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

Warnings and Precautions (5.2)	08/2025

INDICATIONS AND USAGE

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

Non-Small Cell Lung Cancer (NSCLC)

- as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test. (1.1, 14.1)
- for the first-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations. (1.1)
- in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations. (1.1)
- in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations (1.1)
- for the treatment of adult 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. (1.1)

Small Cell Lung Cancer (SCLC)

- in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). (1.2)

Hepatocellular Carcinoma (HCC)

- in combination with bevacizumab for the treatment of adult patients with unresectable or metastatic HCC who have not received prior systemic therapy. (1.3)

Melanoma

- in combination with cobimetinib and vemurafenib for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. (1.4)

Alveolar Soft Part Sarcoma (ASPS)

- for the treatment of adult and pediatric patients 2 years of age and older with unresectable or metastatic ASPS. (1.5)

DOSAGE AND ADMINISTRATION

Administer TECENTRIQ intravenously over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

NSCLC

- In the adjuvant setting, administer TECENTRIQ following resection and up to 4 cycles of platinum-based chemotherapy as 840 mg every 2 weeks, 1200 mg every 3 weeks or 1680 mg every 4 weeks for up to 1 year. (2.2)
- In the metastatic setting, administer TECENTRIQ as 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks. (2.2)
- When administering with chemotherapy with or without bevacizumab, administer TECENTRIQ prior to chemotherapy and bevacizumab when given on the same day. (2.2)

Small Cell Lung Cancer

- Administer TECENTRIQ as 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks. When administering with carboplatin and etoposide, administer TECENTRIQ prior to chemotherapy when given on the same day. (2.2)

Hepatocellular Carcinoma

- Administer TECENTRIQ as 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks. Administer TECENTRIQ prior to bevacizumab when given on the same day. Bevacizumab is administered at 15 mg/kg every 3 weeks. (2.2)

Melanoma

- Following completion of a 28 day cycle of cobimetinib and vemurafenib, administer TECENTRIQ 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks with cobimetinib 60 mg orally once daily (21 days on /7 days off) and vemurafenib 720 mg orally twice daily. (2.2)

ASPS

- Adults: Administer TECENTRIQ as 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks. (2.2)
- Pediatric patients 2 years of age and older: 15 mg/kg (up to a maximum of 1200 mg), every 3 weeks (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 840 mg/14 mL (60 mg/mL) and 1200 mg/20 mL (60 mg/mL) solution in a single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Immune-Mediated Adverse Reactions
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, immune-mediated nephritis and renal dysfunction, and solid organ transplant rejection. (5.1)
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. (5.1)
  - Withhold or permanently discontinue based on severity and type of reaction. (5.1).
- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue based on severity of infusion reactions. (5.2)
- Complications of Allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)

ADVERSE REACTIONS

TECENTRIQ as a single-agent

- Most common adverse reactions (≥ 20%) with TECENTRIQ as a single-agent are fatigue/asthenia, decreased appetite, nausea, cough, and dyspnea. (6.1)

TECENTRIQ in combination with other antineoplastic drugs

- Most common adverse reactions (≥ 20%) in patients with NSCLC and SCLC are fatigue/asthenia, nausea, alopecia, constipation, diarrhea, and decreased appetite. (6.1)

TECENTRIQ in combination with bevacizumab

- Most common adverse reactions (≥ 20%) in patients with HCC are hypertension, fatigue and proteinuria. (6.1)

TECENTRIQ in combination with cobimetinib and vemurafenib

- Most common adverse reactions (≥ 20%) with TECENTRIQ in patients with melanoma are rash, musculoskeletal pain, fatigue, hepatotoxicity, pyrexia, nausea, pruritus, edema, stomatitis, hypothyroidism, and photosensitivity reaction. (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: 08/2025

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-Small Cell Lung Cancer

- TECENTRIQ, as a single-agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage II to IIIA *[see Clinical Studies (14.1)]* non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*.
- TECENTRIQ, as a single agent, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations *[see Dosage and Administration (2.1)]*.
- TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
- TECENTRIQ, in combination with paclitaxel protein-bound and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
- TECENTRIQ, as a single-agent, is indicated for the treatment of adult 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 Small Cell Lung Cancer

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

1.3 Hepatocellular Carcinoma

TECENTRIQ, in combination with bevacizumab, is indicated for the treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

1.4 Melanoma

TECENTRIQ, in combination with cobimetinib and vemurafenib, is indicated for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma *[see Dosage and Administration (2.1)]*.

1.5 Alveolar Soft Part Sarcoma

TECENTRIQ, as a single agent, is indicated for the treatment of adult and pediatric patients 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma (ASPS).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for Treatment of Non-Small Cell Lung Cancer and Melanoma

Select patients with Stage II to IIIA non-small cell lung cancer for treatment with TECENTRIQ as a single agent based on PD-L1 expression on tumor cells *[see Clinical Studies (14.1)]*.

Select patients with first-line metastatic non-small cell lung cancer for treatment with TECENTRIQ as a single agent based on the PD-L1 expression on tumor cells or on tumor-infiltrating immune cells *[see Clinical Studies (14.1)]*.

Information on FDA-approved tests for the determination of PD-L1 expression in metastatic non-small cell lung cancer are available at: http://www.fda.gov/CompanionDiagnostics.

Select patients with unresectable or metastatic melanoma for treatment with TECENTRIQ in combination with cobimetinib and vemurafenib after confirming the presence of a BRAF V600 mutation *[see Clinical Studies (14.4)]*. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage

The recommended dosages of TECENTRIQ are presented in Table 1. Administer TECENTRIQ as an intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

Table 1: Recommended Dosage of TECENTRIQ as a Single Agent

Indication	**Recommended Dosage of TECENTRIQ**	**Duration of Therapy**
Metastatic NSCLC	• 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks	Until disease progression or unacceptable toxicity
Adjuvant Treatment of NSCLC	• 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks	Up to one year, unless there is disease recurrence or unacceptable toxicity
ASPS (adult)	• 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks	Until disease progression or unacceptable toxicity
ASPS (pediatric, 2 years of age and older)	15 mg/kg (up to a maximum 1200 mg) every 3 weeks	

The recommended intravenous dosages of TECENTRIQ in combination with other therapeutic agents are presented in Table 2. Refer to the respective Prescribing Information for each therapeutic agent administered in combination with TECENTRIQ for the recommended dosage information, as appropriate.

Table 2: Recommended Dosage of TECENTRIQ in Combination with Other Therapeutic Agents

Indication	Recommended Dosage of TECENTRIQ	Duration of Therapy
NSCLC	• 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks Administer TECENTRIQ prior to chemotherapy and bevacizumab when given on the same day.	Until disease progression or unacceptable toxicity
SCLC	• 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks Administer TECENTRIQ prior to chemotherapy when given on the same day.	
HCC	• 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks Administer TECENTRIQ prior to bevacizumab when given on the same day. Bevacizumab is administered at 15 mg/kg every 3 weeks.	
Melanoma	• 840 mg every 2 weeks or • 1200 mg every 3 weeks or • 1680 mg every 4 weeks Administer TECENTRIQ with cobimetinib 60 mg orally once daily (21 days on and 7 days off) and vemurafenib 720 mg orally twice daily. Prior to initiating TECENTRIQ, patients should receive a 28 day treatment cycle of cobimetinib 60 mg orally once daily (21 days on and 7 days off) and vemurafenib 960 mg orally twice daily from Days 1-21 and vemurafenib 720 mg orally twice daily from Days 22-28.	

2.3 Dosage Modifications for Adverse Reactions

No dose reduction for TECENTRIQ is recommended. In general, withhold TECENTRIQ for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue TECENTRIQ for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability

to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for TECENTRIQ for adverse reactions that require management different from these general guidelines are summarized in Table 3.

Table 3: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity[a]**	**Dosage Modification**
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold[b]
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold[b]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold[b]
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[c]	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold[b]
	AST or ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grades 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grades 2 or 3 increased blood creatinine	Withhold[b]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue

Adverse Reaction	Severity[a]	Dosage Modification
Myocarditis or Pericarditis	Grades 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[b]
	Grades 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*	Grades 1 or 2	Interrupt or slow the rate of infusion
	Grades 3 or 4	Permanently discontinue

[a] Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4

[b] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids

[c] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue TECENTRIQ based on recommendations for hepatitis with no liver involvement

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit normal, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson syndrome, TEN = toxic epidermal necrolysis

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:

- Select the appropriate vial(s) based on the prescribed dose.
- Withdraw the required volume of TECENTRIQ from the vial(s) using sterile needle and syringe.
- Dilute to a final concentration between 3.2 mg/mL and 16.8 mg/mL in a polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% Sodium Chloride Injection, USP.
- Dilute with only 0.9% Sodium Chloride Injection, USP.
- 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: 840 mg/14 mL (60 mg/mL) and 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 Severe and Fatal Immune-Mediated Adverse Reactions

TECENTRIQ is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*. In general, if TECENTRIQ requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

TECENTRIQ can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

TECENTRIQ as a Single Agent:

Immune-mediated pneumonitis occurred in 3% (83/2616) of patients receiving TECENTRIQ as a single agent, including fatal (<0.1%), Grade 4 (0.2%), Grade 3 (0.8%), and Grade 2 (1.1%) adverse reactions. Pneumonitis led to permanent discontinuation of TECENTRIQ in 0.5% and withholding of TECENTRIQ in 1.5% of patients.

Systemic corticosteroids were required in 55% (46/83) of patients with pneumonitis. Pneumonitis resolved in 69% of the 83 patients. Of the 39 patients in whom TECENTRIQ was withheld for pneumonitis, 25 reinitiated TECENTRIQ after symptom improvement; of these, 4% had recurrence of pneumonitis.

In IMpower010 immune-mediated pneumonitis occurred in 3.8% (19/495) of patients receiving TECENTRIQ as a single agent, including fatal (0.2%), Grade 4 (0.2%), and Grade 3 (0.6%) adverse reactions. Pneumonitis led to permanent discontinuation of TECENTRIQ in 2.2% and withholding of TECENTRIQ in 0.8% of patients.

Systemic corticosteroids were required in 63% (12/19) of patients with pneumonitis. Pneumonitis resolved in 84% of the 19 patients.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Immune-mediated pneumonitis occurred in 13% (29/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 3 (1.3%) and Grade 2 (7%) adverse reactions. Pneumonitis led to permanent discontinuation of TECENTRIQ in 2.6% and withholding of TECENTRIQ in 7.4% of patients.

Systemic corticosteroids were required in 55% (16/29) of patients with pneumonitis. Pneumonitis resolved in 97% of the 29 patients. Of the 17 patients in whom TECENTRIQ was withheld for pneumonitis, 10 reinitiated TECENTRIQ after symptom improvement; of these, 50% had recurrence of pneumonitis.

Immune-Mediated Colitis

TECENTRIQ can cause immune-mediated colitis. Colitis can present with diarrhea, abdominal pain, and lower gastrointestinal (GI) bleeding. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

TECENTRIQ as a Single Agent:

Immune-mediated colitis occurred in 1% (26/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.5%) and Grade 2 (0.3%) adverse reactions. Colitis led to permanent discontinuation of TECENTRIQ in 0.2% and withholding of TECENTRIQ in 0.5% of patients.

Systemic corticosteroids were required in 50% (13/26) of patients with colitis. Colitis resolved in 73% of the 26 patients. Of the 12 patients in whom TECENTRIQ was withheld for colitis, 8 reinitiated treatment with TECENTRIQ after symptom improvement; of these, 25% had recurrence of colitis.

Immune-Mediated Hepatitis

TECENTRIQ can cause immune-mediated hepatitis.

Immune-mediated hepatitis occurred in 1.8% (48/2616) of patients receiving TECENTRIQ as a single agent, including fatal (<0.1%), Grade 4 (0.2%), Grade 3 (0.5%), and Grade 2 (0.5%) adverse reactions. Hepatitis led to permanent discontinuation of TECENTRIQ in 0.2% and withholding of TECENTRIQ in 0.2% of patients.

Systemic corticosteroids were required in 25% (12/48) of patients with hepatitis. Hepatitis resolved in 50% of the 48 patients. Of the 6 patients in whom TECENTRIQ was withheld for hepatitis, 4 reinitiated treatment with TECENTRIQ after symptom improvement; of these, none had recurrence of hepatitis.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Immune-mediated hepatitis occurred in 6.1% (14/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 4 (1.3%), Grade 3 (1.7%) and Grade 2 (1.3%) adverse reactions. Hepatitis led to permanent discontinuation of TECENTRIQ in 2.2% and withholding of TECENTRIQ in 1.7% of patients.

Systemic corticosteroids were required in 50% (7/14) of patients with hepatitis. Hepatitis resolved in 93% of the 14 patients. Of the 4 patients in whom TECENTRIQ was withheld for hepatitis, 3 reinitiated TECENTRIQ after symptom improvement; of these, 33% had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

TECENTRIQ can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Adrenal insufficiency occurred in 0.4% (11/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (<0.1%) and Grade 2 (0.2%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of TECENTRIQ in one patient and withholding of TECENTRIQ in one patient.

Systemic corticosteroids were required in 82% (9/11) of patients with adrenal insufficiency; of these, 3 patients remained on systemic corticosteroids. The single patient in whom TECENTRIQ was withheld for adrenal insufficiency did not reinitiate TECENTRIQ.

In IMpower010 immune-mediated adrenal insufficiency occurred in 1.2% (6/495) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.4%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of TECENTRIQ in 0.6% and withholding of TECENTRIQ in 0.2% of patients.

Systemic corticosteroids were required in 83% (5/6) of patients with adrenal insufficiency; of these, 4 patients remained on systemic corticosteroids.

Hypophysitis

TECENTRIQ can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated.

Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Hypophysitis occurred in <0.1% (2/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (1 patient, <0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of TECENTRIQ in one patient and no patients required withholding of TECENTRIQ.

Systemic corticosteroids were required in 50% (1/2) of patients with hypophysitis. Hypophysitis did not resolve in these 2 patients.

Thyroid disorders

TECENTRIQ can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or medical management for hyperthyroidism as clinically indicated. Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Thyroiditis:

Thyroiditis occurred in 0.2% (4/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (<0.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in one patient.

Hormone replacement therapy was required in 75% (3/4) of patients with thyroiditis. Systemic corticosteroids were required in 25% (1/4) of patients with thyroiditis. Thyroiditis resolved in 50% of patients. The single patient in whom TECENTRIQ was withheld for thyroiditis reinitiated TECENTRIQ; this patient did not have recurrence of thyroiditis.

In IMpower010, thyroiditis occurred in 1.2% (6/495) of patients receiving TECENTRIQ as a single agent, including Grade 2 (0.4%) adverse reactions. Thyroiditis led to withholding of TECENTRIQ in one patient.

Hormone replacement therapy was required in 67% (4/6) of patients with thyroiditis. Systemic corticosteroids were required in 33% (2/6) of patients with thyroiditis. Thyroiditis resolved in 50% of patients.

Hyperthyroidism:

TECENTRIQ as a Single Agent:

Hyperthyroidism occurred in 0.8% (21/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (0.4%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 0.1% of patients.

