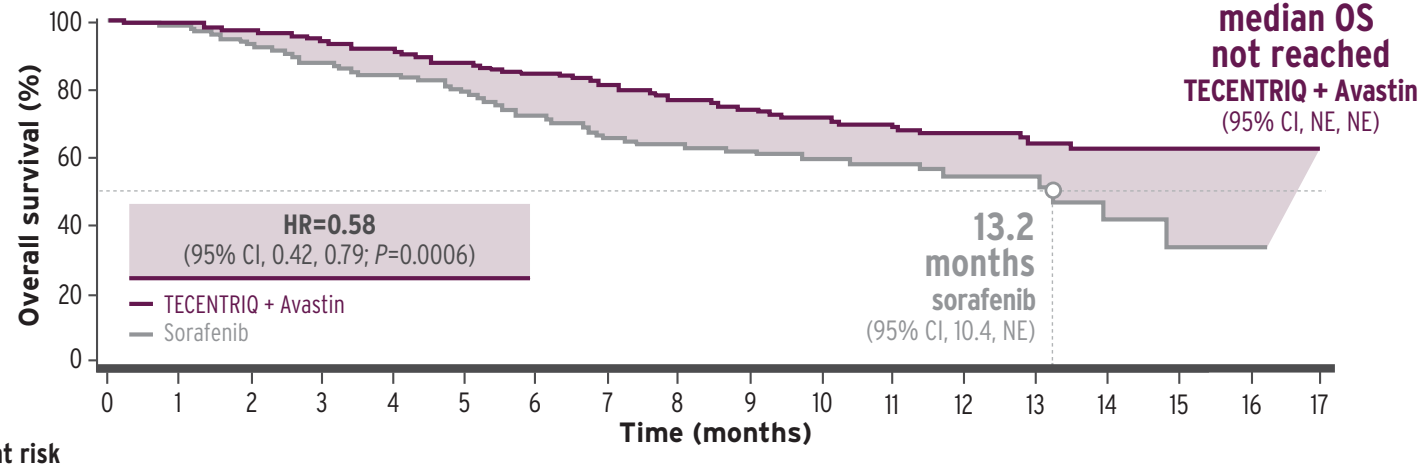
TECENTRIQ + AVASTIN® (bevacizumab)

UNPRECEDENTED OVERALL SURVIVAL IN 1L UNRESECTABLE OR mHCC

TECENTRIQ® atezolizumab 840 mg / 1200 mg INJECTION FOR IV USE

CONNECT WITH PURPOSE

Coprimary endpoint: 42% reduced risk of death demonstrated with TECENTRIQ + Avastin vs sorafenib[1]



Number at risk

TECENTRIQ + Avastin	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE

- **Coprimary endpoint:** significantly improved median PFS of 6.8 months with TECENTRIQ + Avastin (95% CI, 5.8, 8.3) vs 4.3 months with sorafenib (95% CI, 4.0, 5.6) (HR=0.59; 95% CI, 0.47, 0.76; *P*<0.0001)[1]*
- **Secondary endpoint:** 28% ORR with TECENTRIQ + Avastin (n=93/336; 95% CI, 23, 33) vs 12% with sorafenib (n=19/165; 95% CI, 7, 17) (*P*<0.0001)[1]*†
  - 7% of patients demonstrated a complete response vs 0% with sorafenib, while 21% of patients demonstrated a partial response vs 12% with sorafenib

IMbrave150 was a Phase III, multicenter, international, open-label, randomized trial that compared TECENTRIQ + Avastin to sorafenib in 501 patients with locally advanced unresectable and/or metastatic HCC who had not received prior systemic therapy. Patients were randomized (2:1) to receive either TECENTRIQ 1200 mg IV followed by Avastin 15 mg/kg IV on the same day q3w or 400 mg sorafenib given orally twice daily, until disease progression or unacceptable toxicity. The major efficacy outcome measures were OS and IRF-assessed PFS per RECIST v1.1 in the ITT population. Key secondary endpoints included ORR‡ and DoR.[1,2‡]

1L=first line; CI=confidence interval; DoR=duration of response; HCC mRECIST=hepatocellular carcinoma modified Response Evaluation Criteria In Solid Tumors; HR=hazard ratio; IRF=independent review facility; ITT=intent to treat; IV=intravenous; mHCC=metastatic hepatocellular carcinoma; NE=not estimable; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; q3w=every 3 weeks; RECIST=Response Evaluation Criteria In Solid Tumors.

*Assessed by IRF per RECIST v1.1.
†Confirmed responses.
‡Assessed by IRF per RECIST v1.1 and HCC mRECIST.

Indication

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

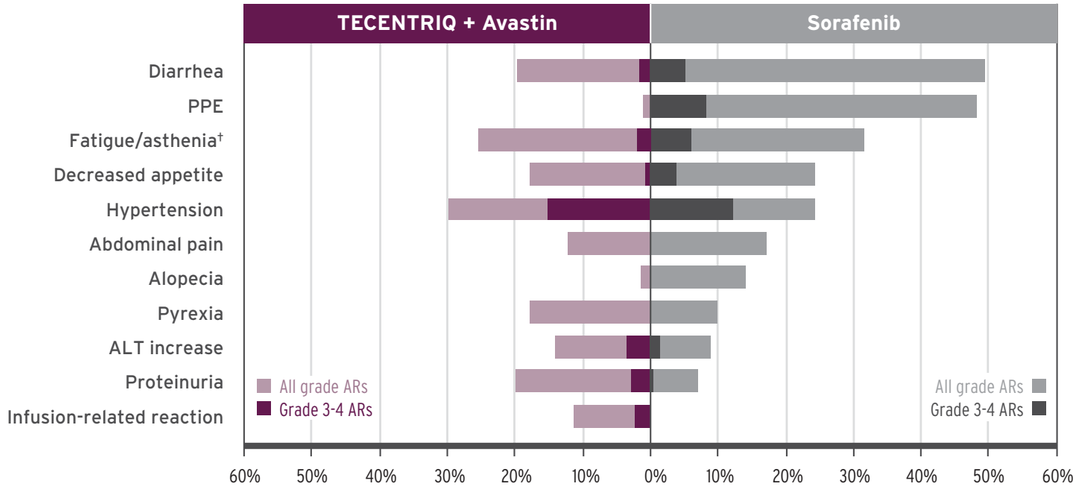
Select Important Safety Information

Serious and sometimes fatal adverse reactions occurred with TECENTRIQ treatment. Warnings and precautions include immune-mediated serious adverse reactions, including pneumonitis, hepatitis, colitis, endocrinopathies, and other immune-mediated adverse reactions. Other warnings and precautions include infections, infusion-related reactions, and embryo-fetal toxicity.

Please see accompanying full Prescribing Information and additional Important Safety Information throughout this brochure.

OBSERVED DIFFERENCES OF SELECT ARs BETWEEN TECENTRIQ + AVASTIN (bevacizumab) VS SORAFENIB

ARs occurring at a frequency of ≥10% in patients in either arm and ≥5% difference between arms[1,3]*



AE=adverse event; ALT=alanine aminotransferase; AR=adverse reaction; PPE=palmar-plantar erythrodysesthesia.

*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).

†Includes fatigue and asthenia.

Consider how certain ARs can impact your 1L unresectable HCC patients

- Treatment-related grade 3 to 4 ARs were 36% with TECENTRIQ + Avastin vs 46% with sorafenib[1,3]
  - The most common grade 3 to 4 ARs (≥2%) were hypertension, proteinuria, infusion-related reaction, and fatigue/asthenia

Important Safety Information

Serious Adverse Reactions
Please refer to the full Prescribing Information for important dose management information specific to adverse reactions.

Immune-Mediated Pneumonitis

- Immune-mediated pneumonitis or interstitial lung disease, including fatal cases, have occurred with TECENTRIQ treatment
- In clinical studies of TECENTRIQ as a single agent, 2.5% of patients developed pneumonitis, including Grade 3 (0.6%), Grade 4 (0.1%), and Grade 5 (<0.1%) events
- Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids followed by a taper. Withhold TECENTRIQ for Grade 2 and permanently discontinue for Grade 3 or 4 pneumonitis

Please see accompanying full Prescribing Information and additional Important Safety Information throughout this brochure.

ADDITIONAL SAFETY DATA REPORTED IN IMBRAVE150[1-3]

- The proportion of patients experiencing grade 3 to 4 bleed rates was 6.4% with TECENTRIQ + Avastin and 5.7% with sorafenib
  - The majority of bleeding/hemorrhage AEs were grade 1 to 2
- 4.6% of patients who were treated with TECENTRIQ + Avastin experienced fatal ARs. The most common ARs leading to death were gastrointestinal and esophageal varices hemorrhage (1.2%) and infections (1.2%)
- Serious ARs occurred in 38% of patients treated with TECENTRIQ + Avastin
  - The most frequent (≥2%) were gastrointestinal hemorrhage (7%), infections (6%), and pyrexia (2.1%)
- ARs leading to discontinuation of TECENTRIQ occurred in 9% of patients in the TECENTRIQ + Avastin arm vs 10% with sorafenib
  - The most common ARs leading to discontinuation of TECENTRIQ 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%)
- ARs leading to interruption of TECENTRIQ + Avastin occurred in 41% of patients
  - The most common (≥2%) were liver function laboratory abnormalities including increased transaminases, bilirubin, or alkaline phosphatate (8%); infections (6%); gastrointestinal hemorrhages (3.6%); thrombocytopenia/decreased platelet count (3.6%); hyperthyroidism (2.7%); and pyrexia (2.1%)
- Immune-related ARs requiring systemic corticosteroid therapy occurred in 12% of patients in the TECENTRIQ + Avastin arm

Important Safety Information (cont'd)

Immune-Mediated Hepatitis

- Liver test abnormalities and immune-mediated hepatitis, including fatal cases, have occurred with TECENTRIQ treatment
- In clinical studies of TECENTRIQ as a single agent, hepatitis occurred in 9% of patients, including Grade 3 (2.3%), Grade 4 (0.6%), and Grade 5 (<0.1%) events
- Monitor patients for signs and symptoms of hepatitis, during and after discontinuation of TECENTRIQ, including clinical chemistry monitoring. Administer corticosteroids followed by a taper for immune-mediated hepatitis. Withhold TECENTRIQ for AST or ALT elevations more than 3 and up to 8 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal. Permanently discontinue TECENTRIQ for AST or ALT elevations more than 8 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal

Immune-Mediated Colitis

- Immune-mediated diarrhea or colitis have occurred with TECENTRIQ treatment
- In clinical studies of TECENTRIQ as a single agent, diarrhea or colitis occurred in 20% of patients, including Grade 3 (1.4%) events
- Monitor patients for signs and symptoms of diarrhea or colitis. Withhold TECENTRIQ for Grade 2 or 3 and permanently discontinue for Grade 4 diarrhea or colitis

Immune-Mediated Endocrinopathies

- TECENTRIQ can cause immune-mediated endocrinopathies, including thyroid disorders; adrenal insufficiency; type 1 diabetes mellitus, including diabetic ketoacidosis; and hypophysitis/hypopituitarism
- Withhold TECENTRIQ for Grades 2 to 4 endocrinopathies

TECENTRIQ®
atezolizumab
840 mg | 1200 mg
INJECTION FOR IV USE

IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-Mediated Endocrinopathies (cont'd)

- Thyroid Disorders
  - In clinical studies of TECENTRIQ as a single agent, hypothyroidism occurred in 4.6% of patients and hyperthyroidism occurred in 1.6% of patients
  - Monitor thyroid function prior to and during treatment with TECENTRIQ. Initiate hormone replacement therapy or medical management of hyperthyroidism as clinically indicated
- Adrenal Insufficiency
  - In clinical studies of TECENTRIQ as a single agent, adrenal insufficiency occurred in 0.4% of patients, including Grade 3 (<0.1%) events
  - Monitor patients for clinical signs and symptoms of adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate corticosteroids and hormone replacement therapy as clinically indicated
- Type 1 Diabetes Mellitus
  - In clinical studies of TECENTRIQ as a single agent, type 1 diabetes mellitus occurred in <0.1% of patients
  - Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated
- Hypophysitis
  - In clinical studies of TECENTRIQ as a single agent, Grade 2 hypophysitis occurred in <0.1% of patients
  - For Grades 2 to 4 hypophysitis, initiate corticosteroids and hormone replacement therapy as clinically indicated

Other Immune-Mediated Adverse Reactions

- TECENTRIQ can cause severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system
- In clinical studies of TECENTRIQ as a single agent or were reported in other products in this class, the immune-mediated adverse reactions occurring at an incidence of <1% were cardiac, dermatologic, gastrointestinal, general, hematological, musculoskeletal, neurological, ophthalmological, renal, and vascular
- For suspected Grade 2 immune-mediated adverse reactions, exclude other causes and initiate corticosteroids as clinically indicated. For severe (Grade 3 or 4) adverse reactions, withhold TECENTRIQ and administer corticosteroids. Permanently discontinue TECENTRIQ for Grade 4 immune-mediated adverse reactions involving a major organ
- Evaluate for Vogt-Koyanagi-Harada syndrome if uveitis occurs in combination with other immune-mediated adverse reactions

Infections

- TECENTRIQ can cause severe infections including fatal cases
- In clinical studies of TECENTRIQ as a single agent, infections occurred in 42% of patients, including Grade 3 (8.7%), Grade 4 (1.5%), and Grade 5 (1%) events
- Monitor patients for signs and symptoms of infection. For Grade 3 or higher infections, withhold TECENTRIQ and resume once clinically stable

Infusion-Related Reactions

- TECENTRIQ can cause severe or life-threatening infusion-related reactions
- In clinical studies of TECENTRIQ as a single agent, infusion-related reactions occurred in 1.3% of patients, including Grade 3 (0.2%) events
- Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2 infusion-related reactions. Permanently discontinue TECENTRIQ in patients with Grade 3 or 4 infusion-related reactions

Embryo-Fetal Toxicity

- Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. 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

Nursing Mothers/Fertility

- Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose
- Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment

Most Common Adverse Reactions

The most common adverse reactions (rate ≥20%) in patients who received TECENTRIQ in combination with bevacizumab for HCC were hypertension (30%), fatigue/asthenia (26%), and proteinuria (20%).

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see accompanying full Prescribing Information for additional Important Safety Information.

References: 1. TECENTRIQ Prescribing Information. Genentech, Inc. **2.** Finn RS, Qin S, Ikeda M, et al; IMbrave150 Investigators. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382:1894-1905. **3.** Data on file. Clinical Study Report YO40245. Genentech, Inc.

Visit **TECENTRIQ-HCP.com/uHCC**

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TECENTRIQ®
atezolizumab 840 mg / 1200 mg INJECTION FOR IV USE
CONNECT WITH PURPOSE

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

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

RECENT MAJOR CHANGES

Indications and Usage, Non-Small Cell Lung Cancer (1.2)	5/2020
Indications and Usage, Hepatocellular Carcinoma (1.5)	5/2020
Dosage and Administration (2.1, 2.3, 2.6)	12/2019
Dosage and Administration (2.7)	5/2020

INDICATIONS AND USAGE

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

Urothelial Carcinoma

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

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

Non-Small Cell Lung Cancer (NSCLC)

- 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. (1.2)
- 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. (1.2)
- 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 (1.2)
- 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)

Triple-Negative Breast Cancer (TNBC)

- in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA approved test. This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (1.3)

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). (1.4)

Heptatocellular Carcinoma (HCC)

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

Urothelial Carcinoma (2.2)

- Administer TECENTRIQ as a single agent as 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks.

NSCLC (2.3)

- Administer TECENTRIQ as a single agent as 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks.
- When administering with chemotherapy with or without bevacizumab, administer TECENTRIQ 1200 mg every 3 weeks prior to chemotherapy and bevacizumab
- Following completion of 4-6 cycles of chemotherapy, and if bevacizumab is discontinued, administer TECENTRIQ 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks.

Metastatic Treatment of TNBC (2.4)

- Administer TECENTRIQ 840 mg, followed by 100 mg/m$_2$ paclitaxel protein-bound. For each 28 day cycle, TECENTRIQ is administered on days 1 and 15, and paclitaxel protein-bound is administered on days 1, 8, and 15.

Small Cell Lung Cancer (2.5)

- When administering with carboplatin and etoposide, administer TECENTRIQ 1200 mg every 3 weeks prior to chemotherapy.
- Following completion of 4 cycles of carboplatin and etoposide, administer TECENTRIQ 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks.

