a significant difference for either subpopulation between Arms A and C based on the final PFS analyses. In the interim analysis of OS, a statistically significant improvement was observed for Arm B compared to Arm C, but not for Arm A compared to Arm C. Efficacy results for the ITT-WT subpopulation are presented in Table 12 and Figure 1.

**Table 12: Efficacy Results in ITT-WT Population in IMpower150**

	<b>Arm C: Bevacizumab, Paclitaxel and Carboplatin</b>	<b>Arm B: TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin</b>	<b>Arm A: TECENTRIQ with Paclitaxel, and Carboplatin</b>
	<b>N = 337</b>	<b>N = 359</b>	<b>N = 349</b>
<b>Overall Survival</b>			
Deaths (%)	197 (59%)	179 (50%)	179 (51%)
Median, months (95% CI)	14.7 (13.3, 16.9)	19.2 (17.0, 23.8)	19.4 (15.7, 21.3)
Hazard ratio <sup>a</sup> (95% CI)	---	0.78 (0.64, 0.96)	0.84 (0.72, 1.08)
p-value <sup>b</sup>	---	0.016 <sup>c</sup>	0.204 <sup>d</sup>
<b>Progression-Free Survival</b>			
Number of events (%)	247 (73%)	247 (69%)	245 (70%)
Median, months (95% CI)	7.0 (6.3, 7.9)	8.5 (7.3, 9.7)	6.7 (5.6, 6.9)
Hazard ratio <sup>a</sup> (95% CI)	---	0.71 (0.59, 0.85)	0.94 (0.79, 1.13)
p-value <sup>b</sup>	---	0.0002 <sup>e</sup>	0.5219
<b>Objective Response Rate</b>			
Number of responders (%) (95% CI)	142 (42%) (37, 48)	196 (55%) (49, 60)	150 (43%) (38, 48)
Complete response	3 (1%)	14 (4%)	9 (3%)
Partial response	139 (41%)	182 (51%)	141 (40%)
<b>Duration of Response<sup>f</sup></b>			
	n = 142	n = 196	n = 150
Median (months) (95% CI)	6.5 (5.6, 7.6)	10.8 (8.4, 13.9)	9.5 (7.0, 13.0)
<sup>g</sup> Based on OS interim analysis . <sup>h</sup> Stratified by sex, presence of liver metastases, and PD-L1 expression status on TC and IC <sup>i</sup> Based on the stratified log-rank test compared to Arm C <sup>j</sup> Compared to the allocated $\alpha=0.0174$ (two sided) for this interim analysis. <sup>k</sup> Compared to the allocated $\alpha=0.0128$ (two sided) for this interim analysis. <sup>l</sup> As determined by independent review facility (IRF) per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1) <sup>m</sup> Compared to the allocated $\alpha=0.006$ (two sided) for the final PFS analysis. CI=confidence interval			

**Figure 1: Kaplan-Meier Curves for Overall Survival in ITT-WT Population in IMpower150**



Exploratory analyses showed that the subset of patients in the four drug regimen arm who were ADA positive by week 4 (30%) appeared to have similar efficacy (effect on overall survival) as

compared to patients who tested negative for treatment-emergent ADA by week 4 (70%) [see *Adverse Reactions* (6.2), *Clinical Pharmacology* (12.3)]. In an exploratory analysis, propensity score matching was conducted to compare ADA positive patients in the TECENTRIQ, bevacizumab, paclitaxel, and carboplatin arm with a matched population in the bevacizumab, paclitaxel, and carboplatin arm. Similarly ADA negative patients in the TECENTRIQ, bevacizumab, paclitaxel, and carboplatin arm were compared with a matched population in the bevacizumab, paclitaxel, and carboplatin arm. Propensity score matching factors were: baseline sum of longest tumor size (BSLD), baseline ECOG, baseline albumin, baseline LDH, sex, tobacco history, metastatic site, TC level, and IC level. The hazard ratio comparing the ADA-positive subgroup with its matched control was 0.69 (95% CI: 0.44, 1.07). The hazard ratio comparing the ADA-negative subgroup with its matched control was 0.64 (95% CI: 0.46, 0.90).