Antithyroid therapy was required in 29% (6/21) of patients with hyperthyroidism. Of these 6 patients, the majority remained on antithyroid treatment. Of the 3 patients in whom TECENTRIQ was withheld for hyperthyroidism, one patient reinitiated TECENTRIQ; this patient did not have recurrence of hyperthyroidism.

In IMpower010 hyperthyroidism occurred in 6% (32/495) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.4%) adverse reactions. Hyperthyroidism led to permanent discontinuation of TECENTRIQ in 0.8% and withholding of TECENTRIQ in 2.8% of patients.

Antithyroid therapy was required in 38% (12/32) of patients with hyperthyroidism. Of these 12 patients, the majority remained on antithyroid treatment. Of the 14 patients in whom TECENTRIQ was withheld for hyperthyroidism, 9 patients reinitiated TECENTRIQ.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Hyperthyroidism occurred in 19% (43/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 3 (0.9%) and Grade 2 (7.8%) adverse reactions. Hyperthyroidism led to permanent discontinuation of TECENTRIQ in 0.4% and withholding of TECENTRIQ in 10% of patients.

Antithyroid therapy was required in 53% (23/43) of patients with hyperthyroidism. Of these 23 patients, the majority remained on antithyroid treatment. Of the 24 patients in whom TECENTRIQ was withheld for hyperthyroidism, 18 patients reinitiated TECENTRIQ; of these, 28% had recurrence of hyperthyroidism.

Hypothyroidism:

TECENTRIQ as a Single Agent:

Hypothyroidism occurred in 4.9% (128/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (0.2%) and Grade 2 (3.4%) adverse reactions. Hypothyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 0.6% of patients.

Hormone replacement therapy was required in 81% (104/128) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 17 patients in whom TECENTRIQ was withheld for hypothyroidism, 8 reinitiated TECENTRIQ after symptom improvement.

In IMpower010 hypothyroidism occurred in 17% (86/495) of patients receiving TECENTRIQ as a single agent. Hypothyroidism led to permanent discontinuation of TECENTRIQ in 1.6% and withholding of TECENTRIQ in 1.6% of patients.

Hormone replacement was required in 57% (49/86) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 8 patients in whom TECENTRIQ was withheld for hypothyroidism, 3 reinitiated TECENTRIQ after symptom improvement.

TECENTRIQ in Combination with Platinum-based Chemotherapy:

Hypothyroidism occurred in 11% (277/2421) of patients with NSCLC and SCLC receiving TECENTRIQ in combination with platinum-based chemotherapy, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (5.7%) adverse reactions. Hypothyroidism led to permanent discontinuation of TECENTRIQ in 0.1% and withholding of TECENTRIQ in 1.6% of patients.

Hormone replacement therapy was required in 71% (198/277) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 39 patients in whom TECENTRIQ was withheld for hypothyroidism, 9 reinitiated TECENTRIQ after symptom improvement.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Hypothyroidism occurred in 26% (60/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 2 (9.1%) adverse reactions. Hypothyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 2.6% of patients.

Hormone replacement therapy was required in 52% (31/60) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 6 patients in whom TECENTRIQ was withheld for hypothyroidism, 4 reinitiated TECENTRIQ after symptom improvement. The majority of patients with hypothyroidism required long term thyroid replacement.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Type 1 diabetes mellitus occurred in 0.3% (7/2616) of patients receiving TECENTRIQ, including Grade 3 (0.2%) and Grade 2 (<0.1%) adverse reactions. Type 1 diabetes mellitus led to permanent discontinuation of TECENTRIQ in one patient and withholding of TECENTRIQ in two patients.

Treatment with insulin was required for all patients with confirmed Type 1 diabetes mellitus and insulin therapy was continued long-term. Of the 2 patients in whom TECENTRIQ was withheld for Type 1 diabetes mellitus, both re-initiated TECENTRIQ treatment.

Immune-Mediated Nephritis with Renal Dysfunction

TECENTRIQ can cause immune-mediated nephritis.

TECENTRIQ as a Single Agent:

Immune-mediated nephritis with renal dysfunction occurred in <0.1% (1/2616) of patients receiving TECENTRIQ as a single agent, and this adverse reaction was a Grade 3 (<0.1%) adverse reaction. Nephritis led to permanent discontinuation of TECENTRIQ in this patient.

This patient required systemic corticosteroids. In this patient, nephritis did not resolve.

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

Immune-mediated nephritis with renal dysfunction occurred in 1.3% (3/230) of patients receiving TECENTRIQ in combination with cobimetinib and vemurafenib, including Grade 2 (1.3%) adverse reactions. Nephritis led to permanent discontinuation of TECENTRIQ in 0.4% and withholding of TECENTRIQ in 0.9% of patients.

Systemic corticosteroids were required in 67% (2/3) of patients with nephritis. Nephritis resolved in all 3 of these patients. Of the 2 patients in whom TECENTRIQ was withheld for nephritis, both reinitiated TECENTRIQ after symptom improvement and neither had recurrence of nephritis.

Immune-Mediated Dermatologic Adverse Reactions

TECENTRIQ can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue TECENTRIQ depending on severity *[see Dosage and Administration (2.3)]*.

Immune-mediated dermatologic adverse reactions occurred in 0.6% (15/2616) of patients receiving TECENTRIQ as a single agent, including Grade 3 (<0.1%) and Grade 2 (0.2%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of TECENTRIQ in 0.1% and withholding of TECENTRIQ in 0.2% of patients.

Systemic corticosteroids were required in 20% (3/15) of patients with dermatologic adverse reactions. Dermatologic adverse reactions resolved in 87% of the 15 patients. Of the 4 patients in whom TECENTRIQ was withheld for immune-mediated dermatologic adverse reactions, none re-initiated TECENTRIQ.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% (unless otherwise noted) in patients who received TECENTRIQ or were

reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis.

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy.

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis.

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatic.

Endocrine: Hypoparathyroidism.

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection.

5.2 Infusion-Related Reactions

TECENTRIQ can cause severe or life-threatening infusion-related reactions, including anaphylaxis. 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 as a single-agent *[see Adverse Reactions (6.1)]*, infusion-related reactions occurred in 1.3% of patients, including Grade 3 (0.2%). The frequency and severity of infusion-related reactions were similar whether TECENTRIQ was given as a single-agent in patients with various cancers, in combination with other antineoplastic drugs in NSCLC and SCLC, and across the recommended dose range (840 mg Q2W to 1680 mg Q4W).

5.3 Complications of Allogeneic HSCT after PD-1/PD-L1 Inhibitors

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockage and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefits versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

5.4 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 clinically significant adverse reactions are described elsewhere in the labeling:

- Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*
- Complications of Allogeneic HSCT after PD-1/PD-L1 Inhibitors *[see Warnings and Precautions (5.3)]*

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 three open-label, single arm studies (PCD4989g, BIRCH, FIR) which enrolled 1636 patients with metastatic NSCLC, and 980 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 who received a single-agent TECENTRIQ, 36% were exposed for longer than 6 months and 20% were exposed for longer than 12 months. Using the dataset described for patients who received TECENTRIQ as a single-agent, the most common adverse reactions in ≥ 20% of patients were fatigue/asthenia (48%), decreased appetite (25%), nausea (24%), cough (22%), and dyspnea (22%). In addition, the data reflect exposure to TECENTRIQ as a single agent as adjuvant therapy in 495 patients with early stage NSCLC enrolled in a randomized study (IMpower010).

In addition, the data reflect exposure to TECENTRIQ in combination with other antineoplastic drugs in 2421 patients with NSCLC (N = 2223) or SCLC (N = 198) enrolled in five randomized, active-controlled trials, including IMpower150, IMpower130 and IMpower133. Among the 2421 patients, 53% were exposed to TECENTRIQ for longer than 6 months and 29% were exposed to TECENTRIQ for longer than 12 months. Among the 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with other antineoplastic drugs, the most common adverse reactions in ≥20% of patients were fatigue/asthenia (49%), nausea (38%), alopecia (35%), constipation (29%), diarrhea (28%) and decreased appetite (27%).

The data also reflect exposure to TECENTRIQ administered in combination with cobimetinib and vemurafenib in 230 patients enrolled in IMspire150. Among the 230 patients, 62% were exposed to TECENTRIQ for longer than 6 months and 42% were exposed to TECENTRIQ for longer than 12 months.

Non-Small Cell Lung Cancer (NSCLC)

Adjuvant Treatment of Early-stage NSCLC

IMpower010

The safety of TECENTRIQ was evaluated in IMpower010, a multicenter, open-label, randomized trial for the adjuvant treatment of patients with stage IB (tumors ≥ 4 cm) - IIIA NSCLC who had complete tumor resection and received up to 4 cycles of cisplatin-based adjuvant chemotherapy. Patients received TECENTRIQ 1200 mg every 3 weeks (n=495) for 1 year (16 cycles), unless disease progression or unacceptable toxicity occurred, or best supportive care *[see Clinical Studies (14.1)]*. The median number of cycles received was 16 (range: 1, 16).

Fatal adverse reactions occurred in 1.8% of patients receiving TECENTRIQ; these included multiple organ dysfunction syndrome, pneumothorax, interstitial lung disease, arrhythmia, acute cardiac failure, myocarditis, cerebrovascular accident, death of unknown cause, and acute myeloid leukemia (1 patient each).

Serious adverse reactions occurred in 18% of patients receiving TECENTRIQ. The most frequent serious adverse reactions (>1%) were pneumonia (1.8%), pneumonitis (1.6%), and pyrexia (1.2%).

TECENTRIQ was discontinued due to adverse reactions in 18% of patients*;* the most common adverse reactions (≥1%) leading to TECENTRIQ discontinuation were pneumonitis (2.2%), hypothyroidism (1.6%), increased aspartate aminotransferase (1.4%), arthralgia (1.0%), and increased alanine aminotransferase (1.0%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 29% of patients; the most common (>1%) were rash (3.0%), hyperthyroidism (2.8%), hypothyroidism (1.6%), increased AST (1.6%), pyrexia (1.6%), increased ALT (1.4%), upper respiratory tract infection (1.4%), headache (1.2%), peripheral neuropathy (1.2%), and pneumonia (1.2%).

Tables 4 and 5 summarize adverse reactions and selected laboratory abnormalities in patients receiving TECENTRIQ in IMpower010.

Table 4: Adverse Reactions Occurring in ≥10% of Patients with Early Stage NSCLC Receiving TECENTRIQ in IMpower010

Adverse Reaction*	TECENTRIQ N = 495		Best Supportive Care N = 495	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Skin and Subcutaneous Tissue				
Rash[1]	17	1.2	1.4	0
Pruritus	10	0	0.6	0
Endocrine Disorders				
Hypothyroidism[2]	14	0	0.6	0
Respiratory, Thoracic and Mediastinal				
Cough[3]	16	0	11	0
General				
Pyrexia[4]	14	0.8	2.2	0.2
Fatigue[5]	14	0.6	5	0.2
Nervous System Disorders				
Peripheral neuropathy[6]	12	0.4	7	0.2
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[7]	14	0.8	9	0.2
Arthralgia[8]	11	0.6	6	0

*Graded per NCI CTCAE v4.0

[1] Includes rash, dermatitis, genital rash, skin exfoliation, rash maculo-papular, rash erythematous, rash papular, lichen planus, eczema asteatotic, dermatitis exfoliative, palmar-plantar erythrodysaesthesia syndrome, dyshidrotic eczema, eczema, drug eruption, rash pruritic, toxic skin eruption, dermatitis acneiform

[2] Includes hypothyroidism, autoimmune hypothyroidism, primary hypothyroidism, blood thyroid stimulating hormone increased

[3] Productive cough, upper airway cough syndrome, cough

[4] Includes pyrexia, body temperature increased, hyperthermia

[5] Includes fatigue, asthenia

[6] Includes paraesthesia, neuropathy peripheral, peripheral sensory neuropathy, hypoaesthesia, polyneuropathy, dysaesthesia, neuralgia, axonal neuropathy

[7] Includes myalgia, bone pain, back pain, spinal pain, musculoskeletal chest pain, pain in extremity, neck pain, non-cardiac chest pain, musculoskeletal discomfort, musculoskeletal stiffness, musculoskeletal pain

[8] Includes arthralgia, arthritis

Table 5: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with Early Stage NSCLC Receiving TECENTRIQ in IMpower010

Laboratory Abnormality[1]	TECENTRIQ[2]		Best Supportive Care[2]	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Chemistry				
Increased aspartate aminotransferase	34	2.5	18	0
Increased alanine aminotransferase	30	3.3	19	0.4
Hyperkalemia	24	3.5	15	2.5
Increased blood creatinine	31	0.2	23	0.2

[1] Graded per NCI CTCAE v4.0, except for increased creatinine which only includes patients with creatinine increase based on upper limit of normal definition for Grade 1 events (NCI CTCAE v5.0).
[2] The denominators used to calculate the rate varied from 78-480 for BSC arm and 483 for TECENTRIQ are for all tests of interest based on the number of patients with a baseline value and at least one post-treatment value.

Metastatic Chemotherapy-Naïve NSCLC

IMpower110

The safety of TECENTRIQ was evaluated in IMpower110, a multicenter, international, randomized, open-label study in 549 chemotherapy-naïve patients with stage IV NSCLC, including those with EGFR or ALK genomic tumor aberrations. Patients received TECENTRIQ 1200 mg every 3 weeks (n=286) or platinum-based chemotherapy consisting of carboplatin or cisplatin with either pemetrexed or gemcitabine (n=263) until disease progression or unacceptable toxicity *[see Clinical Studies (14.1)]*. IMpower110 enrolled patients whose tumors express PD-L1 (PD-L1 stained ≥ 1% of tumor cells [TC] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 1% of the tumor area). The median duration of exposure to TECENTRIQ was 5.3 months (0 to 33 months).

Fatal adverse reactions occurred in 3.8% of patients receiving TECENTRIQ; these included death (reported as unexplained death and death of unknown cause), aspiration, chronic obstructive pulmonary disease, pulmonary embolism, acute myocardial infarction, cardiac arrest, mechanical ileus, sepsis, cerebral infarction, and device occlusion (1 patient each).

Serious adverse reactions occurred in 28% of patients receiving TECENTRIQ. The most frequent serious adverse reactions (>2%) were pneumonia (2.8%), chronic obstructive pulmonary disease (2.1%) and pneumonitis (2.1%).

TECENTRIQ was discontinued due to adverse reactions in 6% of patients; the most common adverse reactions (≥2 patients) leading to TECENTRIQ discontinuation were peripheral neuropathy and pneumonitis.

Adverse reactions leading to interruption of TECENTRIQ occurred in 26% of patients; the most common (>1%) were ALT increased (2.1%), AST increased (2.1%), pneumonitis (2.1%), pyrexia (1.4%), pneumonia (1.4%) and upper respiratory tract infection (1.4%).

Tables 6 and 7 summarize adverse reactions and selected laboratory abnormalities in patients receiving TECENTRIQ in IMpower110.