Hepatocellular Carcinoma (2.6)

- Administer TECENTRIQ 1,200 mg, followed by 15 mg/kg bevacizumab on the same day every 3 weeks
- If bevacizumab is discontinued, administer TECENTRIQ as:
  - 840 mg every 2 weeks, 1,200 mg every 3 weeks, or 1,680 mg every 4 weeks

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 Pneumonitis: Withhold or permanently discontinue based on severity of pneumonitis. (2.6, 5.1)
- Immune-Mediated Hepatitis: Monitor for changes in liver function. Withhold or permanently discontinue based on severity of transaminase or total bilirubin elevation. (2.6, 5.2)
- Immune-Mediated Colitis: Withhold or permanently discontinue based on severity of colitis. (2.6, 5.3)
- Immune-Mediated Endocrinopathies (2.6, 5.4):
  - Hypophysitis: Withhold based on severity of hypophysitis.
  - Thyroid Disorders: Monitor for changes in thyroid function. Withhold based on severity of hyperthyroidism.
  - Adrenal Insufficiency: Withhold based on severity of adrenal insufficiency.
  - Type 1 Diabetes Mellitus: Withhold based on severity of hyperglycemia.
- Infections: Withhold for severe or life-threatening infection. (2.6, 5.6)
- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue based on severity of infusion reactions. (2.6, 5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

ADVERSE REACTIONS

- Most common adverse reactions (≥ 20%) with TECENTRIQ as a single-agent were fatigue/asthenia, nausea, cough, dyspnea, and decreased appetite. (6.1)
- Most common adverse reactions (≥ 20%) with TECENTRIQ in combination with other antineoplastic drugs in patients with NSCLC and SCLC were fatigue/asthenia, nausea, alopecia, constipation, diarrhea, and decreased appetite (6.1)
- The most common adverse reactions (≥ 20%) with TECENTRIQ in combination with paclitaxel protein-bound in patients with TNBC were alopecia, peripheral neuropathies, fatigue, nausea, diarrhea, anemia, constipation, cough, headache, neutropenia, vomiting, and decreased appetite. (6.1)
- The most common adverse reactions (reported in ≥ 20% of patients) with TECENTRIQ in combination with bevacizumab in patients with HCC were hypertension, fatigue and proteinuria. (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: 05/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Urothelial Carcinoma

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

- are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, or
- are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or
- have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy

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

1.2 Non-Small Cell Lung Cancer

- 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.
- 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.

1.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer

TECENTRIQ, in combination with paclitaxel protein-bound, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*. This indication is approved under accelerated approval based on progression free survival *[see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.4 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).

1.5 Hepatocellular Carcinoma

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for Treatment of Urothelial Carcinoma and Triple-Negative Breast Cancer, or Non-Small Cell Lung Cancer

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

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 (14.2)]*.

Select patients with locally advanced or metastatic triple-negative breast cancer for treatment with TECENTRIQ in combination with paclitaxel protein-bound based on the PD-L1 expression on tumor infiltrating immune cells *[see Clinical Studies (14.3)]*.

Information on FDA-approved tests for the determination of PD-L1 expression in locally advanced or metastatic urothelial carcinoma, triple-negative breast cancer, or non-small cell lung cancer are available at: http://www.fda.gov/CompanionDiagnostics

2.2 Recommended Dosage for Urothelial Carcinoma

The recommended dosage of TECENTRIQ is:

- 840 mg every 2 weeks or
- 1200 mg every 3 weeks or
- 1680 mg every 4 weeks

administered intravenously over 60 minutes until disease progression or unacceptable toxicity. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

2.3 Recommended Dosage for NSCLC

Single Agent

The recommended dosage of TECENTRIQ is:

- 840 mg every 2 weeks or
- 1200 mg every 3 weeks or
- 1680 mg every 4 weeks

administered intravenously over 60 minutes until disease progression or unacceptable toxicity. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

TECENTRIQ with Platinum-based Chemotherapy

The recommended dosage of TECENTRIQ is 1200 mg intravenously every 3 weeks until disease progression or unacceptable toxicity.

Administer TECENTRIQ prior to chemotherapy and bevacizumab when given on the same day. Refer to the Prescribing Information for the chemotherapy agents or bevacizumab administered in combination with TECENTRIQ for recommended dosing information.

Following completion of 4-6 cycles of chemotherapy, and if bevacizumab is discontinued, the recommended dosage of TECENTRIQ is:

- 840 mg every 2 weeks or
- 1200 mg every 3 weeks or
- 1680 mg every 4 weeks

administered intravenously until disease progression or unacceptable toxicity.

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

2.4 Recommended Dosage for Locally Advanced or Metastatic TNBC

The recommended dosage of TECENTRIQ is 840 mg administered intravenously over 60 minutes, followed by 100 mg/m^2 paclitaxel protein-bound.

For each 28 day cycle, TECENTRIQ is administered on days 1 and 15, and paclitaxel protein-bound is administered on days 1, 8, and 15 until disease progression or unacceptable toxicity.

TECENTRIQ and paclitaxel protein-bound may be discontinued for toxicity independently of each other.

If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Refer to the Prescribing Information for paclitaxel protein-bound for recommended dosing information.

2.5 Recommended Dosage for SCLC

The recommended dosage of TECENTRIQ is 1200 mg intravenously every 3 weeks, when administered in combination with carboplatin and etoposide, until disease progression or unacceptable toxicity.

Administer TECENTRIQ prior to chemotherapy when given on the same day. Refer to the Prescribing Information for the chemotherapy agents administered in combination with TECENTRIQ for recommended dosing information.

Following completion of 4 cycles of carboplatin and etoposide, the recommended dosage of TECENTRIQ is:

- 840 mg every 2 weeks or
- 1200 mg every 3 weeks or
- 1680 mg every 4 weeks

administered intravenously until disease progression or unacceptable toxicity.

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

2.6 Recommended Dosage for HCC

The recommended dosage of TECENTRIQ is 1,200 mg administered as an intravenous infusion over 60 minutes, followed by 15 mg/kg of bevacizumab on the same day, every 3 weeks until disease progression or unacceptable toxicity.

Refer to the Prescribing Information for bevacizumab prior to initiation.

If bevacizumab is discontinued for toxicity, the recommended dosage of TECENTRIQ is:

- 840 mg every 2 weeks or
- 1,200 mg every 3 weeks or
- 1,680 mg every 4 weeks

administered intravenously until disease progression or unacceptable toxicity.

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

2.7 Dosage Modifications for Adverse Reactions

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

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity of Adverse Reaction[1]**	**Dosage Modifications**
Pneumonitis *[see Warnings and Precautions (5.1)]*	Grade 2	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grade 3 or 4	Permanently discontinue
Hepatitis in patients with cancers other than HCC[2] *[see Warnings and Precautions (5.2)]*	AST or ALT more than 3 and up to 8 times the upper limit of normal (ULN) or total bilirubin more than 1.5 and up to 3 times the upper limit of normal (ULN)	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	AST or ALT more than 8 times the upper limit of normal (ULN) or total bilirubin more than 3 times the upper limit of normal (ULN)	Permanently discontinue
Hepatitis in patients with HCC[2] *[see Warnings and Precautions (5.2)]*	• AST or ALT is within normal limits at baseline and increases to more than 3 and up to 10 times the ULN • AST or ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times the ULN • AST or ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times the ULN	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)

Adverse Reaction	**Severity of Adverse Reaction[1]**	**Dosage Modifications**
	AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Colitis or diarrhea *[see Warnings and Precautions (5.3)]*	Grade 2 or 3	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grade 4	Permanently discontinue
Endocrinopathies (including but not limited to hypophysitis, adrenal insufficiency, hyperthyroidism, and type 1 diabetes mellitus) *[see Warnings and Precautions (5.4)]*	Grade 2, 3, or 4	Withhold dose until Grade 1 or resolved and clinically stable on hormone replacement therapy.
Other immune-mediated adverse reactions involving a major organ *[see Warnings and Precautions (5.5)]*	Grade 3	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grade 4	Permanently discontinue
Infections *[see Warnings and Precautions (5.6)]*	Grade 3 or 4	Withhold dose until Grade 1 or resolved
Infusion-Related Reactions *[see Warnings and Precautions (5.7)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue
Persistent Grade 2 or 3 adverse reaction (excluding endocrinopathies)	Grade 2 or 3 adverse reaction that does not recover to Grade 0 or 1 within 12 weeks after last TECENTRIQ dose	Permanently discontinue
Inability to taper corticosteroid	Inability to reduce to less than or equal to prednisone 10 mg per day (or equivalent) within 12 weeks after last TECENTRIQ dose	Permanently discontinue
Recurrent Grade 3 or 4 adverse reaction	Recurrent Grade 3 or 4 (severe or life-threatening) adverse reaction	Permanently discontinue

1 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0
2 HCC: Hepatocellular Carcinoma

2.8 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).
- 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 Immune-Mediated Pneumonitis

TECENTRIQ can cause immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids, including fatal cases. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids, prednisone 1–2 mg/kg/day or equivalents, followed by a taper for Grade 2 or higher pneumonitis. Withhold or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.7)]*.

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

In clinical studies enrolling 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with platinum-based chemotherapy *[see Adverse Reactions (6.1)]*, immune-mediated pneumonitis occurred in 5.5% of patients, including Grades 3-4 in 1.4% of patients. Systemic corticosteroids were required in 4.2% of patients, including 3.1% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 5 days (1 day to 98 days) followed by a corticosteroid taper.

5.2 Immune-Mediated Hepatitis

TECENTRIQ can cause liver test abnormalities and immune-mediated hepatitis, defined as requiring use of systemic corticosteroids. Fatal cases have been reported. Monitor patients for signs and symptoms of hepatitis, during and after discontinuation of TECENTRIQ, including clinical chemistry monitoring. Administer corticosteroids, prednisone 1–2 mg/kg/day or equivalents, followed by a taper for Grade 2 or higher elevations of ALT, AST and/or total bilirubin. Interrupt or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.7)]*.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent *[see Adverse Reactions (6.1)]*, hepatitis occurred in 9% of patients, including Grade 3 (2.3%), Grade 4 (0.6%), and Grade 5 (< 0.1%). The median time to onset of hepatitis was 1.4 months (1 day to 25.8 months) and median duration was 24 days (1 day to 13 months). Hepatitis resolved in 71% of patients. Hepatitis led to discontinuation of TECENTRIQ in 0.4% of 2616 patients. Systemic corticosteroids were required in 2% of the patients, with 1.3% requiring high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 3 days (1 day to 35 days) followed by a corticosteroid taper.

In clinical studies enrolling 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with platinum-based chemotherapy *[see Adverse Reactions (6.1)]*, immune-mediated hepatitis occurred in 14% of patients, including Grades 3-4 in 4.1% of patients. Systemic corticosteroids were required in 4.8% of patients, including 3.4% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 6 days (1 day to 144 days) followed by a corticosteroid taper.

5.3 Immune-Mediated Colitis

TECENTRIQ can cause immune-mediated colitis or diarrhea, defined as requiring use of systemic corticosteroids. Monitor patients for signs and symptoms of diarrhea or colitis. Withhold treatment with TECENTRIQ for Grade 2 or 3 diarrhea or colitis. If symptoms persist for longer than 5 days or recur, administer corticosteroids, prednisone 1–2 mg/kg/day or equivalents, followed by a taper for Grade 2 diarrhea or colitis. Interrupt or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.6) and Adverse Reactions (6.1)]*.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent *[see Adverse Reactions (6.1)]*, diarrhea or colitis occurred in 20% of patients, including Grade 3 (1.4%) events. The median time to onset of diarrhea or colitis was 1.5 months (1 day to 41 months). Diarrhea and colitis resolved in 85% of the patients. Diarrhea or colitis led to discontinuation of TECENTRIQ in 0.2% of 2616 patients. Systemic corticosteroids were required in 1.1% of patients and high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) was required in 0.4% patients with a median duration of 3 days (1 day to 11 days) followed by a corticosteroid taper.

In clinical studies enrolling 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with platinum-based chemotherapy *[see Adverse Reactions (6.1)]*, diarrhea or colitis occurred in 29% of patients, including Grade 3-4 in 4.3% of patients. Systemic corticosteroids were required in 4.7% of patients, including 2.9% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 4 days (1 day to 170 days) followed by a corticosteroid taper.

5.4 Immune-Mediated Endocrinopathies

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

Thyroid Disorders: Monitor thyroid function prior to and periodically during treatment with TECENTRIQ. Initiate hormone replacement therapy or medical management of hyperthyroidism as clinically indicated. Continue TECENTRIQ for hypothyroidism and interrupt for hyperthyroidism based on the severity *[see Dosage and Administration (2.7)]*.

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

In clinical studies enrolling 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with platinum-based chemotherapy *[see Adverse Reactions (6.1)]*, hypothyroidism occurred in 11% of patients, including Grades 3-4 in 0.3% of patients; 8.2% of the 2421 patients required the use of hormone replacement therapy. The frequency and severity of hyperthyroidism and thyroiditis were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

Adrenal Insufficiency: Monitor patients for clinical signs and symptoms of adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate prednisone 1to 2 mg/kg/day or equivalents, followed by a taper and hormone replacement as clinically indicated. Interrupt TECENTRIQ based on the severity *[see Dosage and Administration (2.7)]*.

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single-agent, adrenal insufficiency occurred in 0.4% of patients, including Grade 3 (< 0.1%) adrenal insufficiency. Median time to onset was 5.7 months (3 days to 19 months). There was insufficient information to adequately characterize the median duration of adrenal insufficiency. Adrenal insufficiency resolved in 27% of patients. Systemic corticosteroids were required in 0.3% of 2616 patients, including 0.1% who required high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent). The frequency and severity of adrenal insufficiency were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

Type 1 Diabetes Mellitus: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Interrupt TECENTRIQ based on the severity *[see Dosage and Administration (2.7)]*.

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single-agent, type 1 diabetes mellitus occurred in < 0.1% of patients. Insulin was required in one patient. The frequency and severity of diabetes mellitus were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

Hypophysitis: For Grade 2 or higher hypophysitis, initiate prednisone 1–2 mg/kg/day or equivalents, followed by a taper and hormone replacement therapy as clinically indicated. Interrupt TECENTRIQ based on the severity *[see Dosage and Administration (2.7)]*.

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single-agent, Grade 2 hypophysitis occurred in < 0.1% of patients. The frequency and severity of hypophysitis were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

5.5 Other Immune-Mediated Adverse Reactions

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

For suspected Grade 2 immune-mediated adverse reactions, exclude other causes and initiate corticosteroids as clinically indicated. For severe (Grades 3 or 4) adverse reactions, administer corticosteroids, prednisone 1 to 2 mg/kg/day or equivalents, followed by a taper. Interrupt or permanently discontinue TECENTRIQ, based on the severity of the reaction *[see Dosage and Administration (2.6)]*.

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

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of < 1% in 2616 patients who received TECENTRIQ as a single-agent and in 2421 patients who received TECENTRIQ in combination with platinum-based chemotherapy or were reported in other products in this class *[see Adverse Reactions (6.1)]*:

Cardiac: myocarditis

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

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

General: systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis

Hematological: autoimmune hemolytic anemia, immune thrombocytopenic purpura.

Musculoskeletal: myositis, rhabdomyolysis.

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

Ophthalmological: uveitis, iritis.

Renal: nephrotic syndrome, nephritis.

Vascular: vasculitis

5.6 Infections

TECENTRIQ can cause severe infections including fatal cases. Monitor patients for signs and symptoms of infection. For Grade 3 or higher infections, withhold TECENTRIQ and resume once clinically stable *[see Dosage and Administration (2.7) and Adverse Reactions (6.1)]*.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent *[see Adverse Reactions (6.1)]*, infections occurred in 42% of patients, including Grade 3 (8.7%), Grade 4 (1.5%), and Grade 5 (1%). In patients with urothelial carcinoma, the most common Grade 3 or higher infection was urinary tract infections, occurring in 6.5% of patients. In patients with NSCLC, the most common Grade 3 or higher infection was pneumonia, occurring in 3.8% of patients. The frequency and severity of infections were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

5.7 Infusion-Related Reactions

TECENTRIQ can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.7)]*. 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).

