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 (1.1)	7/2018
Dosage and Administration (2)	7/2018
Warnings and Precautions (5)	4/2018

——————INDICATIONS AND USAGE——————

TECENTRIQ is a programmed death-ligand 1 (PD-L1) blocking antibody 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 ≥ 5% of the tumor area), as determined by an FDA-approved test, or
  - are not eligible for any platinum-containing chemotherapy regardless of PD-L1status, 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)
- Metastatic non-small cell lung cancer 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 these aberrations prior to receiving TECENTRIQ. (1.2)

——————DOSAGE AND ADMINISTRATION——————

Administer 1200 mg as an intravenous infusion over 60 minutes every 3 weeks. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. (2.1)

——————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. (2.2, 5.1)
- Immune-Mediated Hepatitis: Monitor for changes in liver function. Withhold or permanently discontinue based on severity of transaminase or total bilirubin elevation. (2.2, 5.2)
- Immune-Mediated Colitis: Withhold or permanently discontinue based on severity of colitis. (2.2, 5.3)
- Immune-Mediated Endocrinopathies (2.2, 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. (2.2, 5.6)
- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue based on severity of infusion reactions. (2.2, 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 (≥ 20%) in patients with locally advanced or metastatic urothelial carcinoma were fatigue, decreased appetite, nausea, constipation, urinary tract infection, diarrhea, and pyrexia. (6.1)

Most common adverse reactions (≥ 20%) in patients with metastatic non-small cell lung cancer were fatigue, decreased appetite, dyspnea, and cough. (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*.

——————USE IN SPECIFIC POPULATIONS——————

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

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 ≥ 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 is indicated for the treatment of patients with metastatic non-small cell lung cancer (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 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

The recommended dosage of TECENTRIQ is 1200 mg as an intravenous infusion 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 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

Adverse Reaction	Severity of Adverse Reaction[a]	Dosage Modifications
Pneumonitis *[see Warnings and Precautions (5.1)]*	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

Adverse Reaction	Severity of Adverse Reaction[a]	Dosage Modifications
Hepatitis *[see Warnings and Precautions (5.2)]*	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 *[see Warnings and Precautions (5.3)]*	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) *[see Warnings and Precautions (5.4)]*	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 *[see Warnings and Precautions (5.5)]*	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)
	Grade 4	Permanently discontinue
Infections *[see Warnings and Precautions (5.6)]*	Grade 3 or 4	Withhold dose until Grade 1 or resolved
Infusion-Related Reactions *[see Warnings and Precautions (5.7)]*	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

Adverse Reaction	Severity of Adverse Reaction[a]	Dosage Modifications
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

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0

2.4 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 (2.3)]*.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ *[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 ≥ 40 mg per day or equivalent) for a median duration of 4 days (1 day to 45 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 (2.3)]*.

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 was 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.

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 (2.3) and Adverse Reactions (6.1)]*.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ *[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).

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 (2.2)]*.

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 was noted to have acute 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 (2.3)]*.

In clinical studies enrolling 2616 patients who received TECENTRIQ, 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.

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 (2.3)]*.

In clinical studies enrolling 2616 patients who received TECENTRIQ, type 1 diabetes mellitus occurred in < 0.1% of patients. Insulin was required in one patient.

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 (2.3)]*.

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

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 (2.3)]*.

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 (2.3) 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.

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 (2.3)]*. 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 *[see Adverse Reactions (6.1)]*, infusion-related reactions occurred in 1.3% of patients, including Grade 3 (0.2%).

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 the Warnings and Precautions section reflect exposure to TECENTRIQ 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. TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks in all studies except PCD4989g. Among the 2616 patients, 36% were exposed for longer than 6 months and 20% were exposed for longer than 12 months.

The data described in this section were obtained from one open-label, single arm, multiple cohort study (IMvigor210) and one randomized open-label, active-controlled study (OAK) in which TECENTRIQ was administered to 429 patients with locally advanced and metastatic urothelial carcinoma and 609 patients with metastatic NSCLC. In these trials, TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks.

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 (≥ 20%) were fatigue (52%), decreased appetite (24%), diarrhea (24%), and nausea (22%). The most common Grade 3–4 adverse reactions (≥ 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 (≥ 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 (≥ 2%) were diarrhea, intestinal obstruction, sepsis, acute kidney injury, and renal failure.