Table 6: Adverse Reactions Occurring in ≥10% of Patients with NSCLC Receiving TECENTRIQ in IMpower110

Adverse Reaction	TECENTRIQ N = 286		Platinum-Based Chemotherapy N = 263	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Gastrointestinal				
Nausea	14	0.3	34	1.9
Constipation	12	1.0	22	0.8
Diarrhea	11	0	12	0.8
General				
Fatigue/asthenia	25	1.4	34	4.2
Pyrexia	14	0	9	0.4
Metabolism and Nutrition				
Decreased appetite	15	0.7	19	0
Respiratory, Thoracic and Mediastinal				
Dyspnea	14	0.7	10	0
Cough	12	0.3	10	0

Graded per NCI CTCAE v4.0

Table 7: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving TECENTRIQ in IMpower110

Laboratory Abnormality	TECENTRIQ		Platinum-Based Chemotherapy	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	69	1.8	94	20
Lymphopenia	47	9	59	17
Chemistry				
Hypoalbuminemia	48	0.4	39	2
Increased alkaline phosphatase	46	2.5	42	1.2
Hyponatremia	44	9	36	7
Increased ALT	38	3.2	32	0.8
Increased AST	36	3.2	32	0.8
Hyperkalemia	29	3.9	36	2.7
Hypocalcemia	24	1.4	24	2.7
Increased blood creatinine	24	0.7	33	1.5
Hypophosphatemia	23	3.6	21	2

Each test incidence is based on the number of patients who had at least one on-study laboratory measurement available: TECENTRIQ (range: 278-281); platinum-based chemotherapy (range: 256-260). Graded per NCI CTCAE v4.0. Increased blood creatinine only includes patients with test results above the normal range.

IMpower150

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^2 or 200 mg/m^2, and carboplatin AUC 6 mg/mL/min intravenously every 3 weeks for a maximum of 4 or 6 cycles, followed by TECENTRIQ 1200 mg with bevacizumab 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.1)]*. The median duration of exposure to TECENTRIQ was 8.3 months in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin.

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.

Serious adverse reactions occurred in 44%. The most frequent serious adverse reactions (>2%) were febrile neutropenia, pneumonia, diarrhea, and hemoptysis.

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.

Tables 8 and 9 summarize adverse reactions and laboratory abnormalities in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin in IMpower150.

Table 8: Adverse Reactions Occurring in ≥15% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

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

Adverse Reaction	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin N = 393		Bevacizumab, Paclitaxel and Carboplatin N = 394	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Nausea	39	4	32	2
Diarrhea[4]	33	6	25	0.5
Constipation	30	0.3	23	0.3
Vomiting	19	2	18	1
Metabolism and Nutrition				
Decreased appetite	29	4	21	0.8
Vascular				
Hypertension	25	9	22	8
Respiratory				
Cough	20	0.8	19	0.3
Epistaxis	17	1	22	0.3
Renal				
Proteinuria[5]	16	3	15	3

Graded per NCI CTCAE v4.0

[1] Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paraesthesia, dysesthesia, polyneuropathy

[2] Includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, contact dermatitis, rash erythematous, rash macular, pruritic rash, seborrheic dermatitis, dermatitis psoriasiform

[3] Includes pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain, back pain, myalgia, and bone pain

[4] Includes diarrhea, gastroenteritis, colitis, enterocolitis

[5] Data based on Preferred Terms since laboratory data for proteinuria were not systematically collected

Table 9: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

Laboratory Abnormality	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin		Bevacizumab, Paclitaxel and Carboplatin	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	83	10	83	9
Neutropenia	52	31	45	26
Lymphopenia	48	17	38	13
Chemistry				
Hyperglycemia	61	0	60	0
Increased BUN	52	NA[1]	44	NA[1]
Hypomagnesemia	42	2	36	1
Hypoalbuminemia	40	3	31	2
Increased AST	40	4	28	0.8
Hyponatremia	38	10	36	9

Laboratory Abnormality	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin		Bevacizumab, Paclitaxel and Carboplatin	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Increased Alkaline Phosphatase	37	2	32	1
Increased ALT	37	6	28	0.5
Increased TSH	30	NA[1]	20	NA[1]
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	NA[1]	19	NA[1]

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ with bevacizumab, paclitaxel, and carboplatin range: 337-380); bevacizumab, paclitaxel, and carboplatin (range: 337-382). Graded per NCI CTCAE v4.0
[1] NA = Not applicable. NCI CTCAE does not provide a Grades 3-4 definition for these laboratory abnormalities

IMpower130

The safety of TECENTRIQ with paclitaxel protein-bound and carboplatin was evaluated in IMpower130, a multicenter, international, randomized, open-label trial in which 473 chemotherapy-naïve patients with metastatic non-squamous NSCLC received TECENTRIQ 1200 mg and carboplatin AUC 6 mg/mL/min intravenously on Day 1 and paclitaxel protein-bound 100 mg/m^2 intravenously on Day 1, 8, and 15 of each 21-day cycle for a maximum of 4 or 6 cycles, followed by TECENTRIQ 1200 mg intravenously every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.1)].* Among patients receiving TECENTRIQ, 55% were exposed for 6 months or longer and 3.5% were exposed for greater than one year.

Fatal adverse reactions occurred in 5.3% of patients receiving TECENTRIQ; these included pneumonia (1.1%), pulmonary embolism (0.8%), myocardial infarction (0.6%), cardiac arrest (0.4%), pneumonitis (0.4%) and sepsis, septic shock, staphylococcal sepsis, aspiration, respiratory distress, cardiorespiratory arrest, ventricular tachycardia, death (not otherwise specified), and hepatic cirrhosis (0.2% each).

Serious adverse reactions occurred in 51% of patients receiving TECENTRIQ. The most frequent serious adverse reactions (≥2%) were pneumonia (6%), diarrhea (3%), lung infection (3%), pulmonary embolism (3%), chronic obstructive pulmonary disease exacerbation (2.5%), dyspnea (2.3%), and febrile neutropenia (1.9%).

TECENTRIQ was discontinued due to adverse reactions in 13% of patients; the most common adverse reactions leading to discontinuation were pneumonia (0.8%), pulmonary embolism (0.8%), fatigue (0.6%), dyspnea (0.6%), pneumonitis (0.6%), neutropenia (0.4%), nausea (0.4%), renal failure (0.4%), cardiac arrest (0.4%), and septic shock (0.4%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 62% of patients; the most common (>1%) were neutropenia, thrombocytopenia, anemia, diarrhea, fatigue/asthenia, pneumonia, dyspnea, pneumonitis, pyrexia, nausea, acute kidney injury, vomiting, pulmonary embolism, arthralgia, infusion-related reaction, abdominal pain, chronic obstructive pulmonary disease exacerbation, dehydration, and hypokalemia.

Tables 10 and 11 summarize adverse reactions and laboratory abnormalities in patients receiving TECENTRIQ with paclitaxel protein-bound and carboplatin in IMpower130.

Table 10: Adverse Reactions Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in IMpower130

Adverse Reaction	TECENTRIQ with Paclitaxel Protein-Bound and Carboplatin N = 473		Paclitaxel Protein-Bound and Carboplatin N = 232	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
General				
Fatigue/Asthenia	61	11	60	8
Gastrointestinal				
Nausea	50	3.4	46	2.2
Diarrhea [1]	43	6	32	6
Constipation	36	1.1	31	0
Vomiting	27	2.7	19	2.2
Musculoskeletal and Connective Tissue				
Myalgia/Pain [2]	38	3	22	0.4
Nervous System				
Neuropathy [3]	33	2.5	28	2.2
Respiratory, Thoracic and Mediastinal				
Dyspnea [4]	32	4.9	25	1.3
Cough	27	0.6	17	0
Skin and Subcutaneous Tissue				
Alopecia	32	0	27	0
Rash [5]	20	0.6	11	0.9
Metabolism and Nutrition				
Decreased appetite	30	2.1	26	2.2

Graded per NCI CTCAE v4.0

[1] Includes diarrhea, colitis, and gastroenteritis

[2] Includes back pain, pain in extremity, myalgia, musculoskeletal chest pain, bone pain, neck pain and musculoskeletal discomfort

[3] Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy

[4] Includes dyspnea, dyspnea exertional and wheezing

[5] Includes rash, rash maculo-papular, eczema, rash pruritic, rash erythematous, dermatitis, dermatitis contact, drug eruption, seborrheic dermatitis and rash macular.

Table 11: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving TECENTRIQ in IMpower130

Laboratory Abnormality	TECENTRIQ with Paclitaxel Protein-Bound and Carboplatin N = 473		Paclitaxel Protein-Bound and Carboplatin N = 232	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	92	33	87	25
Neutropenia	75	50	67	39
Thrombocytopenia	73	19	59	13
Lymphopenia	71	23	61	16
Chemistry				
Hyperglycemia	75	8	66	8
Hypomagnesemia	50	3.4	42	3.2
Hyponatremia	37	9	28	7
Hypoalbuminemia	35	1.3	31	0
Increased ALT	31	2.8	24	3.9
Hypocalcemia	31	2.6	27	1.8
Hypophosphatemia	29	6	20	3.2
Increased AST	28	2.2	24	1.8
Increased TSH	26	NA[1]	5	NA[1]
Hypokalemia	26	6	24	4.4
Increased Alkaline Phosphatase	25	2.6	22	1.3
Increased Blood Creatinine	23	2.8	16	0.4
Hyperphosphatemia	21	NA[1]	13	NA[1]

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ with paclitaxel protein-bound and carboplatin (range: 423 - 467); paclitaxel protein-bound and carboplatin (range: 218 - 229). Graded per NCI CTCAE v4.0.
[1] NA = Not applicable. NCI CTCAE does not provide a Grades 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 (14.1)]*. 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^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 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 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.

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.

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.

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. 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.

Tables 12 and 13 summarize adverse reactions and laboratory abnormalities, respectively, in OAK.

Table 12: Adverse Reactions Occurring in ≥10% of Patients with NSCLC Receiving TECENTRIQ in OAK

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

Graded per NCI CTCAE v4.0

[1] Includes fatigue and asthenia

[2] Includes cough and exertional cough

[3] Includes musculoskeletal pain, musculoskeletal stiffness, musculoskeletal chest pain, myalgia

[4] Includes rash, erythematous rash, generalized rash, maculopapular rash, papular rash, pruritic rash, pustular rash, pemphigoid

Table 13: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in OAK

Laboratory Abnormality	TECENTRIQ		Docetaxel	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Anemia	67	3	82	7
Lymphocytopenia	49	14	60	21
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

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). Graded according to NCI CTCAE version 4.0

Small Cell Lung Cancer (SCLC)

The safety of TECENTRIQ with carboplatin and etoposide was evaluated in IMpower133, a randomized, multicenter, double-blind, placebo-controlled trial in which 198 patients with ES-SCLC received TECENTRIQ 1200 mg and carboplatin AUC 5 mg/mL/min on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2 and 3 of each 21-day cycle for a maximum of 4 cycles, followed by TECENTRIQ 1200 mg every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.2)]*. Among 198 patients receiving TECENTRIQ, 32% were exposed for 6 months or longer and 12% were exposed for 12 months or longer.

Fatal adverse reactions occurred in 2% of patients receiving TECENTRIQ. These included pneumonia, respiratory failure, neutropenia, and death (1 patient each).

Serious adverse reactions occurred in 37% of patients receiving TECENTRIQ. Serious adverse reactions in >2% were pneumonia (4.5%), neutropenia (3.5%), febrile neutropenia (2.5%), and thrombocytopenia (2.5%).

TECENTRIQ was discontinued due to adverse reactions in 11% of patients. The most frequent adverse reaction requiring permanent discontinuation in >2% of patients was infusion-related reactions (2.5%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 59% of patients; the most common (>1%) were neutropenia (22%), anemia (9%), leukopenia (7%), thrombocytopenia (5%), fatigue (4.0%), infusion-related reaction (3.5%), pneumonia (2.0%), febrile neutropenia (1.5%), increased ALT (1.5%), and nausea (1.5%).

Tables 14 and 15 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ with carboplatin and etoposide in IMpower133.

Table 14: Adverse Reactions Occurring in ≥20% of Patients with SCLC Receiving TECENTRIQ in IMpower133

Adverse Reaction	TECENTRIQ with Carboplatin and Etoposide N = 198		Placebo with Carboplatin and Etoposide N = 196	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
General				
Fatigue/asthenia	39	5	33	3
Gastrointestinal				
Nausea	38	1	33	1
Constipation	26	1	30	1
Vomiting	20	2	17	3
Skin and Subcutaneous Tissue				
Alopecia	37	0	35	0
Metabolism and Nutrition				
Decreased appetite	27	1	18	0

Graded per NCI CTCAE v4.0

Table 15: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with SCLC Receiving TECENTRIQ in IMpower133

Laboratory Abnormality	TECENTRIQ with Carboplatin and Etoposide		Placebo with Carboplatin and Etoposide	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Anemia	94	17	93	19
Neutropenia	73	45	76	48
Thrombocytopenia	58	20	53	17
Lymphopenia	46	14	38	11
Chemistry				
Hyperglycemia	67	10	65	8
Increased Alkaline Phosphatase	38	1	35	2
Hyponatremia	34	15	33	11
Hypoalbuminemia	32	1	30	0
Decreased TSH[2]	28	NA[1]	15	NA[1]
Hypomagnesemia	31	5	35	6
Hypocalcemia	26	3	28	5
Increased ALT	26	3	31	1
Increased AST	22	1	21	2
Increased Blood Creatinine	22	4	15	1
Hyperphosphatemia	21	NA[1]	23	NA[1]
Increased TSH[2]	21	NA[1]	7	NA[1]

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: 181-193); Placebo (range: 181-196). Graded per NCI CTCAE v4.0

[1] NA = Not applicable. [2] TSH = thyroid-stimulating hormone. NCI CTCAE v4.0 does not include these laboratories.

Hepatocellular Carcinoma (HCC)

The safety of TECENTRIQ in combination with bevacizumab was evaluated in IMbrave150, a multicenter, international, randomized, open-label trial in patients with locally advanced or metastatic or unresectable hepatocellular carcinoma who have not received prior systemic treatment *[see Clinical Studies (14.3)]*. Patients received 1,200 mg of TECENTRIQ intravenously followed by 15 mg/kg bevacizumab (n=329) every 3 weeks, or 400 mg of sorafenib (n=156) given orally twice daily, until disease progression or unacceptable toxicity. The median duration of exposure to TECENTRIQ was 7.4 months (range: 0-16 months) and to bevacizumab was 6.9 months (range: 0-16 months).

Fatal adverse reactions occurred in 4.6% of patients in the TECENTRIQ and bevacizumab arm. The most common adverse reactions leading to death were gastrointestinal and esophageal varices hemorrhage (1.2%) and infections (1.2%).

Serious adverse reactions occurred in 38% of patients in the TECENTRIQ and bevacizumab arm. The most frequent serious adverse reactions (≥ 2%) were gastrointestinal hemorrhage (7%), infections (6%), and pyrexia (2.1%).

Adverse reactions leading to discontinuation of TECENTRIQ occurred in 9% of patients in the TECENTRIQ and bevacizumab arm. The most common adverse reactions leading to TECENTRIQ discontinuation were hemorrhages (1.2%), including gastrointestinal, subarachnoid, and pulmonary hemorrhages; increased transaminases or bilirubin (1.2%); infusion-related reaction/cytokine release syndrome (0.9%); and autoimmune hepatitis (0.6%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 41% of patients in the TECENTRIQ and bevacizumab arm; the most common (≥ 2%) were liver function laboratory abnormalities including increased transaminases, bilirubin, or alkaline phosphatase (8%); infections (6%); gastrointestinal hemorrhages (3.6%); thrombocytopenia/decreased platelet count (3.6%); hyperthyroidism (2.7%); and pyrexia (2.1%).

Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 12% of patients in the TECENTRIQ and bevacizumab arm.

Tables 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ and bevacizumab in IMbrave150.

Table 16: Adverse Reactions Occurring in ≥10% of Patients with HCC Receiving TECENTRIQ in IMbrave150

Adverse Reaction	TECENTRIQ in combination with Bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades[2] (%)	Grades 3–4[2] (%)	All Grades[2] (%)	Grades 3–4[2] (%)
Vascular Disorders				
Hypertension	30	15	24	12
General Disorders and Administration Site Conditions				
Fatigue/asthenia[1]	26	2	32	6
Pyrexia	18	0	10	0
Renal and Urinary Disorders				
Proteinuria	20	3	7	0.6
Investigations				
Weight Decreased	11	0	10	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	19	0	10	0
Rash	12	0	17	2.6
Gastrointestinal Disorders				
Diarrhea	19	1.8	49	5
Constipation	13	0	14	0
Abdominal Pain	12	0	17	0
Nausea	12	0	16	0
Vomiting	10	0	8	0
Metabolism and Nutrition Disorders				
Decreased Appetite	18	1.2	24	3.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	12	0	10	0
Epistaxis	10	0	4.5	0
Injury, Poisoning and Procedural Complications				
Infusion-Related Reaction	11	2.4	0	0

[1] Includes fatigue and asthenia
[2] Graded per NCI CTCAE v4.0

Table 17: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with HCC Receiving TECENTRIQ in IMbrave150

Laboratory Abnormality	TECENTRIQ in combination with Bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
Chemistry				

Laboratory Abnormality	TECENTRIQ in combination with Bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
Increased AST	86	16	90	16
Increased Alkaline Phosphatase	70	4	76	4.6
Increased ALT	62	8	70	4.6
Decreased Albumin	60	1.5	54	0.7
Decreased Sodium	54	13	49	9
Increased Glucose	48	9	43	4.6
Decreased Calcium	30	0.3	35	1.3
Decreased Phosphorus	26	4.7	58	16
Increased Potassium	23	1.9	16	2
Hypomagnesemia	22	0	22	0
Hematology				
Decreased Platelet	68	7	63	4.6
Decreased Lymphocytes	62	13	58	11
Decreased Hemoglobin	58	3.1	62	3.9
Increased Bilirubin	57	8	59	14
Decreased Leukocyte	32	3.4	29	1.3
Decreased Neutrophil	23	2.3	16	1.1

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ plus bevacizumab (222-323) and sorafenib (90-153)

[1] Graded per NCI CTCAE v4.0

Melanoma

The safety of TECENTRIQ, administered with cobimetinib and vemurafenib was evaluated in IMspire150, a double-blind, randomized (1:1), placebo-controlled study conducted in patients with previously untreated BRAF V600 mutation-positive metastatic or unresectable melanoma *[see Clinical Studies (14.4)]*. Patients received TECENTRIQ with cobimetinib and vemurafenib (N=230) or placebo with cobimetinib and vemurafenib (n=281).

Among the 230 patients who received TECENTRIQ administered with cobimetinib and vemurafenib, the median duration of exposure to TECENTRIQ was 9.2 months (range: 0-30 months) to cobimetinib was 10.0 months (range: 1-31 months) and to vemurafenib was 9.8 months (range: 1-31 months).

Fatal adverse reactions occurred in 3% of patients in the TECENTRIQ plus cobimetinib and vemurafenib arm. Adverse reactions leading to death were hepatic failure, fulminant hepatitis, sepsis, septic shock, pneumonia, and cardiac arrest.

Serious adverse reactions occurred in 45% of patients in the TECENTRIQ plus cobimetinib and vemurafenib arm. The most frequent (≥ 2%) serious adverse reactions were hepatotoxicity (7%), pyrexia (6%), pneumonia (4.3%), malignant neoplasms (2.2%), and acute kidney injury (2.2%).

Adverse reactions leading to discontinuation of TECENTRIQ occurred in 21% of patients in the TECENTRIQ plus cobimetinib and vemurafenib arm. The most frequent (≥ 2%) adverse

reactions leading to TECENTRIQ discontinuation were increased ALT (2.2%) and pneumonitis (2.6%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 68% of patients in the TECENTRIQ plus cobimetinib and vemurafenib arm. The most frequent (≥ 2%) adverse reactions leading to TECENTRIQ interruption were pyrexia (14%), increased ALT (13%), hyperthyroidism (10%), increased AST (10%), increased lipase (9%), increased amylase (7%), pneumonitis (5%), increased CPK (4.3%), diarrhea (3.5%), pneumonia (3.5%), asthenia (3%), rash (3%), influenza (3%), arthralgia (2.6%), fatigue (2.2%), dyspnea (2.2%), cough (2.2%), peripheral edema (2.2%), uveitis (2.2%), bronchitis (2.2%), hypothyroidism (2.2%), and respiratory tract infection (2.2%).

Tables 18 and 19 summarize the incidence of adverse reactions and laboratory abnormalities in Study IMspire150.

Table 18: Adverse Reactions Occurring in ≥10% of Patients on the TECENTRIQ plus Cobimetinib and Vemurafenib Arm or the Placebo plus Cobimetinib and Vemurafenib Arm and at a Higher Incidence (Between Arm Difference of ≥ 5% All Grades or ≥ 2% Grades 3-4 TECENTRIQ in IMspire150)

Adverse Reaction	TECENTRIQ in combination with Cobimetinib and Vemurafenib (n=230)		Placebo with Cobimetinib and Vemurafenib (n=281)	
	All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)
Skin and Subcutaneous Tissue Disorders				
Rash [1]	75	27	72	23
Pruritus	26	<1	17	<1
Photosensitivity reaction	21	<1	25	3.2
General Disorders and Administration Site Conditions				
Fatigue [2]	51	3	45	1.8
Pyrexia [3]	49	1.7	35	2.1
Edema [4]	26	<1	21	0
Gastrointestinal Disorders				
Hepatotoxicity [5]	50	21	36	13
Nausea	30	<1	32	2.5
Stomatitis [6]	23	1.3	15	<1
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain [7]	62	4.3	48	3.2
Endocrine Disorders				
Hypothyroidism [8]	22	0	10	0
Hyperthyroidism	18	<1	8	0
Injury, Poisoning and Procedural Complications				
Infusion-related reaction [9]	10	2.6	8	<1
Respiratory, Thoracic and Mediastinal Disorders				
Pneumonitis [10]	12	1.3	6	<1
Vascular Disorders				
Hypertension [11]	17	10	18	7

[1] Includes rash, rash maculo-papular, dermatitis acneiform, rash macular, rash erythematous, eczema, skin exfoliation, rash papular, rash pustular, palmar-plantar erythrodysaesthesia syndrome, dermatitis, dermatitis contact, erythema multiforme, rash pruritic, drug eruption, nodular rash, dermatitis allergic, exfoliative rash, dermatitis exfoliative generalised and rash morbilliform

[2] Includes fatigue, asthenia and malaise

[3] Includes pyrexia and hyperpyrexia

[4] Includes edema peripheral, lymphoedema, oedema, face oedema, eyelid oedema, periorbital oedema, lip oedema and generalised oedema

[5] Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, transaminases increased, hepatitis, hepatic enzyme increased, hepatotoxicity, hypertransaminasaemia, bilirubin conjugated increased, hepatocellular injury, hyperbilirubinaemia, liver function test increased, hepatic failure, hepatitis fulminant and liver function test abnormal

[6] Includes stomatitis, mucosal inflammation, aphthous ulcer, mouth ulceration, cheilitis and glossitis

[7] Includes arthralgia, myalgia, pain in extremity, back pain, musculoskeletal pain, arthritis, neck pain, musculoskeletal chest pain, musculoskeletal stiffness, bone pain, spinal pain, immune-mediated arthritis, joint stiffness and non-cardiac chest pain

[8] Includes hypothyroidism and blood thyroid stimulating hormone increased

[9] Includes infusion related reaction and hypersensitivity

[10] Includes pneumonitis and interstitial lung disease

[11] Includes hypertension, blood pressure increased, hypertensive crisis

Clinically important adverse reactions in < 10% of patients who received TECENTRIQ plus cobimetinib and vemurafenib were:

Cardiac Disorders: Arrhythmias, ejection fraction decreased, electrocardiogram QT prolonged

Eye Disorders: Uveitis

Gastrointestinal disorders: Pancreatitis

Infections and infestations: Pneumonia, urinary tract infection

Metabolism and nutrition disorders: Hyperglycemia

Nervous system Disorders: Dizziness, dysgeusia, syncope

Respiratory, thoracic and mediastinal disorders: Dyspnea, oropharyngeal pain

Skin and Subcutaneous Tissue Disorders: Vitiligo

Table 19: Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients Receiving TECENTRIQ Plus Cobimetinib and Vemurafenib Arm or the Placebo Plus Cobimetinib and Vemurafenib Arm and at a Higher Incidence (Between Arm Difference of ≥ 5% All Grades or ≥ 2% Grades 3-4) in IMspire150

Laboratory Abnormality	TECENTRIQ in combination with Cobimetinib and Vemurafenib (n=230)		Placebo with Cobimetinib and Vemurafenib (n=281)	
	All Grades (%)	Grade 3–4 (%)	All Grades (%)	Grade 3–4 (%)
Hematology				
Decreased Lymphocytes	80	24	72	17
Decreased Hemoglobin	77	2.6	72	2.2
Decreased Platelet	34	1.3	24	0.4
Decreased Neutrophils	26	2.2	19	1.5
Chemistry				
Increased Creatine Kinase	88	22	81	18
Increased AST	80	13	68	6
Increased ALT	79	18	62	12
Increased Triacylglycerol Lipase	75	46	62	35
Increased Alkaline Phosphatase	73	6	63	2.9
Decreased Phosphorus	67	22	64	14
Increased Amylase	51	13	45	13
Increased Blood Urea Nitrogen	47	NA[1]	37	NA[1]
Decreased Albumin	43	0.9	34	1.5
Increased Bilirubin	42	3.1	33	0.7
Decreased Calcium	41	1.3	28	0
Decreased Sodium	40	5	34	7
Decreased Thyroid-Stimulating Hormone	38	NA[1]	23	NA[1]
Increased Thyroid-Stimulating Hormone [2]	37	NA[1]	33	NA[1]
Decreased Potassium	36	5	22	4.3
Increased Triiodothyronine	33	NA[1]	18	NA[1]
Increased Free Thyroxine	32	NA[1]	21	NA[1]
Decreased Total Triiodothyronine	32	NA[1]	8	NA[1]
Increased Potassium	29	1.3	19	1.4
Decreased Triiodothyronine	27	NA[1]	21	NA[1]
Increased Sodium	20	0	13	0.4

Graded per NCI CTCAE v4.0.
Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ plus cobimetinib and vemurafenib (28-277), placebo plus cobimetinib and vemurafenib arm (25-230).
[1] NA= Not applicable. NCI CTCAE v4.0 does not include these laboratories.
[2] Increased Thyroid Stimulating Hormone has a difference <5% (All Grades) between arms and is included for clinical completeness.

Unresectable or Metastatic Alveolar Soft Part Sarcoma (ASPS)

The safety of TECENTRIQ was evaluated in 47 adult and 2 pediatric patients enrolled in Study ML39345 *[see Clinical Studies (14.5)].* Adult patients received TECENTRIQ 1200 mg every 3 weeks and pediatric patients received 15 mg/kg up to a maximum 1200 mg every 3 weeks until disease progression or unacceptable toxicity. The median duration of exposure to TECENTRIQ was 8.9 months (1 to 40 months).

Serious adverse reactions occurred in 41% of patients receiving TECENTRIQ. The most frequent serious adverse reactions (>2%) were fatigue, pain in extremity, pulmonary hemorrhage, and pneumonia (4.1% each).

Dosage interruptions of TECENTRIQ due to an adverse reaction occurred in 35% of patients. The most common adverse reactions (≥3%) leading to dose interruptions were pneumonitis and pain in extremity (4.1% each).

Tables 20 and 21 summarize adverse reactions and laboratory abnormalities in Study ML39345.

Table 20: Adverse Reactions Occurring in ≥15% of Patients with ASPS Receiving TECENTRIQ in ML39345

Adverse Reaction	TECENTRIQ N = 49	
	All Grades (%)	Grades 3–4 (%)
General disorders and administration site conditions		
Fatigue	55	2
Pyrexia	25	2
Influenza like illness	18	0
Gastrointestinal disorders		
Nausea	43	0
Vomiting	37	0
Constipation	33	0
Diarrhea	27	2
Abdominal pain[1]	25	0
Metabolism and nutrition disorders		
Decreased appetite	22	2
Respiratory, Thoracic and Mediastinal		
Cough[2]	45	0
Dyspnea	33	0
Rhinitis allergic	16	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[3]	67	8
Skin and subcutaneous tissue disorders		
Rash[4]	47	2
Nervous system disorders		
Headache	43	4
Dizziness[5]	29	4
Vascular disorders		
Hypertension	43	6
Hemorrhage[6]	29	2
Psychiatric disorders		
Insomnia	27	0
Anxiety	25	0
Cardiac Disorders		
Arrhythmia[7]	22	2
Endocrine disorders		
Hypothyroidism[8]	25	0
Investigations		
Weight decreased	18	0

Weight increased	16	6

Graded per NCI CTCAE v4.0

[1]Includes abdominal pain and abdominal pain upper
[2]Includes cough, upper-airway cough syndrome, and productive cough
[3]Includes arthralgia, pain in extremity, myalgia, non-cardiac chest pain, neck pain, musculoskeletal chest pain, and back pain
[4]Includes rash maculo-papular, rash, dermatitis acneiform, eczema, skin exfoliation, and drug eruption
[5]Includes vertigo and dizziness
[6]Includes pulmonary hemorrhage, hemoptysis, conjunctival hemorrhage, epistaxis, hematuria, rectal hemorrhage, and laryngeal hemorrhage
[7]Includes atrial fibrillation, sinus bradycardia, ventricular tachycardia, and sinus tachycardia
[8]Includes hypothyroidism and blood thyroid stimulating hormone increased

Table 21: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with ASPS Receiving TECENTRIQ in ML39345

Laboratory Abnormality [1]	**TECENTRIQ[2]**	
	All Grades (%)	**Grades 3–4 (%)**
Hematology		
Decreased Hemoglobin	63	0
Decreased Platelets	27	0
Increased Platelets	29	0
Chemistry		
Increased Alkaline Phosphatase	29	0
Decreased Amylase	40	0
Increased Amylase	20	20
Decreased Bilirubin	49	0
Decreased Calcium	47	0
Increased Calcium	25	14
Decreased Glucose	33	0
Increased Glucose	78	0
Decreased Glucose (fasting)	25	0
Decreased Magnesium	21	0
Increased Magnesium	26	26
Increased AST	39	2
Increased ALT	33	2
Decreased Sodium	43	0
Increased Lipase	25	25

[1] Laboratory tests which do not have NCI CTCAE grading criteria are also included for All Grade assessments, which were performed by comparing to respective lab normal ranges.
[2] The denominators used to calculate the rate varied from 4-49 for all tests of interest based on the number of patients with a baseline value and at least one on-study laboratory measurement available.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of TECENTRIQ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Cardiac: pericarditis, pericardial effusion, cardiac tamponade

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

Alveolar Soft Part Sarcoma

The safety and effectiveness of TECENTRIQ for unresectable or metastatic ASPS have been established in pediatric patients aged 2 years and older. Use of TECENTRIQ for this indication is supported by evidence from an adequate and well controlled study of TECENTRIQ in adults and 2 adolescent pediatric patients (≥12 years of age) with ASPS with additional pharmacokinetic and safety data in pediatric patients 2 years to <17 years. These data suggest that atezolizumab exposure in pediatric patients aged 2 years and older is comparable with that of adults and is expected to result in similar safety and efficacy to that of adults *[see Adverse Reactions (6.1), Pharmacokinetics (12.3), Clinical Studies (14.5)]*. The course of unresectable or metastatic ASPS is sufficiently similar between pediatric patients 2 to 11 years old and that of adults and adolescent patients to allow extrapolation of efficacy and safety to pediatric patients 2 years and older.