5.8 Embryo-Fetal Toxicity

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

Verify pregnancy status of females of reproductive potential prior to initiating TECENTRIQ. Advise females of reproductive potential of the potential risk to a fetus. Advise females of

reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

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

6.1 Clinical Trials Experience

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

The data described in WARNINGS AND PRECAUTIONS reflect exposure to TECENTRIQ as a single-agent in 2616 patients in two randomized, active-controlled studies (POPLAR, OAK) and four open-label, single arm studies (PCD4989g, IMvigor210, BIRCH, FIR) which enrolled 524 patients with metastatic urothelial carcinoma, 1636 patients with metastatic NSCLC, and 456 patients with other tumor types. 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 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%).

Urothelial Carcinoma

Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

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

Five patients (4.2%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, cardiac arrest, myocardial infarction, respiratory failure, or respiratory distress. One additional patient (0.8%) was experiencing herpetic meningoencephalitis and disease progression at the time of death.

Serious adverse reactions occurred in 37% of patients. The most frequent serious adverse reactions (≥ 2%) were diarrhea, intestinal obstruction, sepsis, acute kidney injury, and renal failure.

TECENTRIQ was discontinued for adverse reactions in 4.2% of patients. The adverse reactions leading to discontinuation were diarrhea/colitis (1.7%), fatigue (0.8%), hypersensitivity (0.8%), and dyspnea (0.8%).

Adverse reactions leading to interruption occurred in 35% of patients; the most common (≥ 1%) were intestinal obstruction, fatigue, diarrhea, urinary tract infection, infusion- related reaction, cough, abdominal pain, peripheral edema, pyrexia, respiratory tract infection, upper respiratory tract infection, creatinine increase, decreased appetite, hyponatremia, back pain, pruritus, and venous thromboembolism.

Tables 2 and 3 summarize the adverse reactions and Grades 3–4 selected laboratory abnormalities, respectively, in patients who received TECENTRIQ in IMvigor210 (Cohort 1).

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

Adverse Reaction	**TECENTRIQ N = 119**	
	All Grades (%)	**Grades 3–4 (%)**
General		
Fatigue[1]	52	8
Peripheral edema[2]	17	2
Pyrexia	14	0.8
Gastrointestinal		
Diarrhea[3]	24	5
Nausea	22	2
Vomiting	16	0.8
Constipation	15	2
Abdominal pain[4]	15	0.8
Metabolism and Nutrition		
Decreased appetite[5]	24	3
Musculoskeletal and Connective Tissue		
Back/Neck pain	18	3
Arthralgia	13	0
Skin and Subcutaneous Tissue		
Pruritus	18	0.8

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

1 Includes fatigue, asthenia, lethargy, and malaise
2 Includes edema peripheral, scrotal edema, lymphedema, and edema
3 Includes diarrhea, colitis, frequent bowel movements, autoimmune colitis
4 Includes abdominal pain, upper abdominal pain, lower abdominal pain, and flank pain
5 Includes decreased appetite and early satiety
6 Includes rash, dermatitis, dermatitis acneiform, rash maculo-papular, rash erythematous, rash pruritic, rash macular, and rash papular
7 Includes urinary tract infection, urinary tract infection bacterial, cystitis, and urosepsis
8 Includes cough and productive cough
9 Includes dyspnea and exertional dyspnea

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

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

Graded per NCI CTCAE v4.0.

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ was evaluated in IMvigor210 (Cohort 2), a multicenter, open-label, single-arm trial that included 310 patients with locally advanced or metastatic urothelial

carcinoma who had disease progression during or following at least one platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen *[see Clinical Studies (14.1)]*. Patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. The median duration of exposure was 12.3 weeks (0.1 to 46 weeks).

Three patients (1%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, pneumonitis, or intestinal obstruction.

TECENTRIQ was discontinued for adverse reactions in 3.2% of patients. Sepsis led to discontinuation in 0.6% of patients.

Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions (> 2%) were urinary tract infection, hematuria, acute kidney injury, intestinal obstruction, pyrexia, venous thromboembolism, urinary obstruction, pneumonia, dyspnea, abdominal pain, sepsis, and confusional state.

Adverse reactions leading to interruption occurred in 27% of patients; the most common (> 1%) were liver enzyme increase, urinary tract infection, diarrhea, fatigue, confusional state, urinary obstruction, pyrexia, dyspnea, venous thromboembolism, and pneumonitis.

Tables 4 and 5 summarize the adverse reactions and Grades 3–4 selected laboratory abnormalities, respectively, in patients who received TECENTRIQ in IMvigor210 (Cohort 2).

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

Adverse Reaction	**TECENTRIQ N = 310**	
	All Grades (%)	**Grades 3–4 (%)**
General		
Fatigue	52	6
Pyrexia	21	1
Peripheral edema	18	1
Metabolism and Nutrition		
Decreased appetite	26	1
Gastrointestinal		
Nausea	25	2
Constipation	21	0.3
Diarrhea	18	1
Abdominal pain	17	4
Vomiting	17	1
Infections		
Urinary tract infection	22	9
Respiratory, Thoracic, and Mediastinal		
Dyspnea	16	4

Adverse Reaction	TECENTRIQ N = 310	
	All Grades (%)	Grades 3–4 (%)
Cough	14	0.3
Musculoskeletal and Connective Tissue		
Back/Neck pain	15	2
Arthralgia	14	1
Skin and Subcutaneous Tissue		
Rash	15	0.3
Pruritus	13	0.3
Renal and Urinary		
Hematuria	14	3

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

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

Graded per NCI CTCAE v4.0.

Non-small Cell Lung Cancer (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 (14.2)]*. 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 infraction, 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

Laboratory Abnormality	TECENTRIQ		Platinum Based Chemotherapy	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
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 (14.2)]*. 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				
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, backpain, 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
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 unacceptability toxicity *[see Clinical Studies (14.2)]*. 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 including pneumonia (1.1%), pulmonary embolism (0.8%), myocardial infarction (0.6%), cardiac arrest (0.4%) and 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 (3.0%), 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				

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 (%)
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	NA1	5	NA1
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	NA1	13	NA1

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 (14.2)]*. A total of 609 patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel (n=578) 75 mg/m2 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

Adverse Reaction	TECENTRIQ N = 609		Docetaxel N = 578	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
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

Metastatic Triple Negative Breast Cancer (TNBC)

The safety of TECENTRIQ in combination with paclitaxel protein-bound was evaluated in IMpassion130, a multicenter, international, randomized, double-blinded placebo-controlled trial in patients with locally advanced or metastatic TNBC who have not received prior chemotherapy for metastatic disease *[see Clinical Studies (14.3)]*. Patients received TECENTRIQ 840 mg (n=452) or placebo (n=438) intravenously followed by paclitaxel protein-bound (100 mg/m^2) intravenously. For each 28 day cycle, TECENTRIQ was administered on days 1 and 15 and paclitaxel protein-bound was administered on days 1, 8, and 15 until disease progression or unacceptable toxicity. In the safety-evaluable population, the median duration of exposure to TECENTRIQ was 5.5 months (range: 0-32 months) and paclitaxel protein-bound was 5.1

months (range: 0-31.5 months) in the TECENTRIQ and paclitaxel protein-bound arm. The median duration of exposure to placebo was 5.1 months (range: 0-25.1 months) and paclitaxel protein-bound was 5.0 months (range: 0-23.7 months) in the placebo and paclitaxel protein-bound arm.

Fatal adverse reactions occurred in 1.3%) of patients in the TECENTRIQ and paclitaxel protein-bound arm; these included septic shock, mucosal inflammation, auto-immune hepatitis, aspiration, pneumonia, pulmonary embolism.

Serious adverse reactions occurred in 23% of patients. The most frequent serious adverse reactions were pneumonia (2%), urinary tract infection (1%), dyspnea (1%), and pyrexia (1%).

Adverse reactions leading to discontinuation of TECENTRIQ occurred in 6% (29/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm. The most common adverse reaction leading to TECENTRIQ discontinuation was peripheral neuropathy (<1%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 31% of patients; the most common (≥ 2%) were neutropenia, neutrophil count decreased, hyperthyroidism, and pyrexia.

Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 13% (59/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm.

Tables 14 and 15 summarize adverse reactions and selected laboratory abnormalities worsening from baseline in the TECENTRIQ treated patients.

Table 14: Adverse Reactions Occurring in ≥10% of Patients with TNBC in IMpassion130

Adverse Reaction	TECENTRIQ with Paclitaxel Protein-Bound N = 452		Placebo with Paclitaxel Protein-Bound N = 438	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Skin and Subcutaneous Tissue				
Alopecia	56	<1	58	<1
Rash	17	<1	16	<1
Pruritus	14	0	10	0
Nervous System				
Peripheral neuropathies[1]	47	9	44	5
Headache	23	<1	22	<1
Dysgeusia	14	0	14	0
Dizziness	14	0	11	0
General				
Fatigue	47	4	45	3.4
Pyrexia	19	<1	11	0
Peripheral Edema	15	<1	16	1.4
Asthenia	12	<1	11	<1
Gastrointestinal				
Nausea	46	1.1	38	1.8
Diarrhea	33	1.3	34	2.1
Constipation	25	<1	25	<1
Vomiting	20	<1	17	1.1

Adverse Reaction	TECENTRIQ with Paclitaxel Protein-Bound N = 452		Placebo with Paclitaxel Protein-Bound N = 438	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Abdominal pain	10	<1	12	<1
Respiratory, Thoracic, and Mediastinal				
Cough	25	0	19	0
Dyspnea	16	<1	15	<1
Metabolism and Nutrition				
Decreased Appetite	20	<1	18	<1
Musculoskeletal and Connective Tissue				
Arthralgia	18	<1	16	<1
Back pain	15	1.3	13	<1
Myalgia	14	<1	15	<1
Pain in extremity	11	<1	10	<1
Endocrine				
Hypothyroidism	14	0	3.4	0
Infections				
Urinary tract infection	12	<1	11	<1
Upper respiratory tract infection	11	1.1	9	0
Nasopharyngitis	11	0	8	0

Graded per NCI CTCAE v4.0

1 Includes peripheral neuropathy, peripheral sensory neuropathy, paresthesia, and polyneuropathy

Table 15: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with TNBC in IMpassion130

Laboratory Abnormality	TECENTRIQ with Paclitaxel Protein-Bound		Placebo in combination with Paclitaxel Protein-Bound	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Hematology				
Decreased Hemoglobin	79	3.8	73	3
Decreased Leukocytes	76	14	71	9
Decreased Neutrophils	58	13	54	13
Decreased Lymphocytes	54	13	47	8
Increased Prothrombin INR	25	<1	25	<1
Chemistry				
Increased ALT	43	6	34	2.7
Increased AST	42	4.9	34	3.4
Decreased Calcium	28	1.1	26	<1
Decreased Sodium	27	4.2	25	2.7
Decreased Albumin	27	<1	25	<1
Increased Alkaline Phosphatase	25	3.3	22	2.7

Laboratory Abnormality	TECENTRIQ with Paclitaxel Protein-Bound		Placebo in combination with Paclitaxel Protein-Bound	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Decreased Phosphate	22	3.6	19	3.7
Increased Creatinine	21	<1	16	<1

Each test incidence is based on the number of patients who had at least one on-study laboratory measurement available: TECENTRIQ with paclitaxel protein-bound (range: 316-452); placebo with paclitaxel protein-bound (range: 299-438). 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).

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 (14.4)]*. 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 16 and 17 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ with carboplatin and etoposide in IMpower133.

Table 16: 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

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 (%)
Metabolism and Nutrition				
Decreased appetite	27	1	18	0

Graded per NCI CTCAE v4.0

Table 17: 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 hepatocelullar carcinoma who have not received prior systemic treatment *[see Clinical Studies (14.5)]*. 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 phosphatate (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 18 and 19 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ and bevacizumab in IMbrave150.

Table 18: 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[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
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

Adverse Reaction	TECENTRIQ in combination with bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
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 19: 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				
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)
NA = Not applicable.

[1] Graded per NCI CTCAE v4.0

6.2 Immunogenicity

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

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

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

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

Among 434 patients with TNBC in IMpassion130, 13% tested positive for treatment-emergent ADA at one or more post-dose time points. Among 178 patients in PD-L1 positive subgroup with TNBC in IMpassion130, 12% tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA had decreased systemic atezolizumab exposure *[see Clinical Pharmacology (12.3)]*. There are insufficient numbers of patients in the PD-L1 positive subgroup with ADA to determine whether ADA alters the efficacy of atezolizumab. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 315 ADA-evaluable patients with HCC who received TECENTRIQ and bevacizumab in IMbrave150, 28% (n=88) tested positive for treatment-emergent ADA at one or more post-dose time points and 66% (58/88) of these 88 patients tested ADA-positive prior to receiving the third dose of TECENTRIQ. The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA had lower systemic atezolizumab exposure as compared to patients who were ADA-negative *[see Clinical Pharmacology (12.3)]*.

Exploratory analyses showed that the subset of patients who were ADA-positive by week 6 (20%; 58/288) appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 6; *[see Clinical Studies (14.5)]*. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

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

Infertility

Females

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Of 2810 patients with urothelial carcinoma, lung cancer, triple-negative breast cancer, and hepatocellular carcinoma who were treated with TECENTRIQ in clinical studies, 45% were 65 years and over and 12% 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.

12.3 Pharmacokinetics

Patients' exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including a dose of 1200 mg administered every 3 weeks. The clearance (CV%) was 0.20 L/day (29%), the volume of distribution at steady state was 6.9 L, and the terminal half-life was 27 days. Steady state was achieved after 6 to 9 weeks following multiple doses. The systemic accumulation ratio for every 2 weeks administration and every 3 weeks administration was 3.3- and 1.9- fold, respectively. Atezolizumab clearance was found to decrease over time, with a mean maximal reduction (CV%) from baseline value of approximately 17% (41%); however, the decrease in clearance was not considered clinically relevant.

Specific Populations

Age (21 to 89 years), body weight, sex, albumin levels, tumor burden, region or race, mild or moderate renal impairment [estimated glomerular filtration rate (eGFR) 30 to 89 mL/min/1.73 m^2], mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1 to 1.5 × ULN and any AST), moderate hepatic impairment (bilirubin >1.5 to 3x ULN and any AST), level of PD-L1 expression, or performance status had no clinically significant effect on the systemic exposure of atezolizumab. In OAK, IMpower150 (TECENTRIQ, bevacizumab, paclitaxel, carboplatin arm only), IMpassion130 (TECENTRIQ and paclitaxel protein-bound) and IMbrave150 (TECENTRIQ and bevacizumab), atezolizumab clearance in patients who tested positive for treatment-emergent anti-drug antibodies (ADA) was 25%, 18%, 22% and 49% higher, respectively, as compared to clearance in patients who tested negative for treatment-emergent ADA.

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

Drug Interaction Studies

The drug interaction potential of atezolizumab is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Urothelial Carcinoma

Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The efficacy of TECENTRIQ was investigated in IMvigor210 (Cohort 1) (NCT02951767), a multicenter, open-label, single-arm trial that included 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy and were either previously untreated or had disease progression at least 12 months after neoadjuvant or adjuvant chemotherapy. Patients were considered cisplatin-ineligible if they met any one of the following criteria at study entry: impaired renal function [creatinine clearance (CLcr) of 30 to 59 mL/min], Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2, hearing loss of ≥ 25 decibels (dB) at two contiguous frequencies, or Grades 2-4 peripheral neuropathy. This study excluded patients who had: a history of autoimmune disease; active or corticosteroid-dependent brain metastases; administration of a live, attenuated vaccine within 28 days prior to enrollment; or administration of systemic immunostimulatory agents within 6 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Patients received TECENTRIQ 1200 mg as an intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Tumor response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed overall response rate (ORR) as assessed by independent review facility (IRF) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1), duration of response (DoR) and overall survival (OS).

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

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

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

Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 20. The median follow-up time for this study was 14.4 months. In 24 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 33% (95% CI: 16%, 55%).