### Previously Treated Metastatic NSCLC

The efficacy of TECENTRIQ was evaluated in a multicenter, international, randomized (1:1), open-label study (OAK; NCT02008227) conducted in patients with locally advanced or metastatic NSCLC whose disease progressed during or following a platinum-containing regimen. Patients with a history of autoimmune disease, symptomatic or corticosteroid-dependent brain metastases, or requiring systemic immunosuppression within 2 weeks prior to enrollment were ineligible. Randomization was stratified by PD-L1 expression tumor-infiltrating immune cells (IC), the number of prior chemotherapy regimens (1 vs. 2), and histology (squamous vs. non-squamous).

Patients were randomized to receive TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel 75 mg/m<sup>2</sup> intravenously every 3 weeks until unacceptable toxicity or disease progression. Tumor assessments were conducted every 6 weeks for the first 36 weeks and every 9 weeks thereafter. The major efficacy outcome measure was overall survival (OS) in the first 850 randomized patients and OS in the subgroup of patients with PD-L1-expressing tumors (defined as ≥ 1% PD-L1 expression on tumor cells [TC] or immune cells [IC]). Additional efficacy outcome measures were OS in all randomized patients (n = 1225), OS in subgroups based on PD-L1 expression, overall response rate (ORR), and progression free survival as assessed by the investigator per RECIST v.1.1.1.

Among the first 850 randomized patients, the median age was 64 years (33 to 85 years) and 47% were ≥ 65 years old; 61% were male; 70% were White and 21% were Asian; 15% were current smokers and 67% were former smokers; and 37% had baseline ECOG PS of 0 and 63% had a baseline ECOG PS of 1. Nearly all (94%) had metastatic disease, 74% had non-squamous histology, 75% had received only one prior platinum-based chemotherapy regimen, and 55% of patients had PD-L1-expressing tumors.

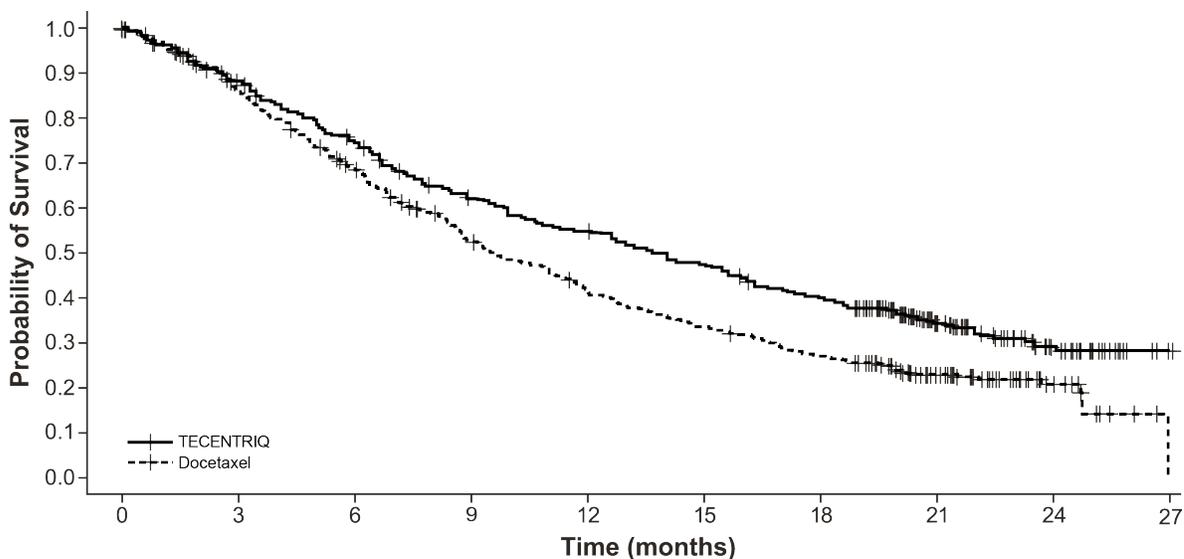
Efficacy results are presented in Table 13 and Figure 2.