The safety and effectiveness of TECENTRIQ for ASPS have not been established in pediatric patients younger than 2 years of age.

Solid Tumors and Lymphomas

The safety and effectiveness of TECENTRIQ in pediatric patients have not been established in non-small cell lung cancer, small-cell lung cancer, hepatocellular carcinoma, or melanoma.

The safety and effectiveness of TECENTRIQ were assessed, but not established in a single-arm, multi-center, multi-cohort trial (NCT02541604) in 60 pediatric patients aged 7 months to <17 years with relapsed or progressive solid tumors and lymphomas. No new safety signals were observed in pediatric patients in this study.

8.5 Geriatric Use

Of 2616 patients with metastatic NSCLC and other tumor types treated with single agent TECENTRIQ in clinical studies, 49% were 65 years and over and 15% were 75 years and over.

Of 2421 patients with NSCLC and SCLC treated with TECENTRIQ in combination with other antineoplastic drugs in clinical studies, 48% were 65 years and over and 10% were 75 years and over.

No overall differences in safety or effectiveness were observed between patients aged 65 years or older 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 (atezolizumab) injection for intravenous use is a sterile, preservative-free, colorless to slightly yellow solution in single-dose vials. Each 20 mL vial contains 1200 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), polysorbate 20 (8 mg), and sucrose (821.6 mg), with a pH of 5.8. Each 14 mL vial contains 840 mg of atezolizumab and is formulated in glacial acetic acid (11.5 mg), L-histidine (43.4 mg), polysorbate 20 (5.6 mg), and sucrose (575.1 mg) with a pH of 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.

In mouse models of cancer, dual inhibition of the PD-1/PD-L1 and MAPK pathways suppresses tumor growth and improves tumor immunogenicity through increased antigen presentation and T cell infiltration and activation compared to targeted therapy alone.

12.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of atezolizumab have not been fully characterized.

12.3 Pharmacokinetics

Atezolizumab exposure increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg (0.07 to 1.33 times of the approved recommended doses), including a dose of 1200 mg administered every 3 weeks. Steady state was achieved after 6 to 9 weeks following multiple doses. The systemic accumulation ratio for every 2 weeks administration and every 3 weeks administration is 3.3- and 1.9- fold, respectively.

Distribution

The volume of distribution at steady state is 6.9 L.

Elimination

The clearance (CV%) is 0.2 L/day (29%) and the terminal half-life is 27 days. Atezolizumab clearance was found to decrease over time, with a mean maximal reduction (CV%) from baseline value of 17% (41%); however, the decrease in clearance was not considered clinically relevant.

Specific Populations

The following factors had no clinically significant effect on the systemic exposure of atezolizumab: age (2 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), moderate hepatic impairment (bilirubin >1.5 to 3x ULN and any AST), level of PD-L1 expression, or performance status.

Pediatric Patients

Atezolizumab serum concentrations with weight-based dosing at 15 mg/kg up to a maximum of 1200 mg every 3 weeks, in pediatric patients (2 years to <17 years) with relapsed or progressive solid tumors and lymphomas, are comparable to those of adult patients receiving 1200 mg every 3 weeks; while the exposure tended to be lower in pediatric patients less than 12 years old, this is not considered to be clinically relevant.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other products.

During the first year of treatment with TECENTRIQ across 8 clinical studies, 13% to 36% of patients developed anti-atezolizumab antibodies. Median atezolizumab clearance in patients who tested positive for ADA was 19% (minimum 18%, maximum 49%) higher as compared to atezolizumab clearance in patients who tested negative for ADA; this change in clearance is not expected to be clinically significant.

In OAK and IMbrave150, exploratory analyses showed that the subset of patients who were ADA-positive appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for ADA *[see Clinical Studies (14.1, 14.3)]*. In study IMpower150, the impact of ADA on efficacy did not appear to be clinically significant *[see Clinical Studies (14.1)]*. In the remaining studies, there is insufficient information to characterize the effect of ADA on efficacy.

The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Across clinical studies, 4.3% to 27.5% of neutralizing antibody (NAb)-evaluable patients had a positive NAb status at any timepoint post-treatment. The effect of NAb on atezolizumab exposure and safety did not appear to be clinically significant. The effect of NAb on key efficacy endpoints is uncertain due to small sample sizes.

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 Non-Small Cell Lung Cancer

Adjuvant Treatment of Stage II-IIIA NSCLC with PD-L1 Expression ≥ 1%

The efficacy of TECENTRIQ was evaluated in IMpower010 (NCT02486718), a multi-center, randomized, open-label trial for the adjuvant treatment of patients with NSCLC who had complete tumor resection and were eligible to receive cisplatin-based adjuvant chemotherapy. Eligible patients were required to have Stage IB (tumors ≥ 4 cm) – Stage IIIA NSCLC per the Union for International Cancer Control/American Joint Committee on Cancer staging system, 7th edition. Patients were excluded if they had a history of autoimmune disease; a history of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis; administration of a live, attenuated vaccine within 28 days prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization.

A total of 1005 patients who had complete tumor resection and received cisplatin-based adjuvant chemotherapy were randomized (1:1) to receive TECENTRIQ 1200 mg intravenous infusion every 3 weeks for 16 cycles, unless disease recurrence or unacceptable toxicity occurred, or best supportive care (BSC). Randomization was stratified by sex, stage of disease, histology, and PD-L1 expression.

Tumor assessments were conducted at baseline of the randomization phase and every 4 months for the first year following Cycle 1, Day 1 and then every 6 months until year five, then annually thereafter.

The median age was 62 years (range: 26 to 84), and 67% of patients were male. The majority of patients were White (73%) and Asian (24%). Most patients were current or previous smokers (78%) and baseline ECOG performance status in patients was 0 (55%) or 1 (44%). Overall, 12% of patients had Stage IB, 47% had Stage II and 41% had Stage IIIA disease. PD-L1 expression, defined as the percentage of tumor cells expressing PD-L1 as measured by the VENTANA PD-L1 (SP263) assay, was ≥ 1% in 53% of patients, <1% in 44% and unknown in 2.6%.

The primary efficacy outcome measure was disease-free survival (DFS) as assessed by the investigator. The primary efficacy analysis population (n = 476) was patients with Stage II – IIIA NSCLC with PD-L1 expression on ≥ 1% of tumor cells (PD-L1 ≥ 1% TC). DFS was defined as the time from the date of randomization to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC, or death due to any cause, whichever occurred first. A key secondary efficacy outcome measure was overall survival (OS) in the intent-to-treat population.

At the time of the interim DFS analysis, the study demonstrated a statistically significant improvement in DFS in the PD-L1 ≥ 1% TC, Stage II – IIIA patient population.

Efficacy results are presented in Table 22 and Figure 1.

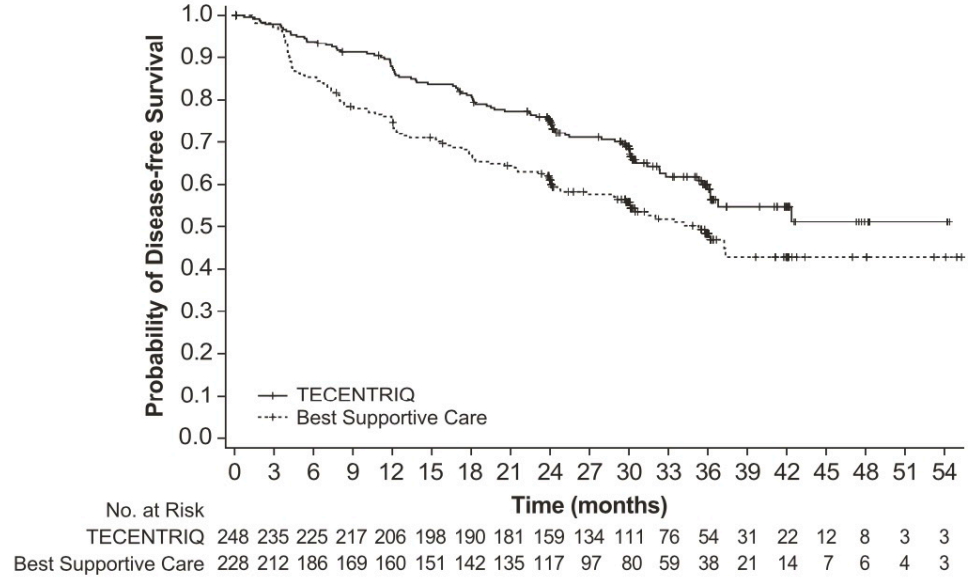
Table 22 Efficacy Results from IMpower010 in Patients with Stage II - IIIA NSCLC with PD-L1 expression ≥ 1% TC

	Arm A: TECENTRIQ N = 248	Arm B: Best Supportive Care N = 228
Disease-Free Survival		
Number of events (%)	88 (35)	105 (46)
Median, months	NR	35.3
(95% CI)	(36.1, NE)	(29.0, NE)
Hazard ratio[1] (95% CI)	0.66 (0.50, 0.88)	
p-value	0.004	

CI = Confidence interval, NE = Not estimable, NR = Not reached
[1] Stratified by stage, sex, and histology

In a pre-specified secondary subgroup analysis of patients with PD-L1 TC ≥ 50% Stage II – IIIA NSCLC (n=229), the median DFS was not reached (95% CI: 42.3 months, NE) for patients in the TECENTRIQ arm and was 35.7 months (95% CI: 29.7, NE) for patients in the best supportive care arm, with a HR of 0.43 (95% CI: 0.27, 0.68). In an exploratory subgroup analysis of patients with PD-L1 TC 1-49% Stage II – IIIA NSCLC (n=247), the median DFS was 32.8 months (95% CI: 29.4, NE) for patients in the TECENTRIQ arm and 31.4 months (95% CI: 24.0, NE) for patients in the best supportive care arm, with a HR of 0.87 (95% CI: 0.60, 1.26).

Figure 1: Kaplan-Meier Plot of Disease-Free Survival in IMpower010 in Patients with Stage II – IIIA NSCLC with PD-L1 expression ≥ 1% TC



At the time of the DFS interim analysis, 19% of patients in the PD-L1 ≥1% TC Stage II – IIIA patient population had died. An exploratory analysis of OS in this population resulted in a stratified HR of 0.77 (95% CI: 0.51, 1.17).

Metastatic Chemotherapy-Naïve NSCLC with High PD-L1 Expression

The efficacy of TECENTRIQ was evaluated in IMpower110 (NCT02409342), a multicenter, international, randomized, open-label trial in patients with stage IV NSCLC whose tumors

express PD-L1 (PD-L1 stained ≥ 1% of tumor cells [TC ≥ 1%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 1% of the tumor area [IC ≥ 1%]), who had received no prior chemotherapy for metastatic disease. PD-L1 tumor status was determined based on immunohistochemistry (IHC) testing using the VENTANA PD-L1 (SP142) Assay. The evaluation of efficacy is based on the subgroup of patients with high PD-L1 expression (TC ≥ 50% or IC ≥ 10%), excluding those with EGFR or ALK genomic tumor aberrations. 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.

Randomization was stratified by sex, ECOG performance status, histology (non-squamous vs. squamous) and PD-L1 expression (TC ≥ 1% and any IC vs. TC < 1% and IC ≥ 1%). Patients were randomized (1:1) to receive one of the following treatment arms:

- Arm A: TECENTRIQ 1200 mg every 3 weeks until disease progression or unacceptable toxicity
- Arm B: Platinum-based chemotherapy

Arm B platinum-based chemotherapy regimens for non-squamous NSCLC consisted of cisplatin (75 mg/m²) and pemetrexed (500 mg/m²) OR carboplatin (AUC 6 mg/mL/min) and pemetrexed (500 mg/m²) on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles followed by pemetrexed (500 mg/m²) until disease progression or unacceptable toxicity.

Arm B platinum-based chemotherapy regimens for squamous NSCLC consisted of cisplatin (75 mg/m²) on Day 1 with gemcitabine (1250 mg/m^2) on Days 1 and 8 of each 21-day cycle OR carboplatin (AUC 5 mg/mL/min) on Day 1 with gemcitabine (1000 mg/m^2) on Days 1 and 8 of each 21-day cycle for a maximum of 4 or 6 cycles followed by best supportive care until disease progression or unacceptable toxicity.

Administration of TECENTRIQ was permitted beyond RECIST-defined disease progression. 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 prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define subgroups for pre-specified analyses.

The major efficacy outcome measure was overall survival (OS) sequentially tested in the following subgroups of patients, excluding those with EGFR or ALK genomic tumor aberrations: TC ≥50% or IC ≥10%; TC ≥5% or IC ≥5%; and TC ≥1% or IC ≥1%.

Among the 205 chemotherapy-naïve patients with stage IV NSCLC with high PD-L1 expression (TC ≥ 50% or IC ≥ 10%) excluding those with EGFR or ALK genomic tumor aberrations, the median age was 65.0 years (range: 33 to 87), and 70% of patients were male. The majority of patients were White (82%) and Asian (17%). Baseline ECOG performance status was 0 (36%) or 1 (64%); 88% were current or previous smokers; and 76% of patients had non-squamous disease while 24% of patients had squamous disease.