Table 20: Efficacy Results in IMvigor210 (Cohort 1)

	All Patients	PD-L1 Expression Subgroups	
	N = 119	PD-L1 Expression of < 5% in ICs[1] N = 87	PD-L1 Expression of ≥ 5% in ICs[1] N = 32
Number of IRF-assessed Confirmed Responders	28	19	9
ORR % (95% CI)	23.5% (16.2, 32.2)	21.8% (13.7, 32)	28.1% (13.8, 46.8)
Complete Response	6.7%	6.9%	6.3%
Partial Response	16.8%	14.9%	21.9%
Median DoR, months (range)	NR (3.7, 16.6+)	NR (3.7, 16.6+)	NR (8.1, 15.6+)

NR = Not reached
+ Denotes a censored value
[1] PD-L1 expression in tumor-infiltrating immune cells (ICs)

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

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

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

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

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

Confirmed ORR and median DOR in all patients and the two PD-L1 subgroups are summarized in Table 21. The median follow-up time for this study was 32.9 months. In 59 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 22.0% (95% CI: 12.3%, 34.7%).

Table 21: Efficacy Results in IMvigor210 (Cohort 2)

	All Patients	**PD-L1 Expression Subgroups**	
	N = 310	**PD-L1 Expression of < 5% in IC[1] N = 210**	**PD-L1 Expression of ≥ 5% in IC[1] N = 100**
Number of IRF-assessed Confirmed Responders	46	20	26
ORR % (95% CI)	14.8% (11.2, 19.3)	9.5% (5.9, 14.3)	26% (17.7, 35.7)
Complete Response	5.5%	2.4%	12.0%
Partial Response	9.4%	7.1%	14.0%
Median DOR, months (range)	27.7 (2.1+, 33.4+)	20.9 (2.1+, 33.4+)	29.7 (4.2, 31.2+)

\+ Denotes a censored value

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

14.2 Non-Small Cell Lung Cancer

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/m2) on Days 1 and 8 of each 21-day cycle OR carboplatin (AUC 5 mg/mL/min) on Day 1 with gemcitabine (1000 mg/m2) 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 22 and Figure 1.

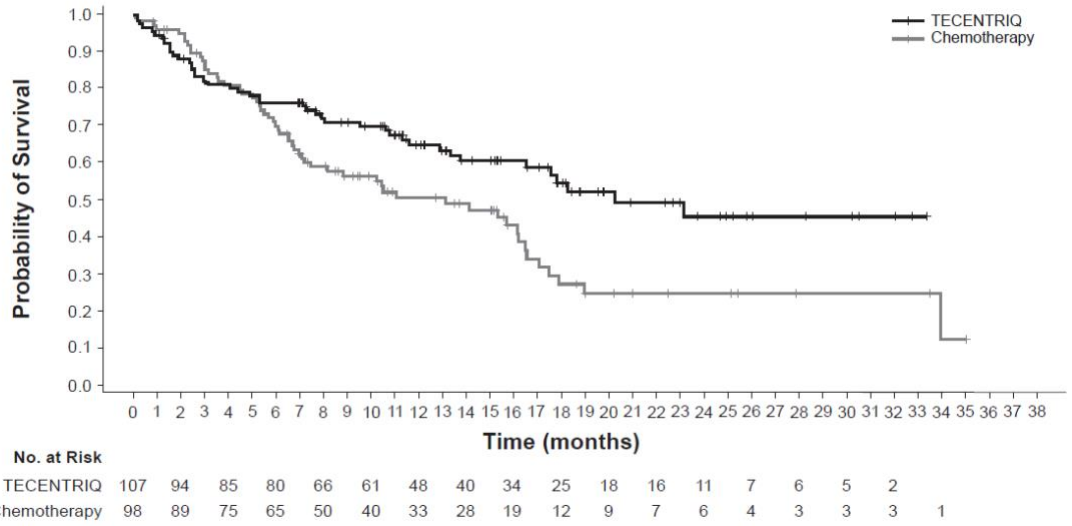
Table 22: Efficacy Results from IMpower110 in Patients with NSCLC with High PD-L1 Expression (TC ≥ 50% or IC ≥ 10%) and without EGFR or ALK Genomic Tumor Aberrations

	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)

	Arm A: TECENTRIQ N = 107	Arm B: Platinum-Based Chemotherapy N = 98
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 1: 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 a 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/m2 while the remaining 87% received paclitaxel at a dose of 200 mg/m2. 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.

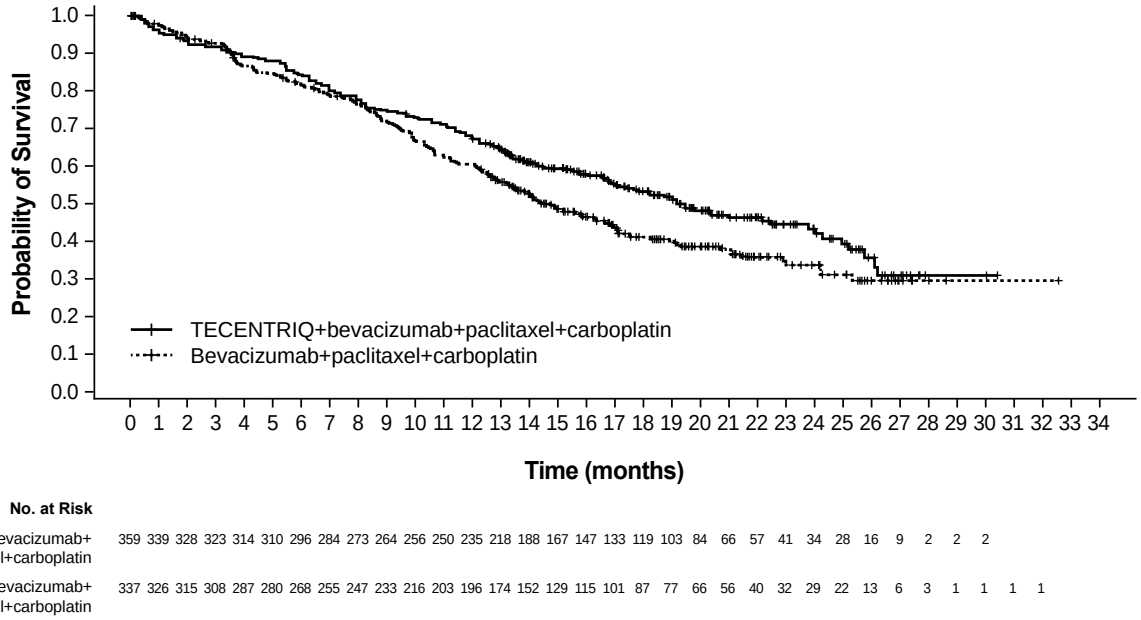
The trial demonstrated a statistically significant improvement in PFS between Arms B and C in both the tGE-WT and ITT-WT subpopulations, but did not demonstrate a significant difference for either subpopulation between Arms A and C based on the final PFS analyses. In the interim analysis of OS, a statistically 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 23 and Figure 2.

Table 23: 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 2: Kaplan-Meier Curves for Overall Survival in ITT-WT Population in IMpower150



No. at Risk																													
TECENTRIQ+bevacizumab+paclitaxel+carboplatin	359	339	328	323	314	310	296	284	273	264	256	250	235	218	188	167	147	133	119	103	84	66	57	41	34	28	16	9	2	2	2
Bevacizumab+paclitaxel+carboplatin	337	326	315	308	287	280	268	255	247	233	216	203	196	174	152	129	115	101	87	77	66	56	40	32	29	22	13	6	3	1	1	1	1

Exploratory analyses showed that the subset of patients in the four drug regimen arm who were ADA positive by week 4 (30%) appeared to have similar efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 (70%) *[see Adverse Reactions (6.2), Clinical Pharmacology (12.3)]*. In an exploratory analysis, propensity score matching was conducted to compare ADA positive patients in the TECENTRIQ, bevacizumab, paclitaxel, and carboplatin arm with a matched population in the bevacizumab, paclitaxel, and carboplatin arm. Similarly ADA negative patients in the TECENTRIQ, bevacizumab, paclitaxel, and carboplatin arm were compared with a matched population in the bevacizumab, paclitaxel, and carboplatin arm. Propensity score matching factors were: baseline sum of longest tumor size (BSLD), baseline ECOG, baseline albumin, baseline LDH, sex, tobacco history, metastatic site, TC level, and IC level. The hazard ratio comparing the ADA-positive subgroup with its matched control was 0.69 (95% CI: 0.44, 1.07). The hazard ratio comparing the ADA-negative subgroup with its matched control was 0.64 (95% CI: 0.46, 0.90).

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 24 and Figure 3.

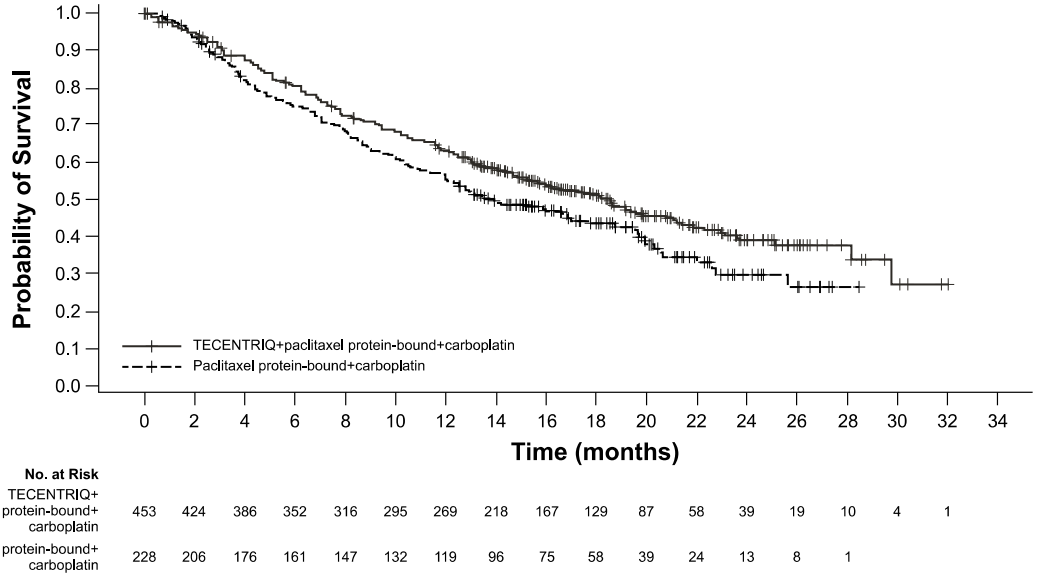
Table 24: Efficacy Results from IMpower130

	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 3: Kaplan-Meier Curves for Overall Survival in IMpower130



No. at Risk																	
TECENTRIQ+ paclitaxel protein-bound+ carboplatin	453	424	386	352	316	295	269	218	167	129	87	58	39	19	10	4	1
Paclitaxel protein-bound+ carboplatin	228	206	176	161	147	132	119	96	75	58	39	24	13	8	1		

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.

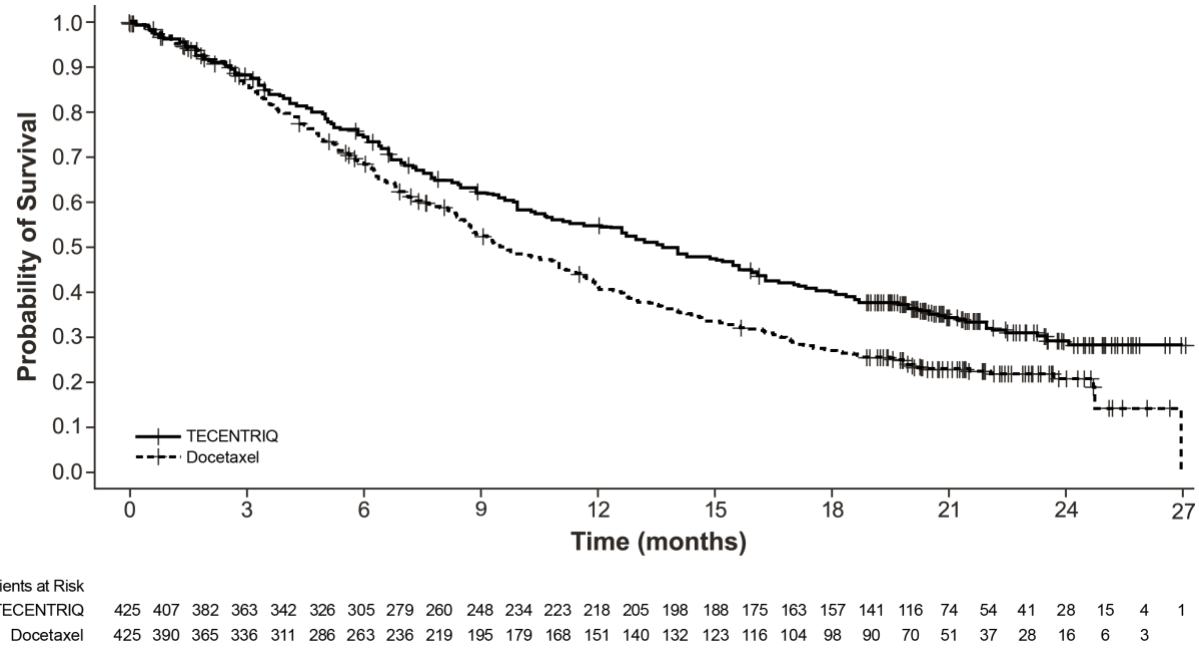
Efficacy results are presented in Table 25 and Figure 4.

Table 25: Efficacy Results in OAK

	TECENTRIQ	Docetaxel
Overall Survival in first 850 patients		
Number of patients	N=425	N=425
Deaths (%)	271 (64%)	298 (70%)
Median, months	13.8	9.6
(95% CI)	(11.8, 15.7)	(8.6, 11.2)
Hazard ratio[1] (95% CI)	0.74 (0.63, 0.87)	
p-value[2]	0.0004[3]	
Progression-Free Survival		
Number of Patients	N=425	N=425
Events (%)	380 (89%)	375 (88%)
Progression (%)	332 (78%)	290 (68%)
Deaths (%)	48 (11%)	85 (20%)
Median, months	2.8	4.0
(95% CI)	(2.6, 3.0)	(3.3, 4.2)
Hazard ratio[1] (95% CI)	0.95 (0.82, 1.10)	
Overall Response Rate [4]		
Number of Patients	N=425	N=425
ORR, n (%)	58 (14%)	57 (13%)
(95% CI)	(11%, 17%)	(10%, 17%)
Complete Response	6 (1%)	1 (0.2%)
Partial Response	52 (12%)	56 (13%)
Duration of Response[3]	N=58	N=57
Median, months	16.3	6.2
(95% CI)	(10.0, NE)	(4.9, 7.6)
Overall Survival in all 1225 patients		
Number of patients	N=613	N=612
Deaths (%)	384 (63%)	409 (67%)
Median, months	13.3	9.8
(95% CI)	(11.3, 14.9)	(8.9, 11.3)
Hazard ratio[1] (95% CI)	0.79 (0.69, 0.91)	
p-value[2]	0.0013[5]	

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

Figure 4: Kaplan-Meier Curves of Overall Survival in the First 850 Patients Randomized in OAK



No. Patients at Risk

TECENTRIQ	425	407	382	363	342	326	305	279	260	248	234	223	218	205	198	188	175	163	157	141	116	74	54	41	28	15	4	1
Docetaxel	425	390	365	336	311	286	263	236	219	195	179	168	151	140	132	123	116	104	98	90	70	51	37	28	16	6	3	

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define the PD-L1 expression subgroups for pre-specified analyses. Of the 850 patients, 16% were classified as having high PD-L1 expression, defined as having PD-L1 expression on ≥ 50% of TC or ≥ 10% of IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in patients who did not have high PD-L1 expression.

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

14.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer

The efficacy of TECENTRIQ in combination with paclitaxel protein-bound was investigated in IMpassion130 (NCT02425891), a multicenter, international, double-blinded, placebo-controlled, randomized (1:1) trial that included 902 unresectable locally advanced or metastatic triple-negative breast cancer patients that had not received prior chemotherapy for metastatic disease. The trial excluded patients with 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.

Randomization was stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumor infiltrating immune cells (IC) (PD-L1 stained tumor-infiltrating immune cells [IC] <1% of tumor area vs. ≥ 1% of the tumor area) by the VENTANA PD-L1 (SP142) Assay. Of the 902 patients in the intent to treat population (ITT), 41% (369 patients) were classified as PD-L1 expression ≥ 1%. Patients were randomized to receive TECENTRIQ 840 mg or placebo intravenously on Days 1 and 15 of every 28-day cycle with paclitaxel protein-bound 100 mg/m^2 intravenously on Days 1, 8 and 15 of every 28-day cycle. Patients received treatment until radiographic disease progression per RECIST v1.1, or unacceptable toxicity. Tumor assessments were performed every 8 weeks (± 1 week) for the first 12 months after Cycle 1, day 1 and every 12 weeks (± 1 week) thereafter. Major efficacy outcomes were investigator-assessed progression free survival (PFS) in the ITT and PD-L1 expressing patient population per RECIST v1.1 and overall survival (OS) in the ITT population.