**Table 13: Efficacy Results in OAK**

	<b>TECENTRIQ</b>	<b>Docetaxel</b>
<b>Overall Survival in first 850 patients</b>		
Number of patients	N=425	N=425
Deaths (%)	271 (64%)	298 (70%)
Median, months	13.8	9.6
(95% CI)	(11.8, 15.7)	(8.6, 11.2)
Hazard ratio <sup>a</sup> (95% CI)	0.74 (0.63, 0.87)	
p-value <sup>a</sup>	0.0004	
<b>Progression-Free Survival</b>		
Number of Patients	N=425	N=425
Events (%)	380 (89%)	375 (88%)
Progression (%)	332 (78%)	290 (68%)

	<b>TECENTRIQ</b>	<b>Docetaxel</b>
Deaths (%)	48 (11%)	85 (20%)
Median, months	2.8	4.0
(95% CI)	(2.6, 3.0)	(3.3, 4.2)
Hazard ratio <sup>c</sup> (95% CI)	0.95 (0.82, 1.10)	
<b>Overall Response Rate<sup>a</sup></b>		
Number of Patients	N=425	N=425
ORR, n (%)	58 (14%)	57 (13%)
(95% CI)	(11%, 17%)	(10%, 17%)
Complete response	6 (1%)	1 (0.2%)
Partial response	52 (12%)	56 (13%)
<b>Duration of Response<sup>b</sup></b>		
	N=58	N=57
Median (months)	16.3	6.2
(95% CI)	(10.0, NE)	(4.9, 7.6)
<b>Overall Survival in all 1225 patients</b>		
Number of patients	N=613	N=612
Deaths (%)	384 (63%)	409 (67%)
Median, months	13.3	9.8
(95% CI)	(11.3, 14.9)	(8.9, 11.3)
Hazard ratio <sup>c</sup> (95% CI)	0.79 (0.69, 0.91)	
p-value <sup>e</sup>	0.0013 <sup>e</sup>	
<sup>a</sup> Stratified by PD-L1 expression in tumor infiltrating immune cells, the number of prior chemotherapy regimens, and histology <sup>b</sup> Based on the stratified log-rank test <sup>c</sup> Compared to the pre-specified allocated $\alpha$ of 0.03 for this analysis <sup>d</sup> Per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1) <sup>e</sup> Compared to the allocated $\alpha$ of 0.0177 for this interim analysis based on 86% information using O'Brien-Fleming boundary CI=confidence interval; NE=not estimable		

**Figure 2: Kaplan-Meier Curves of Overall Survival in the First 850 Patients Randomized in OAK**



No. Patients at Risk	0	3	6	9	12	15	18	21	24	27																		
TECENTRIQ	425	407	382	363	342	326	305	279	260	248	234	223	218	205	198	188	175	163	157	141	116	74	54	41	28	15	4	1
Docetaxel	425	390	365	336	311	286	263	236	219	195	179	168	151	140	132	123	116	104	98	90	70	51	37	28	16	6	3	

Tumor 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, 16% were classified as having high PD-L1 expression, defined as having PD-L1 expression on  $\geq 50\%$  of TC or  $\geq 10\%$  of IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in patients who did not have high PD-L1 expression.