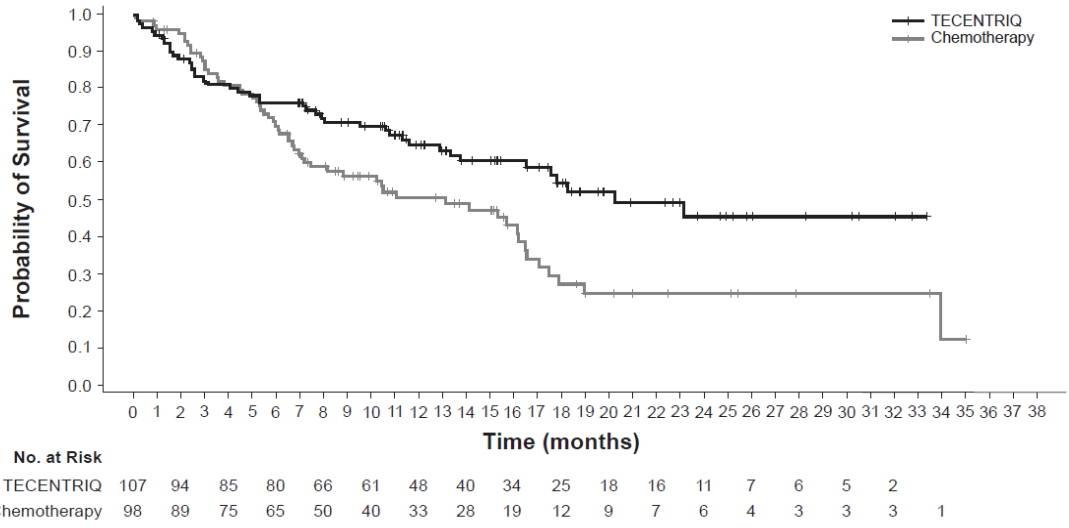
The trial demonstrated a statistically significant improvement in OS for patients with high PD-L1 expression (TC ≥50% or IC ≥10%) at the time of the OS interim analysis. There was no statistically significant difference in OS for the other two PD-L1 subgroups (TC ≥5% or IC ≥5%; and TC ≥1% or IC ≥1%) at the interim or final analyses. Efficacy results for patients with NSCLC with high PD-L1 expression are presented in Table 23 and Figure 2.

Table 23: Efficacy Results from IMpower110 in Patients with NSCLC with High PD-L1 Expression (TC ≥ 50% or IC ≥ 10%) and without EGFR or ALK Genomic Tumor Aberrations

	Arm A: TECENTRIQ N = 107	Arm B: Platinum-Based Chemotherapy N = 98
Overall Survival[1]		
Deaths (%)	44 (41%)	57 (58%)
Median, months	20.2	13.1
(95% CI)	(16.5, NE)	(7.4, 16.5)
Hazard ratio[2] (95% CI)	0.59 (0.40, 0.89)	
p-value[3]	0.0106[4]	

[1]Based on OS interim analysis. The median survival follow-up time in patients was 15.7 months.
[2]Stratified by sex and ECOG performance status
[3]Based on the stratified log-rank test compared to Arm A
[4]Compared to the allocated alpha of 0.0413 (two-sided) for this interim analysis.
CI=confidence interval; NE=not estimable

Figure 2: Kaplan-Meier Plot of Overall Survival in IMpower110 in Patients with NSCLC with High PD-L1 Expression (TC ≥ 50% or IC ≥ 10%) and without EGFR or ALK Genomic Tumor Aberrations



Investigator-assessed PFS showed an HR of 0.63 (95% CI: 0.45, 0.88), with median PFS of 8.1 months (95% CI: 6.8, 11.0) in the TECENTRIQ arm and 5 months (95% CI: 4.2, 5.7) in the platinum-based chemotherapy arm. The investigator-assessed confirmed ORR was 38% (95% CI: 29%, 48%) in the TECENTRIQ arm and 29% (95% CI: 20%, 39%) in the platinum-based chemotherapy arm.

Metastatic Chemotherapy-Naive Non-Squamous NSCLC

IMpower150

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 patients with metastatic non-squamous NSCLC. 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 were eligible. 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/m² or 200 mg/m² and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles
- Arm B: TECENTRIQ 1200 mg, bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles
- Arm C: bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles

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

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

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.

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^2 while the remaining 87% received paclitaxel at a dose of 200 mg/m^2. 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.

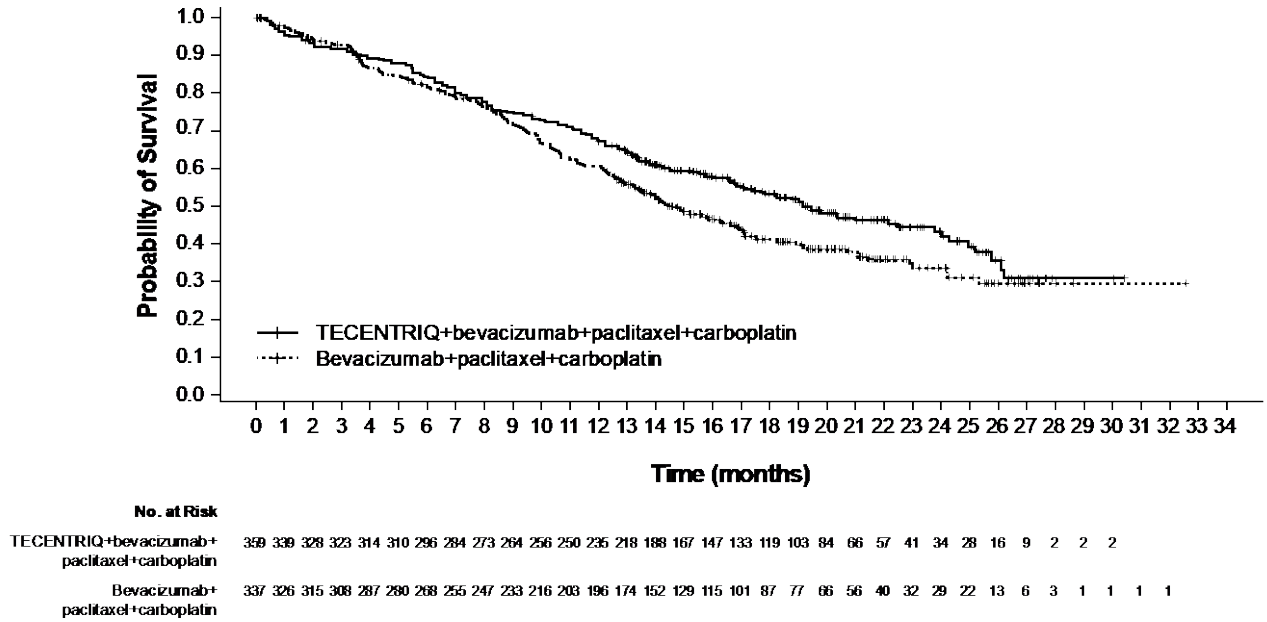
The trial demonstrated a statistically significant improvement in PFS between Arms B and C in both the tGE-WT and ITT-WT subpopulations, but did not demonstrate a significant difference for either subpopulation between Arms A and C based on the final PFS analyses. In the interim analysis of OS, a statistically 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 24 and Figure 3.

Table 24: Efficacy Results in ITT-WT Population in IMpower150

	Arm C: Bevacizumab, Paclitaxel and Carboplatin **N = 337**	**Arm B: TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin** **N = 359**	**Arm A: TECENTRIQ with Paclitaxel, and Carboplatin** **N = 349**
Overall Survival[1]			
Deaths (%)	197 (59%)	179 (50%)	179 (51%)
Median, months	14.7	19.2	19.4
(95% CI)	(13.3, 16.9)	(17.0, 23.8)	(15.7, 21.3)
Hazard ratio[2] (95% CI)	---	0.78 (0.64, 0.96)	0.84 (0.72, 1.08)
p-value[3]	---	0.016[4]	0.204[5]
Progression-Free Survival[6]			
Number of events (%)	247 (73%)	247 (69%)	245 (70%)
Median, months	7.0	8.5	6.7
(95% CI)	(6.3, 7.9)	(7.3, 9.7)	(5.6, 6.9)
Hazard ratio[2] (95% CI)	---	0.71 (0.59, 0.85)	0.94 (0.79, 1.13)
p-value[3]	---	0.0002[7]	0.5219
Objective Response Rate[6]			
Number of responders (%)	142 (42%)	196 (55%)	150 (43%)
(95% CI)	(37, 48)	(49, 60)	(38, 48)
Complete Response	3 (1%)	14 (4%)	9 (3%)
Partial Response	139 (41%)	182 (51%)	141 (40%)
Duration of Response[6]	n = 142	n = 196	n = 150
Median, months	6.5	10.8	9.5
(95% CI)	(5.6, 7.6)	(8.4, 13.9)	(7.0, 13.0)

[1]Based on OS interim analysis
[2]Stratified by sex, presence of liver metastases, and PD-L1 expression status on TC and IC
[3]Based on the stratified log-rank test compared to Arm C
[4]Compared to the allocated α=0.0174 (two sided) for this interim analysis
[5]Compared to the allocated α=0.0128 (two sided) for this interim analysis
[6]As determined by independent review facility (IRF) per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[7]Compared to the allocated α=0.006 (two sided) for the final PFS analysis
CI=confidence interval

Figure 3: 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, Clinical Pharmacology (12.6)]*. 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).

IMpower130

The efficacy of TECENTRIQ with paclitaxel protein-bound and carboplatin was evaluated in IMpower130 (NCT02367781), a multicenter, randomized (2:1), open-label trial in patients with stage IV non-squamous NSCLC. 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, were eligible. The trial excluded patients with history of autoimmune disease, administration of live attenuated vaccine within 28 days prior to randomization, administration of immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization, and active or untreated CNS metastases. Randomization was stratified by sex, presence of liver metastases, and PD-L1 tumor expression according to the VENTANA PD-L1 (SP142) assay 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 treatment regimens:

- TECENTRIQ 1200 mg on Day 1, paclitaxel protein-bound 100 mg/m² on Days 1, 8, and 15, and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles followed by TECENTRIQ 1200 mg once every 3 weeks until disease progression or unacceptable toxicity, or
- Paclitaxel protein-bound 100 mg/m² on Days 1, 8 and 15 and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles followed by best supportive care or pemetrexed.

Tumor assessments were conducted every 6 weeks for the first 48 weeks, then every 9 weeks thereafter. Major efficacy outcome measures were PFS by RECIST v1.1 and OS in the subpopulation of patients evaluated for and documented to have no EGFR or ALK genomic tumor aberrations (ITT-WT).

A total of 724 patients were enrolled; of these, 681 (94%) were in the ITT-WT population. The median age was 64 years (range: 18 to 86) and 59% were male. The majority of patients were white (90%), 2% of patients were Asian, 5% were Hispanic, and 4% were Black. Baseline ECOG performance status was 0 (41%) or 1 (58%). Most patients were current or previous smokers (90%). PD-L1 tumor expression was TC0/1/2 and IC0/1 in 73%; TC3 and any IC in 14%; and TC0/1/2 and IC2/3 in 13%.

Efficacy results for the ITT-WT population are presented in Table 25 and Figure 4.

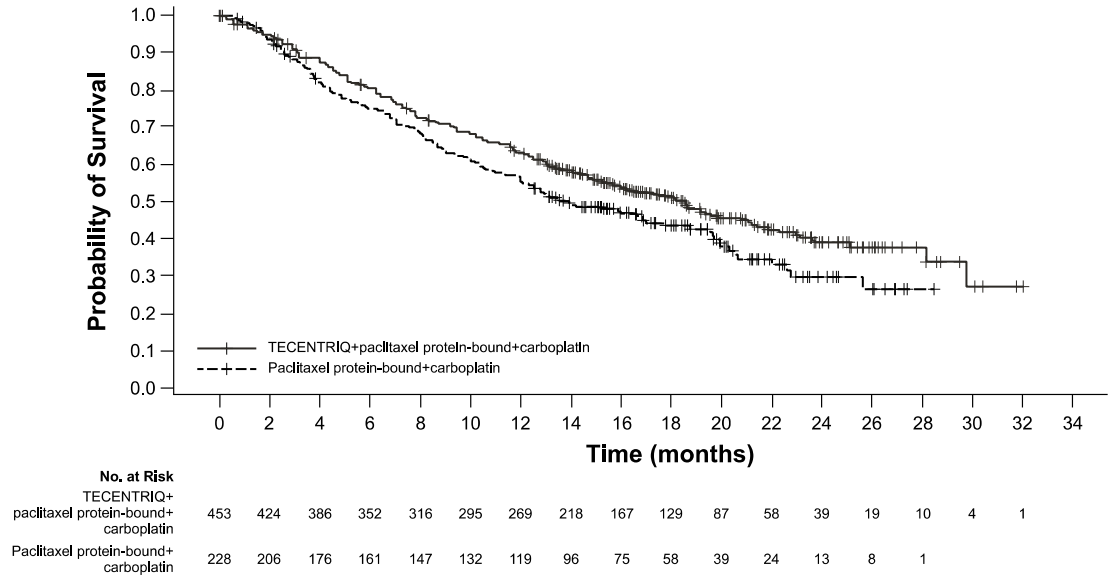
Table 25: Efficacy Results from IMpower130

	TECENTRIQ with Paclitaxel Protein-Bound and Carboplatin	**Paclitaxel Protein-Bound and Carboplatin**
Overall Survival[1]	n=453	n=228
Deaths (%)	228 (50%)	131 (57%)
Median, months	18.6	13.9
(95% CI)	(15.7, 21.1)	(12.0, 18.7)
Hazard ratio[2] (95% CI)	0.80 (0.64, 0.99)	
p-value[3]	0.0384[4]	
Progression-Free Survival[6]	n=453	n=228
Number of events (%)	330 (73%)	177 (78%)
Median, months	7.2	6.5
(95% CI)	(6.7, 8.3)	(5.6, 7.4)
Hazard ratio[2] (95% CI)	0.75 (0.63, 0.91)	
p-value[3]	0.0024[5]	
Overall Response Rate[6,7]	n=453	n=228
Number of responders (%)	207 (46%)	74 (32%)
(95% CI)	(41, 50)	(26, 39)
Complete Response	22 (5%)	2 (1%)
Partial Response	185 (41%)	72 (32%)
Duration of Response[6,7]	n=207	n=74
Median, months	10.8	7.8
(95% CI)	(9.0, 14.4)	(6.8, 10.9)

[1]Based on OS interim analysis
[2]Stratified by sex and PD-L1 tumor expression on tumor cells (TC) and tumor infiltrating cells (IC)

[3]Based on the stratified log-rank test
[4]Compared to the allocated α=0.0428 (two sided) for this interim analysis
[5]Compared to the allocated α=0.006 (two sided) for the final PFS analysis
[6]As determined by independent review facility (IRF) per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[7]Confirmed response
CI=confidence interval

Figure 4: Kaplan-Meier Curves for Overall Survival in IMpower130



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^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. 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 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 26 and Figure 5.