In IMpassion130, the median age was 55 years (range: 20-86). Overall, most patients were women (99.6%) and the majority of patients were white (68%), Asian (18%), Black or African American (7%), and American Indian or Alaskan Native (4.4%). The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. Baseline ECOG performance status was 0 (58%) or 1 (41%). Overall, 41% of enrolled patients had PD-L1 expression ≥ 1%, 27% had liver metastases and 7% brain metastases at baseline. Approximately half the patients had received a taxane (51%) or anthracycline (54%) in the (neo)adjuvant setting. Patient demographics and baseline tumor disease in the PD-L1 expressing population were generally representative of the broader study population.

Tumor specimens (archival or fresh) were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used as a stratification factor for randomization and to define the PD-L1 expression subgroups for pre-specified analyses.

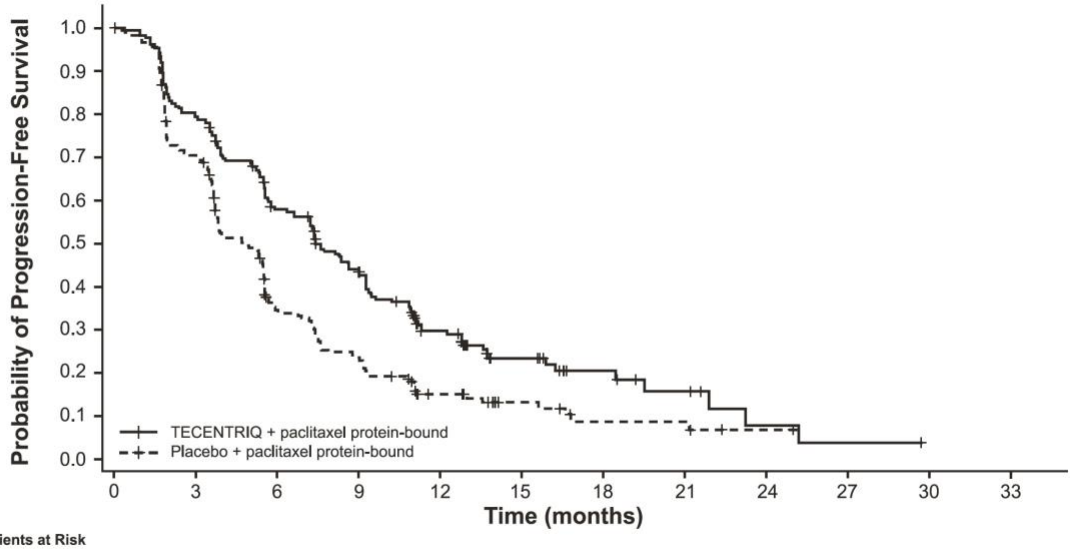
Overall survival data were immature with 43% deaths in the ITT population. The efficacy results of IMpassion130 for the patient population with PD-L1 expression ≥ 1% are presented in Table 26 and Figure 5.

Table 26: Efficacy Results from IMpassion130 in Patients with PD-L1 Expression ≥ 1%

	PD-L1 Expression ≥ 1%[1]	
	TECENTRIQ in combination with paclitaxel protein-bound	**Placebo in combination with paclitaxel protein-bound**
Progression-Free Survival[2,3]	(n=185)	(n=184)
Events (%)	136 (74)	151 (82)
Median, months	7.4 (6.6, 9.2)	4.8 (3.8, 5.5)
Stratified Hazard ratio (95% CI)[4]	0.60 (0.48, 0.77)	
p-value	<0.0001	
Objective Response Rate[2,3,5,6]	n=185	n=183
Number of responders (%)	98 (53)	60 (33)
(95% CI)	(45.5, 60.3)	(26.0, 40.1)
Complete Response (%)	17 (9)	1 (<1)
Partial Response (%)	81 (44)	59 (32)
Duration of Response[2,3,6]	n=98	n=60
Median, months	9.2	6.2
(95% CI)	(7.5, 11.9)	(5.5, 8.8)

[1] PD-L1 expression in tumor-infiltrating immune cells (IC)
[2] As determined by investigator assessment
[3] per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[4] Stratified by presence of liver metastases, and by prior taxane treatment
[5] Patients with measurable disease at baseline
[6] Confirmed responses
PFS=Progression-Free Survival; CI=Confidence Interval; ORR=Objective Response Rate; DOR=Duration of Response; NE=Not Estimable

Figure 5: Kaplan-Meier Plot of Progression-Free-Survival in IMpassion130 in Patients with PD-L1 Expression ≥1%



No. of Patients at Risk												
TECENTRIQ + paclitaxel protein-bound	185	145	102	73	38	19	10	6	2	1	NE	NE
Placebo + paclitaxel protein-bound	184	125	56	38	18	10	5	5	1	NE	NE	NE

14.4 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.

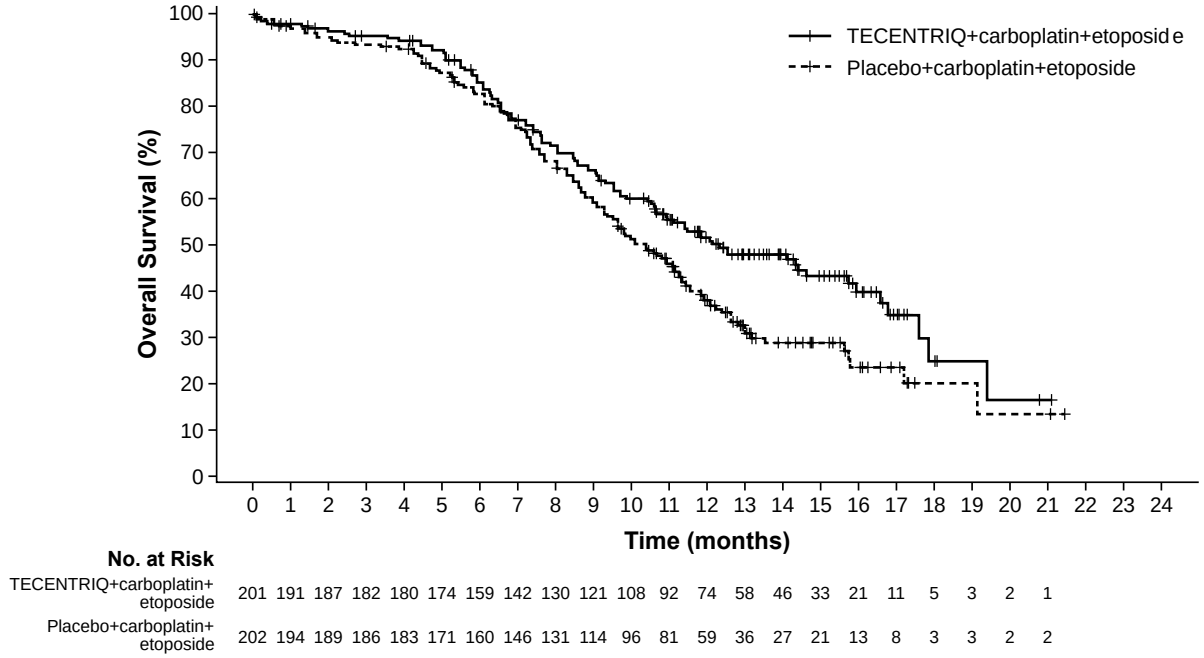
Efficacy results are presented in Table 27 and Figure 6.

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



14.5 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.

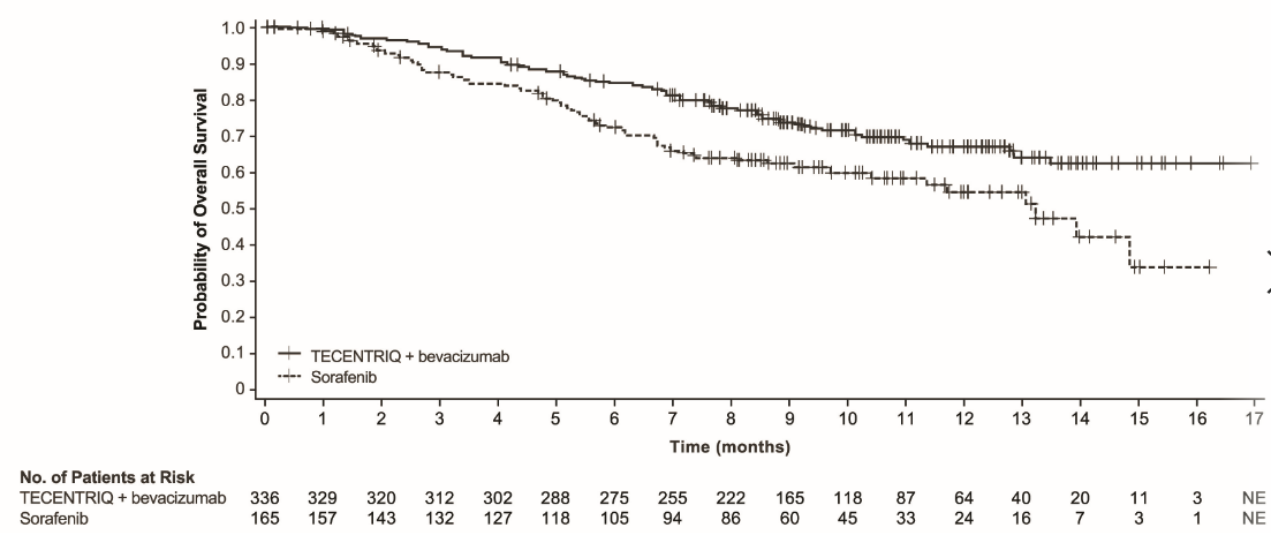
Table 28: Efficacy Results from IMbrave150

	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; N/A=not applicable; 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 Adverse Reactions (6.2), Clinical Pharmacology (12.3)]*. 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).

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

Infections

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

Infusion-Related Reactions

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

Embryo-Fetal Toxicity

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

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

Lactation

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

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

U.S. License No. 1048

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 and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death.

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

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

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

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

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

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

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

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

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

Problems in other organs. Signs and symptoms may include:

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

Severe infections. Signs and symptoms of infection may include:

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

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

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

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

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

What is TECENTRIQ?

TECENTRIQ is a prescription medicine used to treat adults with:

- **a type of bladder and urinary tract cancer called urothelial carcinoma.** TECENTRIQ may be used when your bladder cancer has spread or cannot be removed by surgery, **and if you have any one of the following conditions:**
  - you are not able to take chemotherapy that contains a medicine called cisplatin, and your cancer tests positive for "PD-L1", **or**
  - you are not able to take chemotherapy that contains any platinum regardless of "PD-L1" status, **or**
  - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
- **a type of lung cancer called non-small cell lung cancer (NSCLC).**
  - **TECENTRIQ may be used 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.
- **a type of breast cancer called triple-negative breast cancer (TNBC).** TECENTRIQ may be used with the medicine paclitaxel protein-bound when your breast cancer:
  - has spread or cannot be removed by surgery, **and**
  - your cancer tests positive for "PD-L1".
- **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.
- **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.

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

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

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are being treated for an infection
- are pregnant or plan to become pregnant. TECENTRIQ can harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with TECENTRIQ.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with TECENTRIQ.
  - You should use an effective method of birth control during your treatment and for at least 5 months after the last dose of TECENTRIQ.
- are breastfeeding or plan to breastfeed. It is not known if TECENTRIQ passes into your breast milk. Do not breastfeed during treatment and for at least 5 months after the last dose of TECENTRIQ.

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

How will I receive TECENTRIQ?

- Your healthcare provider will give you TECENTRIQ into your vein through an intravenous (IV) line over 30 to 60 minutes.
- TECENTRIQ is usually given every 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.
- 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
- nausea
- cough
- shortness of breath
- decreased appetite

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 triple-negative breast cancer with paclitaxel protein-bound include:

- hair loss
- tingling or numbness in hands or feet
- feeling tired
- nausea
- diarrhea
- low red blood cells (anemia)
- constipation
- cough
- headache
- low white blood cells
- vomiting
- 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

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

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

General information about the safe and effective use of TECENTRIQ.

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

What are the ingredients in TECENTRIQ?

Active ingredient: atezolizumab

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

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

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. Revised: 05/2020

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

AVASTIN® (bevacizumab) injection, for intravenous use
Initial U.S. Approval: 2004

----------RECENT MAJOR CHANGES----------

Indications and Usage, Hepatocellular Carcinoma (1.7)	05/2020
Dosage and Administration, Hepatocellular Carcinoma (2.8)	05/2020
Boxed Warning, Removed	06/2019
Warnings and Precautions (5.3, 5.9)	05/2020

----------INDICATIONS AND USAGE----------

Avastin is a vascular endothelial growth factor inhibitor indicated for the treatment of:

- Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment. (1.1)
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen. (1.1)

Limitations of Use: Avastin is not indicated for adjuvant treatment of colon cancer. (1.1)

- Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment. (1.2)
- Recurrent glioblastoma in adults. (1.3)
- Metastatic renal cell carcinoma in combination with interferon alfa. (1.4)
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan. (1.5)
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer:
  - in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for stage III or IV disease following initial surgical resection (1.6)
  - in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens (1.6)
  - in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Avastin as a single agent, for platinum-sensitive recurrent disease (1.6)
- Hepatocellular Carcinoma (HCC)
  - in combination with atezolizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy (1.7)

----------DOSAGE AND ADMINISTRATION----------

Do not administer Avastin for 28 days following major surgery and until surgical wound is fully healed. (2.1)
Metastatic colorectal cancer (2.2)
- 5 mg/kg every 2 weeks with bolus-IFL
- 10 mg/kg every 2 weeks with FOLFOX4
- 5 mg/ kg every 2 weeks or 7.5 mg/kg every 3 weeks with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy after progression on a first-line Avastin containing regimen

First-line non–squamous non–small cell lung cancer (2.3)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel

Recurrent glioblastoma (2.4)
- 10 mg/kg every 2 weeks

Metastatic renal cell carcinoma (2.5)
- 10 mg/kg every 2 weeks with interferon alfa

Persistent, recurrent, or metastatic cervical cancer (2.6)
- 15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan

Stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer following initial surgical resection (2.7)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel for up to 6 cycles, followed by 15 mg/kg every 3 weeks as a single agent, for a total of up to 22 cycles

Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer (2.7)
- 10 mg/kg every 2 weeks with paclitaxel, pegylated liposomal doxorubicin, or topotecan given every week
- 15 mg/kg every 3 weeks with topotecan given every 3 weeks

Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (2.7)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent
- 15 mg/kg every 3 weeks with carboplatin and gemcitabine for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent

Hepatocellular Carcinoma (2.8)
- 15 mg/kg after administration of 1,200 mg of atezolizumab every 3 weeks

Administer as an intravenous infusion. (2.10)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) in a single-dose vial (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Gastrointestinal Perforations and Fistula: Discontinue for gastrointestinal perforations, tracheoesophageal fistula, grade 4 fistula, or fistula formation involving any organ (5.1)
- Surgery and Wound Healing Complications: Discontinue in patients who develop wound healing complications that require medical intervention or necrotizing fasciitis. Withhold for at least 28 days prior to elective surgery. Do not administer Avastin for at least 28 days after surgery, and until the wound is fully healed (5.2)
- Hemorrhage: Severe or fatal hemorrhages have occurred. Do not administer for recent hemoptysis. Discontinue for Grade 3-4 hemorrhage (5.3)
- Arterial Thromboembolic Events (ATE): Discontinue for severe ATE. (5.4)
- Venous Thromboembolic Events (VTE): Discontinue for Grade 4 VTE. (5.5)
- Hypertension: Monitor blood pressure and treat hypertension. Withhold if not medically controlled; resume once controlled. Discontinue for hypertensive crisis or hypertensive encephalopathy. (5.6)
- Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue. (5.7)
- Renal Injury and Proteinuria: Monitor urine protein. Discontinue for nephrotic syndrome. Withhold until less than 2 grams of protein in urine. (5.8)
- Infusion-Related Reactions: Decrease rate for infusion-related reactions. Discontinue for severe infusion-related reactions and administer medical therapy. (5.9)
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of potential risk to fetus and need for use of effective contraception. (5.10, 8.1, 8.3)
- Ovarian Failure: Advise females of the potential risk. (5.11, 8.3)
- Congestive Heart Failure (CHF): Discontinue Avastin in patients who develop CHF. (5.12)

----------ADVERSE REACTIONS----------

Most common adverse reactions incidence (incidence > 10%) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech, Inc. 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.