Exploratory analyses showed that the subset of patients who were ADA positive by week 4 (21%) appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 (79%) [see *Adverse Reactions (6.2)*, *Clinical Pharmacology (12.3)*]. ADA positive patients by week 4 appeared to have similar OS compared to docetaxel-treated patients. In an exploratory analysis, propensity score matching was conducted to compare ADA positive patients in the atezolizumab arm with a matched population in the docetaxel arm and ADA negative patients in the atezolizumab arm with a matched population in the docetaxel arm. Propensity score matching factors were: baseline sum of longest tumor size (BSLD), baseline ECOG, histology (squamous vs. non-squamous), baseline albumin, baseline LDH, gender, tobacco history, metastases status (advanced or local), metastatic site, TC level, and IC level. The hazard ratio comparing the ADA positive subgroup with its matched control was 0.89 (95% CI: 0.61, 1.3). The hazard ratio comparing the ADA negative subgroup with its matched control was 0.68 (95% CI: 0.55, 0.83).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

TECENTRIQ injection is a sterile, preservative-free, and colorless to slightly yellow solution for intravenous infusion supplied as a carton containing one 1200 mg/20 mL single-dose vial (NDC 50242-917-01).

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

### Immune-Mediated Adverse Reactions

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

- **Pneumonitis:** Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath [see *Warnings and Precautions (5.1)*].
- **Hepatitis:** Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding [see *Warnings and Precautions (5.2)*].
- **Colitis:** Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain [see *Warnings and Precautions (5.3)*].
- **Endocrinopathies:** Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, hyperthyroidism, hypothyroidism, adrenal insufficiency, or type 1 diabetes mellitus, including diabetic ketoacidosis [see *Warnings and Precautions (5.4)*].
- **Other Immune-Mediated Adverse Reactions:** Advise patients to contact their healthcare provider immediately for signs or symptoms of other potential immune-mediated adverse reactions [see *Warnings and Precautions (5.5)*].

### Infections

Advise patients to contact their healthcare provider immediately for signs or symptoms of infection [see *Warnings and Precautions (5.6)*].

### Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [*see Warnings and Precautions (5.7)*].

#### Embryo-Fetal Toxicity

Advise females of reproductive potential that TECENTRIQ can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.8), Use in Specific Populations (8.1, 8.3)*].

Advise females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of TECENTRIQ [*see Use in Specific Populations (8.3)*].

#### Lactation

Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose [*see Use in Specific Populations (8.2)*].

Manufactured by:

Genentech, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

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**MEDICATION GUIDE**  
**TECENTRIQ® (te-SEN-trik)**  
**(atezolizumab)**  
**injection**

**What is the most important information I should know about TECENTRIQ?**

TECENTRIQ is a medicine that may treat a type of cancer in the bladder and urinary tract or a type of lung cancer by working with your immune system. TECENTRIQ can cause your immune system to attack normal organs and tissues and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death.

**Call or see your healthcare provider right away if you get any symptoms of the following problems or these symptoms get worse:**

**Lung problems (pneumonitis).** Signs and symptoms of pneumonitis may include:

- new or worsening cough
- shortness of breath
- chest pain

**Liver problems (hepatitis).** Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- dark urine (tea colored)
- severe nausea or vomiting
- bleeding or bruising more easily than normal
- pain on the right side of your stomach area (abdomen)
- feeling less hungry than usual
- drowsiness

**Intestinal problems (colitis).** Signs and symptoms of colitis may include:

- diarrhea (loose stools) or more bowel movements than usual
- blood or mucus in your stools or dark, tarry, sticky stools
- severe stomach area (abdomen) pain or tenderness

**Hormone gland problems (especially the thyroid, adrenal glands, pancreas, and pituitary).** Signs and symptoms that your hormone glands are not working properly may include:

- headaches that will not go away or unusual headaches
- feeling cold
- extreme tiredness
- constipation
- weight gain or weight loss
- your voice gets deeper
- dizziness or fainting
- urinating more often than usual
- feeling more hungry or thirsty than usual
- nausea or vomiting
- hair loss
- stomach area (abdomen) pain
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