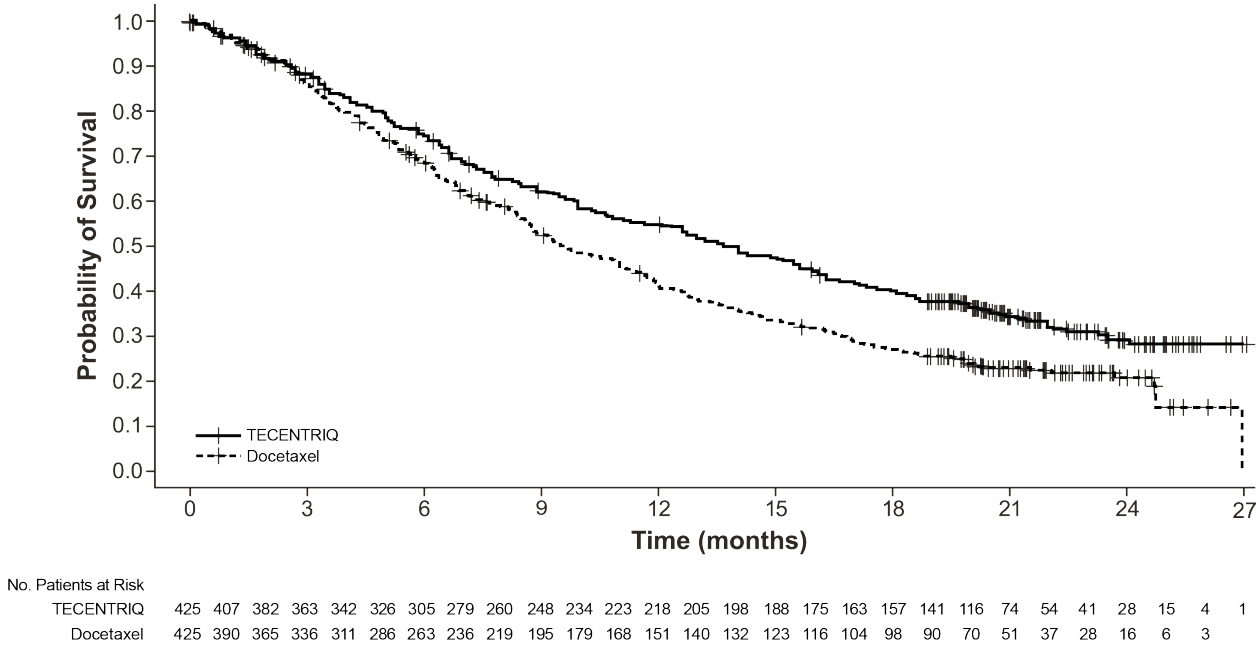
Table 26: Efficacy Results in OAK

	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)

	TECENTRIQ	Docetaxel
[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 5: 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 Clinical Pharmacology (12.6)]*. 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 TECENTRIQ arm with a matched population in the docetaxel arm and ADA negative patients in the TECENTRIQ 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).

14.2 Small Cell Lung Cancer

The efficacy of TECENTRIQ with carboplatin and etoposide was investigated in IMpower133 (NCT02763579), a randomized (1:1), multicenter, double-blind, placebo-controlled trial in 403 patients with ES-SCLC. IMpower133 enrolled patients with ES-SCLC who had received no

prior chemotherapy for extensive stage disease and ECOG performance status 0 or 1. The trial excluded patients with active or untreated CNS metastases, history of autoimmune disease, administration of a live, attenuated vaccine within 4 weeks prior to randomization, or administration of systemic immunosuppressive medications within 1 week prior to randomization. Randomization was stratified by sex, ECOG performance status, and presence of brain metastases. Patients were randomized to receive one of the following two treatment arms:

- TECENTRIQ 1200 mg and carboplatin AUC 5 mg/mL/min on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2 and 3 of each 21-day cycle for a maximum of 4 cycles followed by TECENTRIQ 1200 mg once every 3 weeks until disease progression or unacceptable toxicity, or
- placebo and carboplatin AUC 5 mg/mL/min on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2, and 3 of each 21-day cycle for a maximum of 4 cycles followed by placebo once every 3 weeks until disease progression or unacceptable toxicity.

Administration of TECENTRIQ was permitted beyond RECIST-defined disease progression. Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Patients treated beyond disease progression had tumor assessment conducted every 6 weeks until treatment discontinuation.

Major efficacy outcome measures were OS and PFS as assessed by investigator per RECIST v1.1 in the intent-to-treat population. Additional efficacy outcome measures included ORR and DoR as assessed by investigator per RECIST v1.1.

A total of 403 patients were randomized, including 201 to the TECENTRIQ arm and 202 to the chemotherapy alone arm. The median age was 64 years (range 26 to 90) and 65% were male. The majority of patients were White (80%); 17% were Asian, 4% were Hispanic and 1% were Black. Baseline ECOG performance status was 0 (35%) or 1 (65%); 9% of patients had a history of brain metastases, and 97% were current or previous smokers.

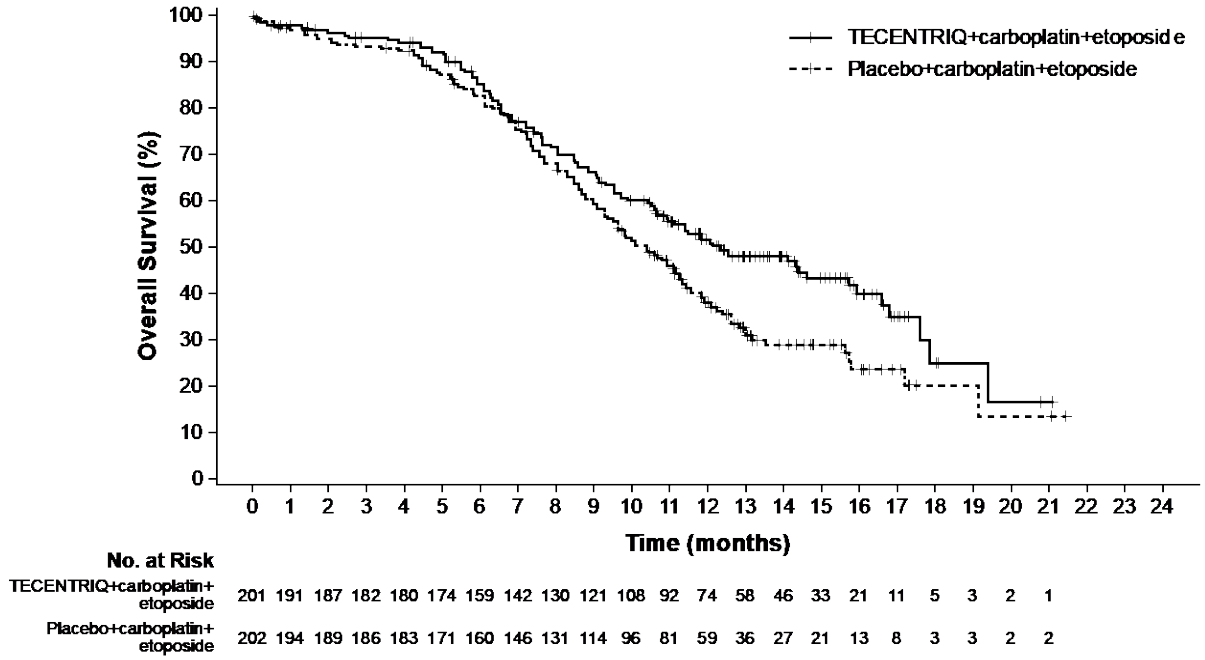
Efficacy results are presented in Table 27 and Figure 6.

Table 27: Efficacy Results from IMpower133

	TECENTRIQ with Carboplatin and Etoposide	Placebo with Carboplatin and Etoposide
Overall Survival	N=201	N=202
Deaths (%)	104 (52%)	134 (66%)
Median, months	12.3	10.3
(95% CI)	(10.8, 15.9)	(9.3, 11.3)
Hazard ratio[3] (95% CI)	0.70 (0.54, 0.91)	
p-value[4, 5]	0.0069	
Progression-Free Survival[1,2]	N=201	N=202
Number of events (%)	171 (85%)	189 (94%)
Median, months	5.2	4.3
(95% CI)	(4.4, 5.6)	(4.2, 4.5)
Hazard ratio[3] (95% CI)	0.77 (0.62, 0.96)	
p-value[4, 6]	0.0170	
Objective Response Rate[1,2,7]	N=201	N=202
Number of responders (%)	121 (60%)	130 (64%)
(95% CI)	(53, 67)	(57, 71)
Complete Response (%)	5 (2%)	2 (1%)
Partial Response (%)	116 (58%)	128 (63%)
Duration of Response[1,2,7]	N=121	N=130
Median, months	4.2	3.9
(95% CI)	(4.1, 4.5)	(3.1, 4.2)

[1]As determined by investigator assessment
[2] per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[3]Stratified by sex and ECOG performance status
[4]Based on the stratified log-rank test
[5]Compared to the allocated α of 0.0193 for this interim analysis based on 78% information using O'Brien-Fleming boundary
[6]Compared to the allocated α of 0.05 for this analysis
[7]Confirmed response
CI=confidence interval

Figure 6: Kaplan-Meier Plot of Overall Survival in IMpower133



14.3 Hepatocellular Carcinoma

The efficacy of TECENTRIQ in combination with bevacizumab was investigated in IMbrave150 (NCT03434379), a multicenter, international, open-label, randomized trial in patients with

locally advanced unresectable and/or metastatic hepatocellular carcinoma who have not received prior systemic therapy. Randomization was stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), baseline AFP (<400 vs. ≥400 ng/mL), and by ECOG performance status (0 vs. 1).

A total of 501 patients were randomized (2:1) to receive either TECENTRIQ as an intravenous infusion of 1200 mg, followed by 15 mg/kg bevacizumab, on the same day every 3 weeks or sorafenib 400 mg given orally twice daily, until disease progression or unacceptable toxicity. Patients could discontinue either TECENTRIQ or bevacizumab (e.g., due to adverse events) and continue on single-agent therapy until disease progression or unacceptable toxicity associated with the single-agent.

The study enrolled patients who were ECOG performance score 0 or 1 and who had not received prior systemic treatment. Patients were required to be evaluated for the presence of varices within 6 months prior to treatment, and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding, or high risk of bleeding. Patients with Child-Pugh B or C cirrhosis, moderate or severe ascites; history of hepatic encephalopathy; a history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; or untreated or corticosteroid-dependent brain metastases were excluded. Tumor assessments were performed every 6 weeks for the first 54 weeks and every 9 weeks thereafter.

The demographics and baseline disease characteristics of the study population were balanced between the treatment arms. The median age was 65 years (range: 26 to 88) and 83% of patients were male. The majority of patients were Asian (57%) or White (35%); 40% were from Asia (excluding Japan). Approximately 75% of patients presented with macrovascular invasion and/or extrahepatic spread and 37% had a baseline AFP ≥400 ng/mL. Baseline ECOG performance status was 0 (62%) or 1 (38%). HCC risk factors were Hepatitis B in 48% of patients, Hepatitis C in 22%, and 31% of patients had non-viral liver disease. The majority of patients had BCLC stage C (82%) disease at baseline, while 16% had stage B, and 3% had stage A.

The major efficacy outcome measures were overall survival (OS) and independent review facility (IRF)-assessed progression free survival (PFS) per RECIST v1.1. Additional efficacy outcome measures were IRF-assessed overall response rate (ORR) per RECIST and mRECIST.

Efficacy results are presented in Table 28 and Figure 7.

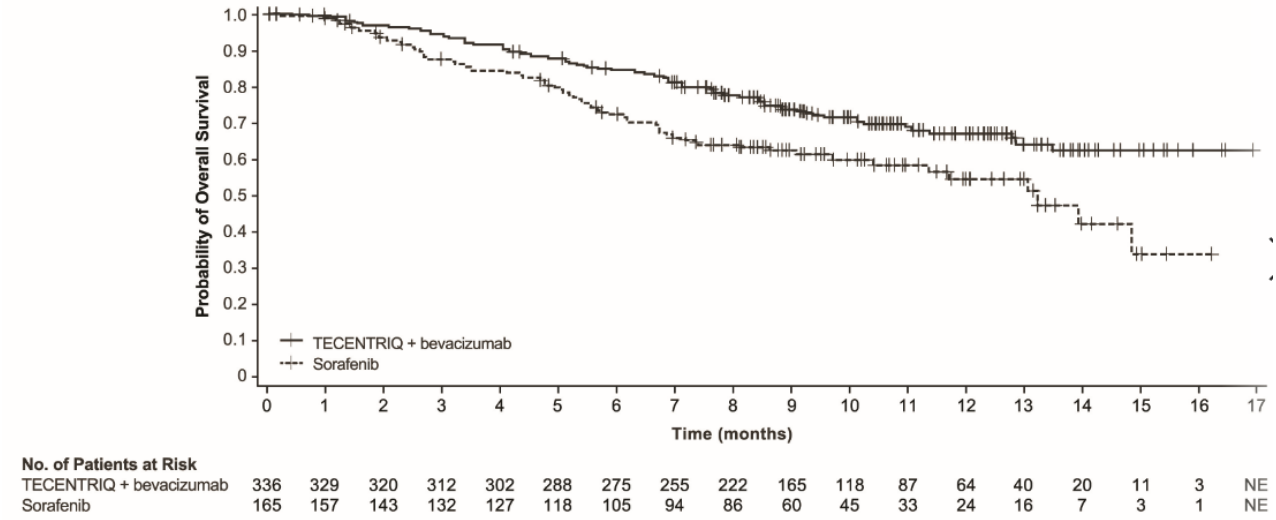
Table 28: Efficacy Results from IMbrave150

	TECENTRIQ in combination with Bevacizumab (N= 336)	**Sorafenib (N=165)**
Overall Survival		
Number of deaths (%)	96 (29)	65 (39)
Median OS in months (95% CI)	NE (NE, NE)	13.2 (10.4, NE)
Hazard ratio[1] (95% CI)	0.58 (0.42, 0.79)	
p-value[2]	0.0006[2]	
Progression-Free Survival[3]		
Number of events (%)	197 (59)	109 (66)
Median PFS in months (95% CI)	6.8 (5.8, 8.3)	4.3 (4.0, 5.6)
Hazard ratio[1] (95% CI)	0.59 (0.47, 0.76)	
p-value	<0.0001	
Overall Response Rate[3,5](ORR), RECIST 1.1		
Number of responders (%)	93 (28)	19 (12)

(95% CI)	(23, 33)	(7,17)
p-value[4]	<0.0001	
Complete responses, n (%)	22 (7)	0
Partial responses, n (%)	71 (21)	19 (12)
Duration of Response[3,5] (DOR) RECIST 1.1		
	(n=93)	(n=19)
Median DOR in months (95% CI)	NE (NE, NE)	6.3 (4.7, NE)
Range (months)	(1.3+, 13.4+)	(1.4+, 9.1+)
Overall Response Rate[3,5] (ORR), HCC mRECIST		
Number of responders (%)	112 (33)	21 (13)
(95% CI)	(28, 39)	(8, 19)
p-value[4]	<0.0001	
Complete responses, n (%)	37 (11)	3 (1.8)
Partial responses, n (%)	75 (22)	18 (11)
Duration of Response[3,5] (DOR) HCC mRECIST		
	(n=112)	(n=21)
Median DOR in months (95% CI)	NE (NE, NE)	6.3 (4.9, NE)
Range (months)	(1.3+, 13.4+)	(1.4+, 9.1+)

[1] Stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥400 ng/mL)
[2] Based on two-sided stratified log-rank test; as compared to significance level 0.004 (2-sided) based on 161/312=52% information using the OBF method
[3] Per independent radiology review
[4] Based on two-sided Cochran-Mantel-Haesnszel test
[5] Confirmed responses
+ Denotes a censored value
CI=confidence interval; HCC mRECIST=Modified RECIST Assessment for Hepatocellular Carcinoma; NE=not estimable; RECIST 1.1=Response Evaluation Criteria in Solid Tumors v1.1

Figure 7: Kaplan-Meier Plot of Overall Survival in IMbrave150



Exploratory analyses showed that the subset of patients (20%) who were ADA-positive by week 6 appeared to have reduced efficacy (effect on OS) as compared to patients (80%) who tested negative for treatment-emergent ADA by week 6 *[see Clinical Pharmacology (12.6)]*. ADA-positive patients by week 6 appeared to have similar overall survival compared to sorafenib-treated patients. In an exploratory analysis, inverse probability weighting was conducted to compare ADA-positive patients and ADA-negative patients in the TECENTRIQ and bevacizumab arm to the sorafenib arm. Inverse probability weighting factors were: baseline sum

of longest tumor size (BSLD), baseline ECOG, baseline albumin, baseline LDH, sex, age, race, geographic region, weight, neutrophil-to-lymphocyte ratio, AFP (<400 ng/mL vs ≥400 ng/mL), number of metastatic sites, MVI and/or EHS present at study entry, etiology (HBV vs. HCV vs. non-viral) and Child-Pugh Score (A5 vs. A6). The OS hazard ratio comparing the ADA-positive subgroup of the TECENTRIQ and bevacizumab arm to sorafenib was 0.93 (95% CI: 0.57, 1.53). The OS hazard ratio comparing the ADA-negative subgroup to sorafenib was 0.39 (95% CI: 0.26, 0.60).