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

Table 2: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

Adverse Reaction	TECENTRIQ N = 119	
	All Grades (%)	Grades 3–4 (%)
General		
Fatigue[a]	52	8
Peripheral edema[b]	17	2
Pyrexia	14	0.8
Gastrointestinal		
Diarrhea[c]	24	5
Nausea	22	2
Vomiting	16	0.8
Constipation	15	2
Abdominal pain[d]	15	0.8
Metabolism and Nutrition		
Decreased appetite[e]	24	3
Musculoskeletal and Connective Tissue		
Back/Neck pain	18	3
Arthralgia	13	0
Skin and Subcutaneous Tissue		
Pruritus	18	0.8
Rash[f]	17	0.8
Infections		
Urinary tract infection[g]	17	5
Respiratory, Thoracic, and Mediastinal		
Cough[h]	14	0
Dyspnea[i]	12	0

[a] Includes fatigue, asthenia, lethargy, and malaise
[b] Includes edema peripheral, scrotal edema, lymphedema, and edema
[c] Includes diarrhea, colitis, frequent bowel movements, autoimmune colitis
[d] Includes abdominal pain, upper abdominal pain, lower abdominal pain, and flank pain
[e] Includes decreased appetite and early satiety
[f] Includes rash, dermatitis, dermatitis acneiform, rash maculo-papular, rash erythematous, rash pruritic, rash macular, and rash papular
[g] Includes urinary tract infection, urinary tract infection bacterial, cystitis, and urosepsis
[h] Includes cough and productive cough
[i] 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 (%)
Hyponatremia	15
Hyperglycemia	10
Lymphopenia	9
Anemia	7
Increased Alkaline Phosphatase	7
Increased Creatinine	5
Hypophosphatemia	4
Increased ALT	4
Increased AST	4
Hyperkalemia	3
Hypermagnesemia	3
Hyperbilirubinemia	3

Previously Treated Patients with 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 (≥ 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 (≥ 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 ≥ 10% of patients and Table 5 summarizes Grade 3–4 selected laboratory abnormalities that occurred in ≥ 1% of patients treated with TECENTRIQ in IMvigor210 (Cohort 2).

Table 4: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 2)

	TECENTRIQ N=310	
Adverse Reaction	**All Grades (%)**	**Grades 3–4 (%)**
Gastrointestinal		
Nausea	25	2
Constipation	21	0.3
Diarrhea	18	1
Abdominal pain	17	4
Vomiting	17	1
General		
Fatigue	52	6
Pyrexia	21	1
Peripheral edema	18	1
Infections		
Urinary tract infection	22	9
Metabolism and Nutrition		
Decreased appetite	26	1
Musculoskeletal and Connective Tissue		
Back/Neck pain	15	2
Arthralgia	14	1
Renal and Urinary		
Hematuria	14	3
Respiratory, Thoracic, and Mediastinal		
Dyspnea	16	4
Cough	14	0.3
Skin and Subcutaneous Tissue		
Rash	15	0.3
Pruritus	13	0.3

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

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

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 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel (n=578) 75 mg/m^2 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 (≥ 20%) in patients receiving TECENTRIQ were fatigue (43.5%), decreased appetite (23.5%), dyspnea (22%), and cough (26.4%). The most common Grade 3–4 adverse reactions (≥ 2%) were dyspnea, pneumonia, fatigue, anemia, 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 6 summarizes adverse reactions that occurred in at least 10% of patients treated with TECENTRIQ. Table 7 summarizes selected laboratory abnormalities worsening from baseline that occurred in ≥ 20% of patients treated with TECENTRIQ.

Table 6: Adverse Reactions Occurring in ≥ 10% of Patients with NSCLC Receiving TECENTRIQ in OAK

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

[1] Graded per NCI CTCAE v4.0
[2] Includes fatigue and asthenia
[3] Includes cough and exertional cough
[4] Includes musculoskeletal pain, musculoskeletal stiffness, musculoskeletal chest pain, myalgia
[5] Includes rash, erythematous rash, generalized rash, maculopapular rash, papular rash, pruritic rash, pustular rash, pemphigoid

Table 7: 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^2 every 3 weeks	
Grade	**All Grades[1] (%)[2]**	**Grade 3-4 (%)**	**All Grades[1] (%)[2]**	**Grade 3-4 (%)**
Chemistry				
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
Increased Creatinine	23	2	16	1
Hematology				
Anemia	67	3	82	7
Lymphocytopenia	49	14	60	21

[1] Graded according to NCI CTCAE version 4.0
[2] 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.