Revised: 05/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer

Avastin, in combination with intravenous fluorouracil-based chemotherapy, is indicated for the first-or second-line treatment of patients with metastatic colorectal cancer (mCRC).

Avastin, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with mCRC who have progressed on a first-line Avastin-containing regimen.

Limitations of Use: Avastin is not indicated for adjuvant treatment of colon cancer *[see Clinical Studies (14.2)]*.

1.2 First-Line Non-Squamous Non–Small Cell Lung Cancer

Avastin, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer (NSCLC).

1.3 Recurrent Glioblastoma

Avastin is indicated for the treatment of recurrent glioblastoma (GBM) in adults.

1.4 Metastatic Renal Cell Carcinoma

Avastin, in combination with interferon alfa, is indicated for the treatment of metastatic renal cell carcinoma (mRCC).

1.5 Persistent, Recurrent, or Metastatic Cervical Cancer

Avastin, in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

1.6 Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Avastin, in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.

Avastin, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, is indicated for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.

Avastin, in combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by Avastin as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

1.7 Hepatocellular Carcinoma

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

Do not administer Avastin until at least 28 days following surgery and the wound is fully healed.

2.2 Metastatic Colorectal Cancer

The recommended dosage when Avastin is administered in combination with intravenous fluorouracil-based chemotherapy is:

- 5 mg/kg intravenously every 2 weeks in combination with bolus-IFL.
- 10 mg/kg intravenously every 2 weeks in combination with FOLFOX4.
- 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg intravenously every 3 weeks in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy in patients who have progressed on a first-line Avastin-containing regimen.

2.3 First-Line Non-Squamous Non-Small Cell Lung Cancer

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel.

2.4 Recurrent Glioblastoma

The recommended dosage is 10 mg/kg intravenously every 2 weeks.

2.5 Metastatic Renal Cell Carcinoma

The recommended dosage is 10 mg/kg intravenously every 2 weeks in combination with interferon alfa.

2.6 Persistent, Recurrent, or Metastatic Cervical Cancer

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with paclitaxel and cisplatin or in combination with paclitaxel and topotecan.

2.7 Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Stage III or IV Disease Following Initial Surgical Resection

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent for a total of up to 22 cycles or until disease progression, whichever occurs earlier.

Recurrent Disease

Platinum Resistant

The recommended dosage is 10 mg/kg intravenously every 2 weeks in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan (every week).

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with topotecan (every 3 weeks).

Platinum Sensitive

The recommended dosage is 15 mg/kg intravenously every 3 weeks, in combination with carboplatin and paclitaxel for 6 to 8 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent until disease progression.

The recommended dosage is 15 mg/kg intravenously every 3 weeks, in combination with carboplatin and gemcitabine for 6 to 10 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent until disease progression.

2.8 Hepatocellular Carcinoma

The recommended dosage is 15 mg/kg intravenously after administration of 1,200 mg of atezolizumab intravenously on the same day, every 3 weeks until disease progression or unacceptable toxicity.

Refer to the Prescribing Information for atezolizumab prior to initiation for recommended dosage information.

2.9 Dosage Modifications for Adverse Reactions

Table 1 describes dosage modifications for specific adverse reactions. No dose reductions for Avastin are recommended.

Table 1: Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Gastrointestinal Perforations and Fistulae *[see Warnings and Precautions (5.1)]*.	• Gastrointestinal perforation, any grade • Tracheoesophageal fistula, any grade • Fistula, Grade 4 • Fistula formation involving any internal organ	Discontinue Avastin
Wound Healing Complications *[see Warnings and Precautions (5.2)]*.	• Wound healing complications requiring medical intervention • Necrotizing fasciitis	Discontinue Avastin
Hemorrhage *[see Warnings and Precautions (5.3)]*.	• Grade 3 or 4	Discontinue Avastin
	• Recent history of hemoptysis of 1/2 teaspoon (2.5 mL) or more	Withhold Avastin
Thromboembolic Events *[see Warnings and Precautions (5.4, 5.5)]*.	• Arterial thromboembolism, severe	Discontinue Avastin
	• Venous thromboembolism, Grade 4	Discontinue Avastin
Hypertension *[see Warnings and Precautions (5.6)]*.	• Hypertensive crisis • Hypertensive encephalopathy	Discontinue Avastin
	• Hypertension, severe	Withhold Avastin if not controlled with medical management; resume once controlled
Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.7)]*.	• Any	Discontinue Avastin
Renal Injury and Proteinuria *[see Warnings and Precautions (5.8)]*.	• Nephrotic syndrome	Discontinue Avastin
	• Proteinuria greater than or equal to 2 grams per 24 hours in absence of nephrotic syndrome	Withhold Avastin until proteinuria less than 2 grams per 24 hours
Infusion-Related Reactions *[see Warnings and Precautions (5.9)]*.	• Severe	Discontinue Avastin
	• Clinically significant	Interrupt infusion; resume at a decreased rate of infusion after symptoms resolve
	• Mild, clinically insignificant	Decrease infusion rate
Congestive Heart Failure *[see Warnings and Precautions (5.12)]*.	Any	Discontinue Avastin

2.10 Preparation and Administration

Preparation

- Use appropriate aseptic technique.
- Visually inspect vial for particulate matter and discoloration prior to preparation for administration. Discard vial if solution is cloudy, discolored or contains particulate matter.
- Withdraw necessary amount of Avastin and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.
- Discard any unused portion left in a vial, as the product contains no preservatives.
- Store diluted Avastin solution at 2°C to 8°C (36°F to 46°F) for up to 8 hours.
- No incompatibilities between Avastin and polyvinylchloride or polyolefin bags have been observed.

Administration

- Administer as an intravenous infusion.
- First infusion: Administer infusion over 90 minutes.
- Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated. Administer all subsequent infusions over 30 minutes if second infusion over 60 minutes is tolerated.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) clear to slightly opalescent, colorless to pale brown solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforations and Fistulae

Serious, and sometimes fatal, gastrointestinal perforation occurred at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. The incidence ranged from 0.3% to 3% across clinical studies, with the highest incidence in patients with a history of prior pelvic radiation. Perforation can be complicated by intra-abdominal abscess, fistula formation, and the need for diverting ostomies. The majority of perforations occurred within 50 days of the first dose *[see Adverse Reactions (6.1)]*.

Serious fistulae (including, tracheoesophageal, bronchopleural, biliary, vaginal, renal and bladder sites) occurred at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. The incidence ranged from < 1% to 1.8% across clinical studies, with the highest incidence in patients with cervical cancer. The majority of fistulae occurred within 6 months of the first dose. Patients who develop a gastrointestinal vaginal fistula may also have a bowel obstruction and require surgical intervention, as well as a diverting ostomy.

Avoid Avastin in patients with ovarian cancer who have evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction. Discontinue in patients who develop gastrointestinal perforation, tracheoesophageal fistula or any Grade 4 fistula. Discontinue in patients with fistula formation involving any internal organ.

5.2 Surgery and Wound Healing Complications

In a controlled clinical study in which Avastin was not administered within 28 days of major surgical procedures, the incidence of wound healing complications, including serious and fatal complications, was 15% in patients with mCRC who underwent surgery while receiving Avastin and 4% in patients who did not receive Avastin. In a controlled clinical study in patients with relapsed or recurrent GBM, the incidence of wound healing events was 5% in patients who received Avastin and 0.7% in patients who did not receive Avastin *[see Adverse Reactions (6.1)]*.

Discontinue Avastin in patients with wound healing complications requiring medical intervention. Withhold for at least 28 days prior to elective surgery. Do not administer for at least 28 days following surgery and until the wound is fully healed.

Necrotizing fasciitis including fatal cases, has been reported in patients receiving Avastin, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Discontinue Avastin in patients who develop necrotizing fasciitis.

5.3 Hemorrhage

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, which is most commonly Grade 1 epistaxis, and serious hemorrhage, which in some cases has been fatal. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grades 3-5 hemorrhagic events ranged from 0.4% to 7% in patients receiving Avastin *[see Adverse Reactions (6.1)]*.

Serious or fatal pulmonary hemorrhage occurred in 31% of patients with squamous NSCLC and 4% of patients with non-squamous NSCLC receiving Avastin with chemotherapy compared to none of the patients receiving chemotherapy alone.

An evaluation for the presence of varices is recommended within 6 months of initiation of Avastin in patients with HCC. There is lack of clinical data to support the safety of Avastin in patients with variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding, or high risk of bleeding because these patients were excluded from clinical trials of Avastin in HCC *[see Clinical Studies (14.10)]*.

Do not administer Avastin to patients with recent history of hemoptysis of 1/2 teaspoon or more of red blood. Discontinue in patients who develop a Grades 3-4 hemorrhage.

5.4 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina, occurred at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. Across clinical studies, the incidence of Grades 3-5 ATE was 5% in patients receiving Avastin with chemotherapy compared to ≤2% in patients receiving chemotherapy alone; the highest incidence occurred in patients with GBM. The risk of developing ATE was increased in patients with a history of arterial thromboembolism, diabetes, or >65 years *[see Use in Specific Populations (8.5)]*.

Discontinue in patients who develop a severe ATE. The safety of reinitiating Avastin after an ATE is resolved is not known.

5.5 Venous Thromboembolic Events

An increased risk of venous thromboembolic events (VTE) was observed across clinical studies *[see Adverse Reactions (6.1)]*. In Study GOG-0240, Grades 3-4 VTE occurred in 11% of patients receiving Avastin with

chemotherapy compared with 5% of patients receiving chemotherapy alone. In EORTC 26101, the incidence of Grades 3-4 VTE was 5% in patients receiving Avastin with chemotherapy compared to 2% in patients receiving chemotherapy alone.

Discontinue Avastin in patients with a Grade 4 VTE, including pulmonary embolism.

5.6 Hypertension

Severe hypertension occurred at a higher incidence in patients receiving Avastin as compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grades 3-4 hypertension ranged from 5% to 18%.

Monitor blood pressure every two to three weeks during treatment with Avastin. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension after discontinuing Avastin. Withhold Avastin in patients with severe hypertension that is not controlled with medical management; resume once controlled with medical management. Discontinue in patients who develop hypertensive crisis or hypertensive encephalopathy.

5.7 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) was reported in < 0.5% of patients across clinical studies. The onset of symptoms occurred from 16 hours to 1 year after the first dose. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES.

Discontinue Avastin in patients who develop PRES. Symptoms usually resolve or improve within days after discontinuing Avastin, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating Avastin in patients who developed PRES is not known.

5.8 Renal Injury and Proteinuria

The incidence and severity of proteinuria was higher in patients receiving Avastin as compared to patients receiving chemotherapy. Grade 3 (defined as urine dipstick 4+ or > 3.5 grams of protein per 24 hours) to Grade 4 (defined as nephrotic syndrome) ranged from 0.7% to 7% in clinical studies. The overall incidence of proteinuria (all grades) was only adequately assessed in Study BO17705, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (15 days to 37 months) after initiating Avastin. Median time to resolution was 6.1 months (95% CI: 2.8, 11.3). Proteinuria did not resolve in 40% of patients after median follow-up of 11.2 months and required discontinuation of Avastin in 30% of the patients who developed proteinuria *[see Adverse Reactions (6.1)]*.

In an exploratory, pooled analysis of patients from seven randomized clinical studies, 5% of patients receiving Avastin with chemotherapy experienced Grades 2-4 (defined as urine dipstick 2+ or greater or > 1 gram of protein per 24 hours or nephrotic syndrome) proteinuria. Grades 2-4 proteinuria resolved in 74% of patients. Avastin was reinitiated in 42% of patients. Of the 113 patients who reinitiated Avastin, 48% experienced a second episode of Grades 2-4 proteinuria.

Nephrotic syndrome occurred in < 1% of patients receiving Avastin across clinical studies, in some instances with fatal outcome. In a published case series, kidney biopsy of 6 patients with proteinuria showed findings consistent with thrombotic microangiopathy. Results of a retrospective analysis of 5805 patients who received Avastin with chemotherapy and 3713 patients who received chemotherapy alone, showed higher rates of elevated serum creatinine levels (between 1.5 to 1.9 times baseline levels) in patients who received Avastin. Serum creatinine levels did not return to baseline in approximately one-third of patients who received Avastin.

Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during Avastin therapy. Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. Withhold for proteinuria greater than or equal to 2 grams per 24 hours and resume when less than 2 grams per 24 hours. Discontinue in patients who develop nephrotic syndrome.

Data from a postmarketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24-hour urine protein [Pearson Correlation 0.39 (95% CI: 0.17, 0.57)].

5.9 Infusion-Related Reactions

Infusion-related reactions reported across clinical studies and postmarketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion-related reactions with the first dose occurred in < 3% of patients and severe reactions occurred in 0.4% of patients.

Decrease the rate of infusion for mild, clinically insignificant infusion-related reactions. Interrupt the infusion in patients with clinically significant infusion-related reactions and consider resuming at a slower rate following resolution. Discontinue in patients who develop a severe infusion-related reaction and administer appropriate medical therapy (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators and/or oxygen).

5.10 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, Avastin may cause fetal harm when administered to pregnant women. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.11 Ovarian Failure

The incidence of ovarian failure was 34% vs. 2% in premenopausal women receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone for adjuvant treatment of a solid tumor. After discontinuing Avastin, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% of women receiving Avastin. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or an FSH level < 30 mIU/mL during the post-treatment period. Long-term effects of Avastin on fertility are unknown. Inform females of reproductive potential of the risk of ovarian failure prior to initiating Avastin *[see Adverse Reactions (6.1), Use in Specific Populations (8.3)]*.

5.12 Congestive Heart Failure (CHF)

Avastin is not indicated for use with anthracycline-based chemotherapy. The incidence of Grade ≥ 3 left ventricular dysfunction was 1% in patients receiving Avastin compared to 0.6% of patients receiving chemotherapy alone. Among patients who received prior anthracycline treatment, the rate of CHF was 4% for patients receiving Avastin with chemotherapy as compared to 0.6% for patients receiving chemotherapy alone.

In previously untreated patients with a hematological malignancy, the incidence of CHF and decline in left ventricular ejection fraction (LVEF) were increased in patients receiving Avastin with anthracycline-based chemotherapy compared to patients receiving placebo with the same chemotherapy regimen. The proportion of patients with a decline in LVEF from baseline of ≥ 20% or a decline from baseline of 10% to < 50%, was 10% in patients receiving Avastin with chemotherapy compared to 5% in patients receiving chemotherapy alone.

Time to onset of left-ventricular dysfunction or CHF was 1 to 6 months after the first dose in at least 85% of the patients and was resolved in 62% of the patients who developed CHF in the Avastin arm compared to 82% in the placebo arm. Discontinue Avastin in patients who develop CHF.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Gastrointestinal Perforations and Fistulae *[see Warnings and Precautions (5.1)]*.
- Surgery and Wound Healing Complications *[see Warnings and Precautions (5.2)]*.
- Hemorrhage *[see Warnings and Precautions (5.3)]*.
- Arterial Thromboembolic Events *[see Warnings and Precautions (5.4)]*.
- Venous Thromboembolic Events *[see Warnings and Precautions (5.5)]*.
- Hypertension *[see Warnings and Precautions (5.6)]*.
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.7)]*.
- Renal Injury and Proteinuria *[see Warnings and Precautions (5.8)]*.
- Infusion-Related Reactions *[see Warnings and Precautions (5.9)]*.
- Ovarian Failure *[see Warnings and Precautions (5.11)]*.
- Congestive Heart Failure *[see Warnings and Precautions (5.12)]*.

6.1 Clinical Trials Experience

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

The safety data in Warnings and Precautions and described below reflect exposure to Avastin in 4463 patients including those with mCRC (AVF2107g, E3200), non-squamous NSCLC (E4599), GBM (EORTC 26101), mRCC (BO17705), cervical cancer (GOG-0240), epithelial ovarian, fallopian tube, or primary peritoneal cancer (MO22224, AVF4095, GOG-0213, and GOG-0218), or HCC (IMbrave150) at the recommended dose and schedule for a median of 6 to 23 doses. The most common adverse reactions observed in patients receiving Avastin as a single agent or in combination with other anti-cancer therapies at a rate > 10% were epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, hemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis.