**Problems in other organs.** Signs and symptoms may include:

- severe muscle weakness
- neck stiffness
- numbness or tingling in hands or feet
- eye pain or redness
- confusion
- skin blisters or peeling
- blurry vision, double vision, or other vision problems
- chest pain, irregular heartbeat, shortness of breath or swelling of the ankles
- changes in mood or behavior
- extreme sensitivity to light

**Severe infections.** Signs and symptoms of infection may include:

- fever
- flu-like symptoms
- cough
- pain when urinating, frequent urination or back pain

**Severe infusion reactions.** Signs and symptoms of infusion reactions may include:

- chills or shaking
- dizziness
- itching or rash
- fever
- flushing
- feeling like passing out
- shortness of breath or wheezing
- back or neck pain
- swelling of your face or lips

**Getting medical treatment right away may help keep these problems from becoming more serious.**

Your healthcare provider will check you for these problems during your treatment with TECENTRIQ. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may delay or completely stop treatment with TECENTRIQ if you have severe side effects.

## What is TECENTRIQ?

TECENTRIQ is a prescription medicine used to treat:

- **a type of bladder and urinary tract cancer called urothelial carcinoma.** TECENTRIQ may be used when your bladder cancer:
  - has spread or cannot be removed by surgery, **and if you have any one of the following conditions:**
    - you are not able to take chemotherapy that contains a medicine called cisplatin, and your doctor has tested your cancer and found high levels of a specific protein on your cancer called programmed death-ligand 1 (PD-L1), **or**
    - you are not able to take chemotherapy that contains any platinum regardless of the levels of PD-L1 on your cancer, **or**
    - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
- **a type of lung cancer called non-small cell lung cancer (NSCLC).**
  - **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 NSCLC
    - your tumor 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 tumor has an abnormal “EGFR” or “ALK” gene, you should have also tried an FDA-approved therapy for tumors with these abnormal genes, and it did not work or is no longer working.

It is not known if TECENTRIQ is safe and effective in children.

## Before you receive TECENTRIQ, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems such as Crohn’s disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are being treated for an infection
- are pregnant or plan to become pregnant. TECENTRIQ can harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with TECENTRIQ.

### Females who are able to become pregnant:

- Your healthcare provider should do a pregnancy test before you start treatment with TECENTRIQ.
- You should use an effective method of birth control during your treatment and for at least 5 months after the last dose of TECENTRIQ.
- are breastfeeding or plan to breastfeed. It is not known if TECENTRIQ passes into your breast milk. Do not breastfeed during treatment and for at least 5 months after the last dose of TECENTRIQ.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

## How will I receive TECENTRIQ?

- Your healthcare provider will give you TECENTRIQ into your vein through an intravenous (IV) line over 30 to 60 minutes.
- TECENTRIQ is usually given every 3 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will test your blood to check you for certain side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

**What are the possible side effects of TECENTRIQ?****TECENTRIQ can cause serious side effects, including:**

- See “What is the most important information I should know about TECENTRIQ?”

The most common side effects of TECENTRIQ when used alone include:

- feeling tired
- nausea
- constipation
- cough
- shortness of breath
- decreased appetite

The most common side effects of TECENTRIQ when used with bevacizumab, paclitaxel and carboplatin include:

- feeling tired or weak
- hair loss
- nausea
- diarrhea
- constipation
- decreased appetite
- joint pain
- high blood pressure
- tingling or numbness in hands and feet

TECENTRIQ may cause fertility problems in females, which may affect the ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of TECENTRIQ. Ask your healthcare provider or pharmacist for more information. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of TECENTRIQ.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about TECENTRIQ, talk with your healthcare provider. You can ask your healthcare provider for information about TECENTRIQ that is written for health professionals.

**What are the ingredients in TECENTRIQ?**

**Active ingredient:** atezolizumab

**Inactive ingredients:** glacial acetic acid, L-histidine, sucrose, polysorbate 20

Manufactured by: **Genentech, Inc.**, A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990 USA

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For more information, call 1-844-832-3687 or go to [www.TECENTRIQ.com](http://www.TECENTRIQ.com).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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