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 609 patients with NSCLC treated with TECENTRIQ in OAK, 45% were 65 years or older. No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients.

Of the 310 previously-treated patients with urothelial carcinoma treated with TECENTRIQ in IMvigor210 (Cohort 2), 59% were 65 years or older. Of the 119 cisplatin-ineligible patients with urothelial carcinoma treated with TECENTRIQ in IMvigor210 (Cohort 1), 83% were 65 years or older and 41% were 75 years or older. The overall response rate in patients 65 years or older was 23% and in patients 75 years or older was 29%. Grade 3 or 4 adverse reactions occurred in 53% of patients 65 years or older and 51% of patients 75 years or older. No overall differences in safety or efficacy were observed between patients ≥ 75 years of age and younger patients.

10 OVERDOSAGE

There is no information on overdose with TECENTRIQ.

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 (Cmax) and trough concentration (Cmin) 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^2], 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, atezolizumab clearance in patients who tested positive for treatment-emergent anti-drug antibodies (ADA) was 25% higher as compared to that 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 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 (CrCL) of 30 to 59 mL/min], Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2, hearing loss of ≥ 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 ≥ 25dB, 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 ≥ 5% (defined as PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 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 ≥ 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 ≥ 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 8. 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 8: Efficacy Results in IMvigor210 (Cohort 1)

	All Patients	PD-L1 Expression Subgroups	
	N=119	PD-L1 Expression of < 5% in ICs[1] (N=87)	PD-L1 Expression of ≥ 5% in ICs[1] (N=32)
Number of IRF-assessed Confirmed Responders	28	19	9
ORR % (95% CI)	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%
Median DoR, months (range)	NR (3.7, 16.6+)	NR (3.7, 16.6+)	NR (8.1, 15.6+)

NR = Not reached

\+ Denotes a censored value

[1] 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 Patients with 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 CrCl < 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 ≥ 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 9. 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 9: Efficacy Results in IMvigor210 (Cohort 2)

	All Patients	**PD-L1 Expression Subgroups**	
	N=310	**PD-L1 Expression of < 5% in IC[1] (N=210)**	**PD-L1 Expression of ≥ 5% in IC[1] (N=100)**
Number of IRF-assessed Confirmed Responders	46	20	26
ORR % (95% CI)	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%
Median DOR, months (range)	27.7 (2.1+, 33.4+)	20.9 (2.1+, 33.4+)	29.7 (4.2, 31.2+)

+ Denotes a censored value

[1] PD-L1 expression in tumor-infiltrating immune cells (IC)

14.2 Metastatic Non-Small Cell Lung Cancer

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^2 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.

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 an 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.