Across clinical studies, Avastin was discontinued in 8% to 22% of patients because of adverse reactions *[see Clinical Studies (14)]*.

Metastatic Colorectal Cancer

In Combination with bolus-IFL

The safety of Avastin was evaluated in 392 patients who received at least one dose of Avastin in a double-blind, active-controlled study (AVF2107g), which compared Avastin (5 mg/kg every 2 weeks) with bolus-IFL to placebo with bolus-IFL in patients with mCRC *[see Clinical Studies (14.1)]*. Patients were randomized (1:1:1) to placebo with bolus-IFL, Avastin with bolus-IFL, or Avastin with fluorouracil and leucovorin. The demographics of the safety population were similar to the demographics of the efficacy population. All Grades 3–4 adverse reactions and selected Grades 1–2 adverse reactions (i.e., hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Adverse reactions are presented in Table 2.

Table 2: Grades 3-4 Adverse Reactions Occurring at Higher Incidence (≥2%) in Patients Receiving Avastin vs. Placebo in Study AVF2107g

Adverse Reaction[a]	Avastin with IFL (N=392)	Placebo with IFL (N=396)
Hematology		
Leukopenia	37%	31%
Neutropenia	21%	14%
Gastrointestinal		
Diarrhea	34%	25%
Abdominal pain	8%	5%
Constipation	4%	2%
Vascular		
Hypertension	12%	2%
Deep vein thrombosis	9%	5%
Intra-abdominal thrombosis	3%	1%
Syncope	3%	1%
General		
Asthenia	10%	7%
Pain	8%	5%

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In Combination with FOLFOX4
The safety of Avastin was evaluated in 521 patients in an open-label, active-controlled study (E3200) in patients who were previously treated with irinotecan and fluorouracil for initial therapy for mCRC. Patients were randomized (1:1:1) to FOLFOX4, Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1) with FOLFOX4, or Avastin alone (10 mg/kg every 2 weeks). Avastin was continued until disease progression or unacceptable toxicity.

The demographics of the safety population were similar to the demographics of the efficacy population.

Selected Grades 3–5 non-hematologic and Grades 4–5 hematologic occurring at a higher incidence (≥2%) in patients receiving Avastin with FOLFOX4 compared to FOLFOX4 alone were fatigue (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%), vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8% vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache (3% vs. 0%). These data are likely to under-estimate the true adverse reaction rates due to the reporting mechanisms.

First-Line Non Squamous Non-Small Cell Lung Cancer

The safety of Avastin was evaluated as first-line treatment in 422 patients with unresectable NSCLC who received at least one dose of Avastin in an active-controlled, open-label, multicenter trial (E4599) *[see Clinical Studies (14.3)]*. Chemotherapy naïve patients with locally advanced, metastatic or recurrent non–squamous NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel and carboplatin with or without Avastin (15 mg/kg every 3 weeks). After completion or upon discontinuation of chemotherapy, patients randomized to receive Avastin continued to receive Avastin alone until disease progression or until unacceptable toxicity. The trial excluded patients with predominant squamous histology (mixed cell type tumors only), CNS metastasis, gross hemoptysis (1/2 teaspoon or more of red blood), unstable angina, or receiving

therapeutic anticoagulation. The demographics of the safety population were similar to the demographics of the efficacy population.

Only Grades 3-5 non-hematologic and Grades 4-5 hematologic adverse reactions were collected. Grades 3-5 non-hematologic and Grades 4-5 hematologic adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with paclitaxel and carboplatin compared with patients receiving chemotherapy alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs. 0.7%), infection without neutropenia (7% vs. 3%), venous thromboembolism (5% vs. 3%), febrile neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3% vs. 0%).

Recurrent Glioblastoma

The safety of Avastin was evaluated in a multicenter, randomized, open-label study (EORTC 26101) in patients with recurrent GBM following radiotherapy and temozolomide of whom 278 patients received at least one dose of Avastin and are considered safety evaluable *[see Clinical Studies (14.4)]*. Patients were randomized (2:1) to receive Avastin (10 mg/kg every 2 weeks) with lomustine or lomustine alone until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population. In the Avastin with lomustine arm, 22% of patients discontinued treatment due to adverse reactions compared with 10% of patients in the lomustine arm. In patients receiving Avastin with lomustine, the adverse reaction profile was similar to that observed in other approved indications.

Metastatic Renal Cell Carcinoma

The safety of Avastin was evaluated in 337 patients who received at least one dose of Avastin in a multicenter, double-blind study (BO17705) in patients with mRCC. Patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10 mg/kg every 2 weeks) or placebo with interferon alfa *[see Clinical Studies (14.5)]*. Patients were treated until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-5 adverse reactions occurring at a higher incidence (>2%) were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, hemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma). Adverse reactions are presented in Table 3.

Table 3: Grades 1-5 Adverse Reactions Occurring at Higher Incidence (≥5%) of Patients Receiving Avastin vs. Placebo with Interferon Alfa in Study BO17705

Adverse Reaction[a]	Avastin with Interferon Alfa (N=337)	Placebo with Interferon Alfa (N=304)
Metabolism and nutrition		
Decreased appetite	36%	31%
Weight loss	20%	15%
General		
Fatigue	33%	27%
Vascular		
Hypertension	28%	9%
Respiratory, thoracic and mediastinal		
Epistaxis	27%	4%
Dysphonia	5%	0%
Nervous system		
Headache	24%	16%
Gastrointestinal		
Diarrhea	21%	16%
Renal and urinary		
Proteinuria	20%	3%
Musculoskeletal and connective tissue		
Myalgia	19%	14%
Back pain	12%	6%

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The following adverse reactions were reported at a 5-fold greater incidence in patients receiving Avastin with interferon-alfa compared to patients receiving placebo with interferon-alfa and not represented in Table 3: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs. 0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs. 1); tinnitus (7 vs. 1); tooth abscess (7 vs. 0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

Persistent, Recurrent, or Metastatic Cervical Cancer

The safety of Avastin was evaluated in 218 patients who received at least one dose of Avastin in a multicenter study (GOG-0240) in patients with persistent, recurrent, or metastatic cervical cancer*[see Clinical Studies (14.6)]*. Patients were randomized (1:1:1:1) to receive paclitaxel and cisplatin with or without Avastin (15 mg/kg every 3 weeks), or paclitaxel and topotecan with or without Avastin (15 mg/kg every 3 weeks). The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in 218 patients receiving Avastin with chemotherapy compared to 222 patients receiving chemotherapy alone were abdominal pain (12% vs. 10%), hypertension (11% vs. 0.5%), thrombosis (8% vs. 3%), diarrhea (6% vs. 3%), anal fistula (4% vs. 0%), proctalgia (3% vs. 0%), urinary tract infection (8% vs. 6%), cellulitis (3% vs. 0.5%), fatigue (14% vs. 10%), hypokalemia (7% vs. 4%), hyponatremia (4% vs. 1%), dehydration (4% vs. 0.5%), neutropenia (8% vs. 4%), lymphopenia (6% vs. 3%), back pain (6% vs. 3%), and pelvic pain (6% vs. 1%). Adverse reactions are presented in Table 4.

Table 4: Grades 1-4 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study GOG-0240

Adverse Reaction[a]	Avastin with Chemotherapy (N=218)	Chemotherapy (N=222)
General		
Fatigue	80%	75%
Peripheral edema	15%	22%
Metabolism and nutrition		
Decreased appetite	34%	26%
Hyperglycemia	26%	19%
Hypomagnesemia	24%	15%
Weight loss	21%	7%
Hyponatremia	19%	10%
Hypoalbuminemia	16%	11%
Vascular		
Hypertension	29%	6%
Thrombosis	10%	3%
Infections		
Urinary tract infection	22%	14%
Infection	10%	5%
Nervous system		
Headache	22%	13%
Dysarthria	8%	1%
Psychiatric		
Anxiety	17%	10%
Respiratory, thoracic and mediastinal		
Epistaxis	17%	1%
Renal and urinary		
Increased blood creatinine	16%	10%
Proteinuria	10%	3%
Gastrointestinal		
Stomatitis	15%	10%
Proctalgia	6%	1%
Anal fistula	6%	0%
Reproductive system and breast		
Pelvic pain	14%	8%
Hematology		
Neutropenia	12%	6%
Lymphopenia	12%	5%

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Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Stage III or IV Following Initial Surgical Resection
The safety of Avastin was evaluated in GOG-0218, a multicenter, randomized, double-blind, placebo controlled, three arm study, which evaluated the addition of Avastin to carboplatin and paclitaxel for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer following initial surgical resection *[see Clinical Studies (14.7)]*. Patients were randomized (1:1:1) to carboplatin and paclitaxel without Avastin (CPP), carboplatin and paclitaxel with Avastin for up to six cycles (CPB15), or carboplatin and paclitaxel with Avastin for six cycles followed by Avastin as a single agent for up to 16 additional doses (CPB15+). Avastin was given at 15 mg/kg every three weeks. On this trial, 1215 patients received at least one dose of Avastin. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥2%) in either of the Avastin arms versus the control arm were fatigue (CPB15+ - 9%, CPB15 - 6%, CPP - 6%), hypertension (CPB15+ - 10%, CPB15 - 6%, CPP - 2%), thrombocytopenia (CPB15+ - 21%, CPB15 - 20%, CPP - 15%) and leukopenia (CPB15+ - 51%, CPB15 - 53%, CPP - 50%). Adverse reactions are presented in Table 5.

Table 5: Grades 1-5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in GOG-0218

Adverse Reaction[a]	**Avastin with carboplatin and paclitaxel followed by Avastin alone[*] (N=608)**	**Avastin with carboplatin and paclitaxel[**] (N= 607)**	**Carboplatin and paclitaxel[***] (N= 602)**
General			
Fatigue	80%	72%	73%
Gastrointestinal			
Nausea	58%	53%	51%
Diarrhea	38%	40%	34%
Stomatitis	25%	19%	14%
Musculoskeletal and connective tissue			
Arthralgia	41%	33%	35%
Pain in extremity	25%	19%	17%
Muscular weakness	15%	13%	9%
Nervous system			
Headache	34%	26%	21%
Dysarthria	12%	10%	2%
Vascular			
Hypertension	32%	24%	14%
Respiratory, thoracic and mediastinal			
Epistaxis	31%	30%	9%
Dyspnea	26%	28%	20%
Nasal mucosal disorder	10%	7%	4%

a NCI-CTC version 3, * CPB15+, ** CPB15, ***CPP

Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
The safety of Avastin was evaluated in 179 patients who received at least one dose of Avastin in a multicenter, open-label study (MO22224) in which patients were randomized (1:1) to Avastin with chemotherapy or chemotherapy alone in patients with platinum resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that recurred within < 6 months from the most recent platinum based therapy *[see Clinical*

Studies (14.8)]. Patients were randomized to receive Avastin 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks. Patients had received no more than 2 prior chemotherapy regimens. The trial excluded patients with evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction. Patients were treated until disease progression or unacceptable toxicity. Forty percent of patients on the chemotherapy alone arm received Avastin alone upon progression. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in 179 patients receiving Avastin with chemotherapy compared to 181 patients receiving chemotherapy alone were hypertension (6.7% vs. 1.1%) and palmar-plantar erythrodysaesthesia syndrome (4.5% vs. 1.7%).
Adverse reactions are presented in Table 6.

Table 6: Grades 2−4 Adverse Reactions Occurring at Higher Incidence (≥5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study MO22224

Adverse Reaction[a]	Avastin with Chemotherapy (N=179)	Chemotherapy (N=181)
Hematology		
Neutropenia	31%	25%
Vascular		
Hypertension	19%	6%
Nervous system		
Peripheral sensory neuropathy	18%	7%
General		
Mucosal inflammation	13%	6%
Renal and urinary		
Proteinuria	12%	0.6%
Skin and subcutaneous tissue		
Palmar-plantar erythrodysaesthesia	11%	5%
Infections		
Infection	11%	4%
Respiratory, thoracic and mediastinal		
Epistaxis	5%	0%

a NCI-CTC version 3

Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study AVF4095g
The safety of Avastin was evaluated in 247 patients who received at least one dose of Avastin in a double-blind study (AVF4095g) in patients with platinum sensitive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer *[see Clinical Studies (14.9]*. Patients were randomized (1:1) to receive Avastin (15 mg/kg) or placebo every 3 weeks with carboplatin and gemcitabine for 6 to 10 cycles followed by Avastin or placebo alone until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with chemotherapy compared to placebo with chemotherapy were: thrombocytopenia (40% vs. 34%), nausea (4% vs. 1.3%), fatigue (6% vs. 4%), headache (4% vs. 0.9%), proteinuria (10% vs. 0.4%), dyspnea (4% vs. 1.7%), epistaxis (5% vs. 0.4%), and hypertension (17% vs. 0.9%). Adverse reactions are presented in Table 7.

Table 7: Grades 1−5 Adverse Reactions Occurring at a Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Placebo with Chemotherapy in Study AVF4095g

Adverse Reaction[a]	Avastin with Carboplatin and Gemcitabine (N=247)	Placebo with Carboplatin and Gemcitabine (N=233)
General		
Fatigue	82%	75%
Mucosal inflammation	15%	10%
Gastrointestinal		
Nausea	72%	66%
Diarrhea	38%	29%
Stomatitis	15%	7%
Hemorrhoids	8%	3%
Gingival bleeding	7%	0%
Hematology		
Thrombocytopenia	58%	51%
Respiratory, thoracic and mediastinal		
Epistaxis	55%	14%
Dyspnea	30%	24%
Cough	26%	18%
Oropharyngeal pain	16%	10%
Dysphonia	13%	3%
Rhinorrhea	10%	4%
Sinus congestion	8%	2%
Nervous system		
Headache	49%	30%
Dizziness	23%	17%
Vascular		
Hypertension	42%	9%
Musculoskeletal and connective tissue		
Arthralgia	28%	19%
Back pain	21%	13%
Psychiatric		
Insomnia	21%	15%
Renal and urinary		
Proteinuria	20%	3%
Injury and procedural		
Contusion	17%	9%
Infections		
Sinusitis	15%	9%

a NCI-CTC version 3

Study GOG-0213

The safety of Avastin was evaluated in an open-label, controlled study (GOG-0213) in 325 patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have not received more than one previous regimen of chemotherapy*[see Clinical Studies (14.9)]*. Patients were randomized (1:1) to receive carboplatin and paclitaxel for 6 to 8 cycles or Avastin (15 mg/kg every 3 weeks) with carboplatin and paclitaxel for 6 to 8 cycles followed by Avastin as a single agent until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with chemotherapy compared to chemotherapy alone were: hypertension (11% vs. 0.6%), fatigue (8% vs. 3%), febrile neutropenia (6% vs. 3%), proteinuria (8% vs. 0%), abdominal pain (6% vs. 0.9%), hyponatremia (4% vs. 0.9%), headache (3% vs. 0.9%), and pain in extremity (3% vs. 0%).
Adverse reactions are presented in Table 8.

Table 8: Grades 1−5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study GOG-0213

Adverse Reaction[a]	Avastin with Carboplatin and Paclitaxel (N=325)	Carboplatin and Paclitaxel (N=332)
Musculoskeletal and connective tissue		
Arthralgia	45%	30%
Myalgia	29%	18%
Pain in extremity	25%	14%
Back pain	17%	10%
Muscular weakness	13%	8%
Neck pain	9%	0%
Vascular		
Hypertension	42%	3%
Gastrointestinal		
Diarrhea	39%	32%
Abdominal pain	33%	28%
Vomiting	33%	25%
Stomatitis	33%	16%
Nervous system		
Headache	38%	20%
Dysarthria	14%	2%
Dizziness	13%	8%
Metabolism and nutrition		
Decreased appetite	35%	25%
Hyperglycemia	31%	24%
Hypomagnesemia	27%	17%
Hyponatremia	17%	6%
Weight loss	15%	4%
Hypocalcemia	12%	5%
Hypoalbuminemia	11%	6%
Hyperkalemia	9%	3%
Respiratory, thoracic and mediastinal		
Epistaxis	33%	2%
Dyspnea	30%	25%
Cough	30%	17%
Rhinitis allergic	17%	4%
Nasal mucosal disorder	14%	3%
Skin and subcutaneous tissue		
Exfoliative rash	23%	16%
Nail disorder	10%	2%
Dry skin	7%	2%
Renal and urinary		
Proteinuria	17%	1%
Increased blood creatinine	13%	5%
Hepatic		

Adverse Reaction[a]	Avastin with Carboplatin and Paclitaxel (N=325)	Carboplatin and Paclitaxel (N=332)
Increased aspartate aminotransferase	15%	9%
General		
Chest pain	8%	2%
Infections		
Sinusitis	7%	2%

a NCI-CTC version 3

Hepatocellular Carcinoma (HCC)

The safety of Avastin in combination with atezolizumab 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 (14.10)]*. Patients received 1,200 mg of atezolizumab intravenously followed by 15 mg/kg Avastin (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 Avastin was 6.9 months (range: 0-16 months) and to atezolizumab was 7.4 months (range: 0-16 months).