14.4 Melanoma

The efficacy of TECENTRIQ in combination with cobimetinib and vemurafenib was evaluated in a double-blind, randomized (1:1), placebo-controlled, multicenter trial (IMspire150; NCT02908672) conducted in 514 patients. Randomization was stratified by geographic location (North America vs. Europe vs. Australia, New Zealand, and others) and baseline lactate dehydrogenase (LDH) [less than or equal to upper limit of normal (ULN) vs. greater than ULN]. Eligible patients were required to have previously untreated unresectable or metastatic BRAF V600 mutation-positive melanoma as detected by a locally available test and centrally confirmed with the FoundationOne™ assay. Patients were excluded if they had history of autoimmune disease; administration of a live, attenuated vaccine within 28 days prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; and active or untreated CNS metastases.

TECENTRIQ was initiated after patients received a 28-day treatment cycle of cobimetinib 60 mg orally once daily (21 days on / 7 days off) and vemurafenib 960 mg orally twice daily Days 1-21 and 720 mg orally twice daily Days 22-28. Patients received TECENTRIQ 840 mg intravenous infusion over 60 minutes every 2 weeks in combination with cobimetinib 60 mg orally once daily and vemurafenib 720 mg orally twice daily, or placebo in combination with cobimetinib 60 mg orally once daily and vemurafenib 960 mg orally twice daily. Treatment continued until disease progression or unacceptable toxicity. There was no crossover at the time of disease progression. Tumor assessments were performed every 8 weeks (± 1 week) for the first 24 months and every 12 weeks (± 1 week) thereafter.

The major efficacy outcome measure was investigator-assessed progression-free survival (PFS) per RECIST v1.1. Additional efficacy outcomes included PFS assessed by an independent central review, investigator-assessed ORR, OS, and DOR.

The median age of the study population was 54 years (range: 22-88), 58% of patients were male, 95% were White, a baseline ECOG performance status of 0 (77%) or 1 (23%), 33% had elevated LDH, 94% had metastatic disease, 60% were Stage IV (M1C), 56% had less than three metastatic sites at baseline, 3% had prior treatment for brain metastases, 30% had liver metastases at baseline, and 14% had received prior adjuvant systemic therapy. Based on central testing, 74% were identified as having a V600E mutation, 11% as having V600K mutation, and 1% as having V600D or V600R mutations.

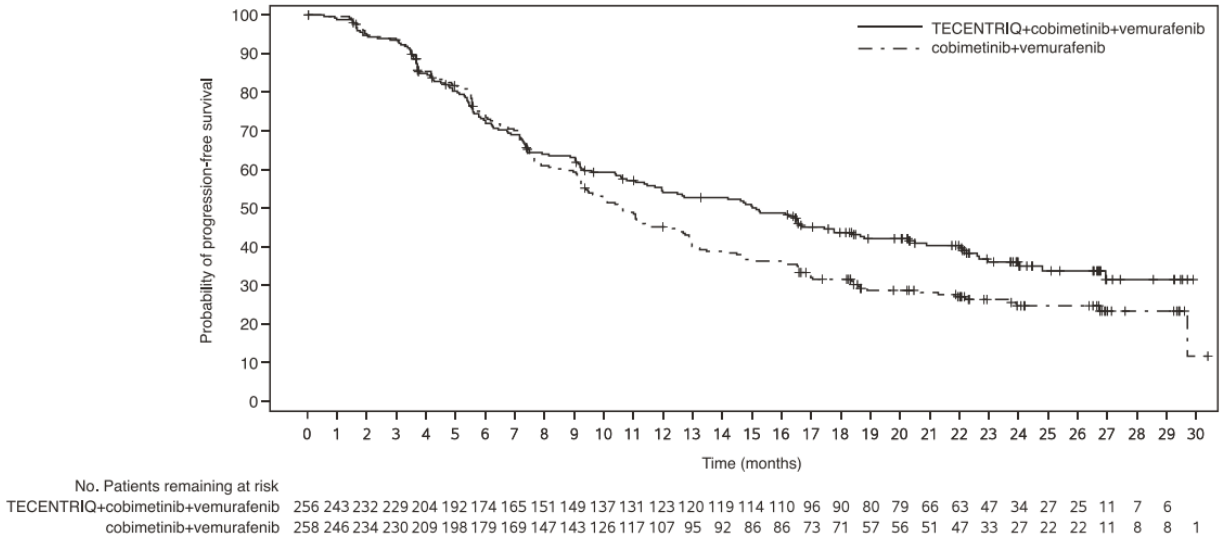
Efficacy results are summarized in Table 29 and Figure 8. Patients had a median survival follow up time of 18.9 months.

Table 29 Efficacy Results from IMspire150

	TECENTRIQ + Cobimetinib + Vemurafenib N=256	Placebo + Cobimetinib + Vemurafenib N=258
Progression-Free Survival[1]		
Number of events (%)	148 (58)	179 (69)
Median, months	15.1	10.6
(95% CI)	(11.4, 18.4)	(9.3, 12.7)
Hazard ratio[2] (95% CI)	0.78 (0.63, 0.97)	
p-value[3]	0.0249	
Overall Response Rate[1,4]		
Number of responders (%)	170 (66)	168 (65)
(95% CI)	(60, 72)	(59, 71)
Complete responses, n (%)	41 (16)	46 (18)
Partial response, n (%)	129 (50)	122 (47)
Duration of Response[1,4]	n=170	n=168
Median, months	20.4	12.5
(95% CI)	(15.1, NE)	(10.7, 16.6)

[1] As determined by investigator assessment with Response Evaluation Criteria in Solid Tumors v1.1.; CI=confidence interval;
[2] Stratified by baseline LDH
[3] Based on the stratified log-rank test
[4] Confirmed Responses

Figure 8: Kaplan-Meier Plot for Progression-Free Survival in IMspire150



At a pre-specified analysis at the time of the primary analysis of PFS, the OS data were not mature. The median OS was 28.8 months with 93 (36%) deaths in the TECENTRIQ plus cobimetinib and vemurafenib arm, and 25.1 months with 112 (43%) deaths in the placebo plus cobimetinib and vemurafenib arm. The hazard ratio for OS was 0.85 (95% CI: 0.64, 1.11) and the p-value was 0.2310.

14.5 Alveolar soft part sarcoma (ASPS)

The efficacy of TECENTRIQ was evaluated in study ML39345 (NCT03141684), an open-label, single-arm study, in 49 adult and pediatric patients aged 2 years and older with unresectable or metastatic ASPS. Eligible patients were required to have histologically or cytologically confirmed ASPS that was not curable by surgery, and an ECOG performance status of ≤ 2.

Patients were excluded if they had known primary central nervous system (CNS) malignancy or symptomatic CNS metastases, known clinically significant liver disease, or history of idiopathic pulmonary fibrosis, pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest computed tomography (CT) scan.

Adult patients received 1200 mg intravenously and pediatric patients received 15 mg/kg (up to a maximum of 1200 mg) intravenously once every 21 days until disease progression or unacceptable toxicity.

The major efficacy outcomes were Overall Response Rate (ORR) and Duration of Response (DOR) by Independent Review Committee according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

A total of 49 patients were enrolled. The median age of patients was 31 years (range: 12-70); 2% of adult patients (n=47) were ≥65 years of age and the pediatric patients (n=2) were ≥12 years of age; 51% of patients were female, 55% White, 29% Black or African American, 10% Asian; 53% had an ECOG performance status of 0 and 45% had an ECOG performance status of 1. All patients had prior surgery for ASPS and 55% received at least one prior line of treatment for ASPS; 55% received radiotherapy and 53% received chemotherapy. Of the patients who reported staging at initial diagnosis, all were Stage IV.

Efficacy results of this study are summarized in Table 30.

Table 30: Efficacy Results from Study ML39345

Endpoint	**All Patients** (N=49)
Overall response rate (95% CI)[a]	24% (13, 39)
Complete Responses, n	0
Partial Responses, n (%)	12 (24)
Duration of response	
Median, month	NE
(95% CI)	(17.0, NE)
Range	1+, 41+
Durability of Response	
≥6 months, n (%)	8 (67%)
≥12 months, n (%)	5 (42%)

CI: confidence interval; N: number of patients; +: Censored

[a] 95% CI based on Clopper–Pearson exact method.

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 840 mg/14 mL single-dose vial (NDC 50242-918-01) or 1,200 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)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain *[see Warnings and Precautions (5.1)]*.
- 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 (5.1)]*.
- 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 (5.1)]*.
- Nephritis: Advise patients to contact their healthcare provider immediately for pelvic pain, frequent urination, or unusual swelling. *[see Warnings and Precautions (5.1)]*.
- Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately for generalized rash, skin eruption, or painful skin and mucous membrane lesions *[see Warnings and Precautions (5.1)]*.
- 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 (5.1)]*.

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT after PD-1/PD-L1 inhibitors

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefits versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT *[see Warnings and Precautions (5.3)]*.

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 (5.4), 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 certain cancers by working with your immune system. TECENTRIQ can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You can have more than one of these problems at the same time. These problems may happen anytime during your treatment or even after your treatment has ended.

Call or see your healthcare provider right away if you develop any new or worse signs or symptoms, including:

Lung problems.

- cough
- shortness of breath
- chest pain

Intestinal problems.

- diarrhea (loose stools) or more frequent bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdomen) pain or tenderness

Liver problems.

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

Hormone gland problems.

- headaches that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heart beat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems.

- decrease in your amount of urine
- blood in your urine
- swelling of your ankles
- loss of appetite

Skin problems.

- rash
- itching
- skin blistering or peeling
- painful sores or ulcers in mouth or nose, throat, or genital area
- fever or flu-like symptoms
- swollen lymph nodes

Problems can also happen in other organs.

These are not all of the signs and symptoms of immune system problems that can happen with TECENTRIQ. Call or see your healthcare provider right away for any new or worse signs or symptoms, including:

- chest pain, irregular heartbeat, shortness of breath, or swelling of ankles
- confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- double vision, blurry vision, sensitivity to light, eye pain, changes in eye sight
- persistent or severe muscle pain or weakness, muscle cramps
- low red blood cells, bruising

Infusion reactions that can sometimes be severe or life-threatening. Signs and symptoms of infusion reactions may include:

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

Complications, including graft-versus-host disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with TECENTRIQ. Your healthcare provider will monitor you for these complications.

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 also need to delay or completely stop treatment with TECENTRIQ if you have severe side effects.

What is TECENTRIQ?

TECENTRIQ is a prescription medicine used to treat adults with:

- **a type of lung cancer called non-small cell lung cancer (NSCLC).**
  - **TECENTRIQ may be used alone as a treatment for your lung cancer:**
    - to help prevent your lung cancer from coming back after your tumor(s) has been removed by surgery and you have received platinum-based chemotherapy, **and**
    - you have stage 2 to stage 3A NSCLC (talk to your healthcare provider about what these stages mean), **and**
    - your cancer tests positive for “PD-L1”.
  - **TECENTRIQ may be used alone as your first treatment when your lung cancer:**
    - has spread or grown, **and**
    - your cancer tests positive for “high PD-L1”, **and**
    - your tumor does not have an abnormal “EGFR” or “ALK” gene.
  - **TECENTRIQ may be used with the medicines bevacizumab, paclitaxel, and carboplatin as your first treatment when your lung cancer:**
    - has spread or grown, **and**
    - is a type called “non-squamous NSCLC”, **and**
    - your tumor does not have an abnormal “EGFR” or “ALK” gene.
  - **TECENTRIQ may be used with the medicines paclitaxel protein-bound and carboplatin as your first treatment when your lung cancer:**
    - has spread or grown, **and**
    - is a type called “non-squamous NSCLC”, **and**
    - your tumor does not have an abnormal “EGFR” or “ALK” gene.
  - **TECENTRIQ may also be used alone 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.
- **adults with a type of lung cancer called small cell lung cancer (SCLC). TECENTRIQ may be used with the chemotherapy medicines carboplatin and etoposide as your first treatment when your lung cancer**
  - is a type called “extensive-stage SCLC,” which means that it has spread or grown.
- **adults with a type of liver cancer called hepatocellular carcinoma (HCC). TECENTRIQ may be used with the medicine bevacizumab when your liver cancer:**
  - has spread or cannot be removed by surgery, **and**
  - you have not received other medicines by mouth or injection through your vein (IV) to treat your cancer.
- **adults with a type of skin cancer called melanoma. TECENTRIQ may be used with the medicines cobimetinib and vemurafenib when your melanoma:**
  - has spread to other parts of the body or cannot be removed by surgery, **and**
  - has a certain type of abnormal “BRAF” gene. Your healthcare provider will perform a test to make sure this TECENTRIQ combination is right for you.
- **adults and children 2 years of age and older with a type of soft tissue tumor (cancer) called alveolar soft part sarcoma (ASPS). TECENTRIQ may be used when your sarcoma:**
  - has spread to other parts of the body or cannot be removed by surgery.

It is not known if TECENTRIQ is safe and effective when used:

- in children younger than 2 years of age for the treatment of ASPS.
- in children for the treatment of NSCLC, SCLC, HCC, or melanoma.

Before receiving 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 received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have received radiation treatment to your chest area
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- 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 2, 3, or 4 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.
- For treatment of a type of skin cancer called melanoma, your healthcare provider will also prescribe you cobimetinib and vemurafenib. Take cobimetinib and vemurafenib exactly as your healthcare provider tells you.
- 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 or weak
- decreased appetite
- nausea
- cough
- shortness of breath

The most common side effects of TECENTRIQ when used in lung cancer with other anti-cancer medicines include:

- feeling tired or weak
- nausea
- hair loss
- constipation
- diarrhea
- decreased appetite

The most common side effects of TECENTRIQ when used in hepatocellular carcinoma with bevacizumab include:

- high blood pressure
- feeling tired or weak
- too much protein in the urine

The most common side effects of TECENTRIQ when used in melanoma with cobimetinib and vemurafenib include:

- skin rash
- joint, muscle, or bone pain
- feeling tired or weak
- liver injury
- fever
- nausea
- itching
- swelling of legs or arms
- mouth swelling (sometimes with sores)
- low thyroid hormone levels
- sunburn or sun sensitivity

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.

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. You can ask your pharmacist or 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, polysorbate 20 and sucrose

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.

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