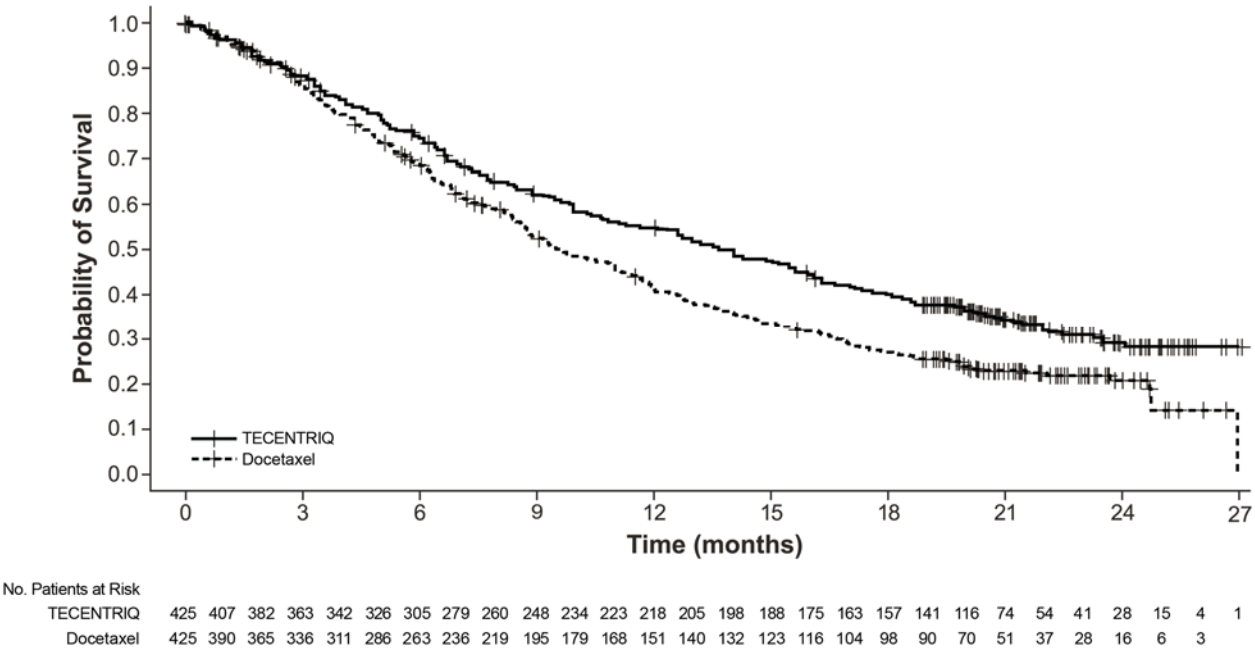
Efficacy results are presented in Table 10 and Figure 1.

Table 10: Efficacy Results in OAK

	TECENTRIQ		Docetaxel
Overall Survival in first 850 patients			
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[1] (95% CI)		0.74 (0.63, 0.87)	
p-value[2]		0.0004[3]	
Progression-Free Survival			
Number of Patients	N=425		N=425
Events (%)	380 (89%)		375 (88%)
Progression (%)	332 (78%)		290 (68%)
Deaths (%)	48 (11%)		85 (20%)
Median, months	2.8		4.0
(95% CI)	(2.6, 3.0)		(3.3, 4.2)
Hazard ratio[1] (95% CI)		0.95 (0.82, 1.10)	
Overall Response Rate [4]			
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%)
Duration of Response[3]	N=58		N=57
Median (months)	16.3		6.2
(95% CI)	(10.0, NE)		(4.9, 7.6)
Overall Survival in all 1225 patients			
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[1] (95% CI)		0.79 (0.69, 0.91)	
p-value[2]		0.0013[5]	

[1] Stratified by PD-L1 expression in tumor infiltrating immune cells, the number of prior chemotherapy regimens, and histology
[2] Based on the stratified log-rank test
[3] Compared to the pre-specified allocated α of 0.03 for this analysis
[4] Per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[5] Compared to the allocated α of 0.0177 for this interim analysis based on 86% information using O'Brien-Fleming boundary
CI=confidence interval; NE=not estimable

Figure 1: Kaplan-Meier Curves of Overall Survival in the First 850 Patients Randomized in OAK



No. Patients at Risk																										
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 ≥ 50% of TC or ≥ 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:
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A Member of the Roche Group
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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
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- drowsiness
- dark urine (tea colored)
- bleeding or bruising more easily than normal
- feeling less hungry than usual

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
- extreme tiredness
- weight gain or weight loss
- dizziness or fainting
- feeling more hungry or thirsty than usual
- hair loss
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- feeling cold
- constipation
- your voice gets deeper
- urinating more often than usual
- nausea or vomiting
- stomach area (abdomen) pain

Problems in other organs. Signs and symptoms may include:

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

Severe infections. Signs and symptoms of infection may include:

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

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

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

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 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.
  If you 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 in people with urothelial carcinoma include:

- feeling tired
- decreased appetite
- nausea
- constipation
- urinary tract infection
- diarrhea
- fever

The most common side effects of TECENTRIQ in people with NSCLC include:

- feeling tired
- decreased appetite
- muscle pain
- cough
- shortness of breath

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

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For more information, call 1-*844-832-3687* or go to www.TECENTRIQ.com.

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