Fatal adverse reactions occurred in 4.6% of patients in the Avastin and atezolizumab 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 Avastin and atezolizumab arm. The most frequent serious adverse reactions (≥ 2%) were gastrointestinal hemorrhage (7%), infections (6%), and pyrexia (2.1%).

Adverse reactions leading to discontinuation of Avastin occurred in 15% of patients in the Avastin and atezolizumab arm. The most common adverse reactions leading to Avastin discontinuation were hemorrhages (4.9%), including bleeding varicose vein, hemorrhage and gastrointestinal, subarachnoid, and pulmonary hemorrhages; and increased transaminases or bilirubin (0.9%).

Adverse reactions leading to interruption of Avastin occurred in 46% of patients in the Avastin and atezolizumab arm; the most common (≥ 2%) were proteinuria (6%); infections (6%); hypertension (6%); liver function laboratory abnormalities including increased transaminases, bilirubin, or alkaline phosphatate (4.6%); gastrointestinal hemorrhages (3%); thrombocytopenia/decreased platelet count (4.3%); and pyrexia (2.4%).

Tables 9 and 10 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received Avastin and atezolizumab in IMbrave150.

Table 9: Adverse Reactions Occurring in ≥10% of Patients with HCC Receiving Avastin in IMbrave150

Adverse Reaction	Avastin in combination with atezolizumab (n = 329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
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 10: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with HCC Receiving Avastin in IMbrave150

Laboratory Abnormality	Avastin in combination with atezolizumab (n=329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
Chemistry				
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: Avastin plus atezolizumab (222-323) and sorafenib (90-153) NA = Not applicable.
[1] Graded per NCI CTCAE v4.0

6.2 Immunogenicity

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

In clinical studies for adjuvant treatment of a solid tumor, 0.6% (14/2233) of patients tested positive for treatment-emergent anti-bevacizumab antibodies as detected by an electrochemiluminescent (ECL) based assay. Among these 14 patients, three tested positive for neutralizing antibodies against bevacizumab using an enzyme-linked immunosorbent assay (ELISA). The clinical significance of these anti-bevacizumab antibodies is not known.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Avastin. 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.

General: Polyserositis
Cardiovascular: Pulmonary hypertension, Mesenteric venous occlusion
Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration
Hemic and lymphatic: Pancytopenia
Hepatobiliary disorders: Gallbladder perforation
Musculoskeletal and Connective Tissue Disorders: Osteonecrosis of the jaw
Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)
Respiratory: Nasal septum perforation

7 DRUG INTERACTIONS

Effects of Avastin on Other Drugs

No clinically meaningful effect on the pharmacokinetics of irinotecan or its active metabolite SN38, interferon alfa, carboplatin or paclitaxel was observed when Avastin was administered in combination with these drugs; however, 3 of the 8 patients receiving Avastin with paclitaxel and carboplatin had lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel and carboplatin alone had a greater paclitaxel exposure at Day 63 than at Day 0.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, Avastin may cause fetal harm in pregnant women. Limited postmarketing reports describe cases of fetal malformations with use of Avastin in pregnancy; however, these reports are insufficient to determine drug-associated risks. In animal reproduction studies, intravenous administration of bevacizumab to pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects *(see Data)*. Furthermore, animal models link angiogenesis and VEGF and VEGFR2 to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women 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

Pregnant rabbits dosed with 10 mg/kg to 100 mg/kg bevacizumab (approximately 1 to 10 times the clinical dose of 10 mg/kg) every three days during the period of organogenesis (gestation day 6–18) exhibited decreases in maternal and fetal body weights and increased number of fetal resorptions. There were dose-related increases in the number of litters containing fetuses with any type of malformation (42% for the 0 mg/kg dose, 76% for the 30 mg/kg dose, and 95% for the 100 mg/kg dose) or fetal alterations (9% for the 0 mg/kg dose, 15% for the 30 mg/kg dose, and 61% for the 100 mg/kg dose). Skeletal deformities were observed at all dose levels, with some abnormalities including meningocele observed only at the 100 mg/kg dose level. Teratogenic effects included:

reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb phalanges.

8.2 Lactation

Risk Summary

No data are available regarding the presence of bevacizumab in human milk, the effects on the breast fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with Avastin and for 6 months after the last dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Avastin may 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 Avastin and for 6 months after the last dose.

Infertility

Females

Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to the first-dose of Avastin. Long-term effects of Avastin on fertility are not known.

In a clinical study of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in patients who received Avastin with chemotherapy (34%) compared to patients who received chemotherapy alone (2%). After discontinuing Avastin with chemotherapy, recovery of ovarian function occurred in 22% of these patients *[see Warnings and Precautions (5.11), Adverse Reactions (6.1)]*.

8.4 Pediatric Use

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

In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years who have received Avastin. Avastin is not approved for use in patients under the age of 18 years.

Antitumor activity was not observed among eight pediatric patients with relapsed GBM who received bevacizumab and irinotecan. Addition of Avastin to standard of care did not result in improved event-free survival in pediatric patients enrolled in two randomized clinical studies, one in high grade glioma (n= 121) and one in metastatic rhabdomyosarcoma or non-rhabdomyosarcoma soft tissue sarcoma (n= 154).

Based on the population pharmacokinetics analysis of data from 152 pediatric and young adult patients with cancer (7 months to 21 years of age), bevacizumab clearance normalized by body weight in pediatrics was comparable to that in adults.

Juvenile Animal Toxicity Data
Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

8.5 Geriatric Use
In an exploratory pooled analysis of 1745 patients from five randomized, controlled studies, 35% of patients were ≥ 65 years old. The overall incidence of ATE was increased in all patients receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone, regardless of age; however, the increase in the incidence of ATE was greater in patients ≥ 65 years (8% vs. 3%) as compared to patients < 65 years (2% vs. 1%) *[see Warnings and Precautions (5.4)]*.

11 DESCRIPTION
Bevacizumab is a vascular endothelial growth factor inhibitor. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that contains human framework regions and murine complementarity-determining regions. Bevacizumab has an approximate molecular weight of 149 kDa. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system.

Avastin (bevacizumab) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale brown solution in a single-dose vial for intravenous use. Avastin contains bevacizumab at a concentration of 25 mg/mL in either a 100 mg/4 mL or 400 mg/16 mL single-dose vial.

Each mL of solution contains 25 mg bevacizumab, α,α-trehalose dihydrate (60 mg), polysorbate 20 (0.4 mg), sodium phosphate dibasic, anhydrous (1.2 mg), sodium phosphate monobasic, monohydrate (5.8 mg), and Water for Injection, USP. The pH is 6.2.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

12.3 Pharmacokinetics
The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of Avastin every week, every 2 weeks, or every 3 weeks, bevacizumab pharmacokinetics are linear and the predicted time to reach more than 90% of steady state concentration is 84 days. The accumulation ratio following a dose of 10 mg/kg once every 2 weeks is 2.8.

Population simulations of bevacizumab exposures provide a median trough concentration of 80.3 mcg/mL on Day 84 (10^{th}, 90^{th} percentile: 45, 128) following a dose of 5 mg/kg once every two weeks.

Distribution
The mean (% coefficient of variation [CV%]) central volume of distribution is 2.9 (22%) L.

Elimination
The mean (CV%) clearance is 0.23 (33) L/day. The estimated half-life is 20 days (11 to 50 days).

Specific Populations

The clearance of bevacizumab varied by body weight, sex, and tumor burden. After correcting for body weight, males had a higher bevacizumab clearance (0.26 L/day vs. 0.21 L/day) and a larger central volume of distribution (3.2 L vs. 2.7 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher bevacizumab clearance (0.25 L/day vs. 0.20 L/day) than patients with tumor burdens below the median. In Study AVF2107g, there was no evidence of lesser efficacy (hazard ratio for overall survival) in males or patients with higher tumor burden treated with Avastin as compared to females and patients with low tumor burden.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to assess potential of bevacizumab for carcinogenicity or mutagenicity.

Bevacizumab may impair fertility. Female cynomolgus monkeys treated with 0.4 to 20 times the recommended human dose of bevacizumab exhibited arrested follicular development or absent corpora lutea, as well as dose-related decreases in ovarian and uterine weights, endometrial proliferation, and the number of menstrual cycles. Following a 4- or 12-week recovery period, there was a trend suggestive of reversibility. After the 12-week recovery period, follicular maturation arrest was no longer observed, but ovarian weights were still moderately decreased. Reduced endometrial proliferation was no longer observed at the 12-week recovery time point; however, decreased uterine weight, absent corpora lutea, and reduced number of menstrual cycles remained evident.

13.2 Animal Toxicology and/or Pharmacology

Rabbits dosed with bevacizumab exhibited reduced wound healing capacity. Using full-thickness skin incision and partial thickness circular dermal wound models, bevacizumab dosing resulted in reductions in wound tensile strength, decreased granulation and re-epithelialization, and delayed time to wound closure.

14 CLINICAL STUDIES

14.1 Metastatic Colorectal Cancer

Study AVF2107g

The safety and efficacy of Avastin was evaluated in a double-blind, active-controlled study [AVF2107g (NCT00109070)] in 923 patients with previously untreated mCRC who were randomized (1:1:1) to placebo with bolus-IFL (irinotecan 125 mg/m^2, fluorouracil 500 mg/m^2, and leucovorin 20 mg/m^2 given once weekly for 4 weeks every 6 weeks), Avastin (5 mg/kg every 2 weeks) with bolus-IFL, or Avastin (5 mg/kg every 2 weeks) with fluorouracil and leucovorin. Enrollment to the Avastin with fluorouracil and leucovorin arm was discontinued after enrollment of 110 patients in accordance with the protocol-specified adaptive design. Avastin was continued until disease progression or unacceptable toxicity or for a maximum of 96 weeks. The main outcome measure was overall survival (OS).

The median age was 60 years; 60% were male, 79% were White, 57% had an ECOG performance status of 0, 21% had a rectal primary and 28% received prior adjuvant chemotherapy. The dominant site of disease was extra-abdominal in 56% of patients and was the liver in 38% of patients.

The addition of Avastin improved survival across subgroups defined by age (<65 years, ≥ 65 years) and sex. Results are presented in Table 11 and Figure 1.

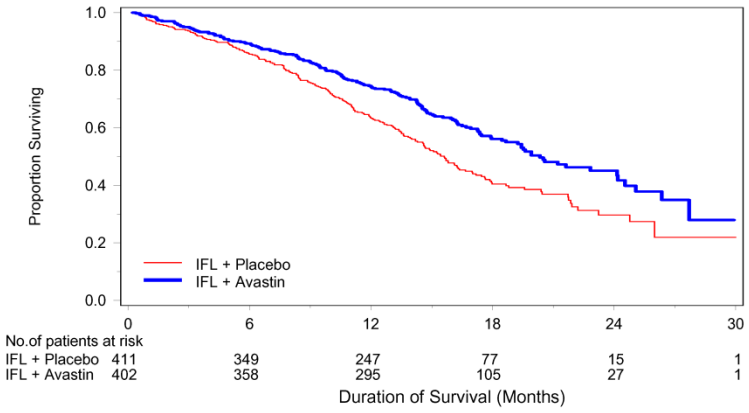
Table 11: Efficacy Results in Study AVF2107g

Efficacy Parameter	Avastin with bolus-IFL (N=402)	Placebo with bolus-IFL (N=411)
Overall Survival		
Median, in months	20.3	15.6
Hazard ratio (95% CI)	0.66 (0.54, 0.81)	
p-value[a]	< 0.001	
Progression-Free Survival		
Median, in months	10.6	6.2
Hazard ratio (95% CI)	0.54 (0.45, 0.66)	
p-value[a]	< 0.001	
Overall Response Rate		
Rate (%)	45%	35%
p-value[b]	< 0.01	
Duration of Response		
Median, in months	10.4	7.1

[a] by stratified log-rank test.

[b] by χ^2 test

Figure 1: Kaplan-Meier Curves for Duration of Survival in Metastatic Colorectal Cancer in Study AVF2107g



Among the 110 patients randomized to Avastin with fluorouracil and leucovorin, median OS was 18.3 months, median progression-free survival (PFS) was 8.8 months, overall response rate (ORR) was 39%, and median duration of response was 8.5 months.

Study E3200

The safety and efficacy of Avastin were evaluated in a randomized, open-label, active-controlled study [E3200 (NCT00025337)] in 829 patients who were previously treated with irinotecan and fluorouracil for initial therapy for metastatic disease or as adjuvant therapy. Patients were randomized (1:1:1) to FOLFOX4 (Day 1: oxaliplatin 85 mg/m^2 and leucovorin 200 mg/m^2 concurrently, then fluorouracil 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; Day 2: leucovorin 200 mg/m^2, then fluorouracil 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; every 2 weeks), Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1) with FOLFOX4, or Avastin alone (10 mg/kg every 2 weeks). Avastin was continued until disease progression or unacceptable toxicity. The main outcome measure was OS.

The Avastin alone arm was closed to accrual after enrollment of 244 of the planned 290 patients following a planned interim analysis by the data monitoring committee based on evidence of decreased survival compared to FOLFOX4 alone.

The median age was 61 years; 60% were male, 87% were White, 49% had an ECOG performance status of 0, 26% received prior radiation therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan with or without fluorouracil for metastatic disease, and 1% received prior irinotecan and fluorouracil as adjuvant therapy.

The addition of Avastin to FOLFOX4 resulted in significantly longer survival as compared to FOLFOX4 alone; median OS was 13.0 months vs. 10.8 months [hazard ratio (HR) 0.75 (95% CI: 0.63, 0.89), p-value of 0.001 stratified log-rank test] with clinical benefit seen in subgroups defined by age (<65 years, ≥ 65 years) and sex. PFS and ORR based on investigator assessment were higher in patients receiving Avastin with FOLFOX4.

Study TRC-0301

The activity of Avastin with fluorouracil (as bolus or infusion) and leucovorin was evaluated in a single arm study [TRC-0301 (NCT00066846)] enrolling 339 patients with mCRC with disease progression following both irinotecan- and oxaliplatin-based chemotherapy. Seventy-three percent of patients received concurrent bolus fluorouracil and leucovorin. One objective partial response was verified in the first 100 evaluable patients for an ORR of 1% (95% CI: 0%, 5.5%).

Study ML18147

The safety and efficacy of Avastin were evaluated in a prospective, randomized, open-label, multinational, controlled study [ML18147 (NCT00700102)] in 820 patients with histologically confirmed mCRC who had progressed on a first-line Avastin containing regimen. Patients were excluded if they progressed within 3 months of initiating first-line chemotherapy and if they received Avastin for less than 3 consecutive months in the first-line setting. Patients were randomized (1:1) within 3 months after discontinuing Avastin as first-line treatment to receive fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy with or without Avastin (5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks). The choice of second-line treatment was contingent upon first-line chemotherapy. Second-line treatment was administered until progressive disease or unacceptable toxicity. The main outcome measure was OS. A secondary outcome measure was ORR.

The median age was 63 years (21 to 84 years); 64% were male, 52% had an ECOG performance status of 1, 44% had an ECOG performance status of 0, 58% received irinotecan-based therapy as first-line treatment, 55% progressed on first-line treatment within 9 months, and 77% received their last dose of Avastin as first-line treatment within 42 days of being randomized. Second-line chemotherapy regimens were generally balanced between each arm.

The addition of Avastin to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of OS and PFS. There was no significant difference in ORR. Results are presented in Table 12 and Figure 2.

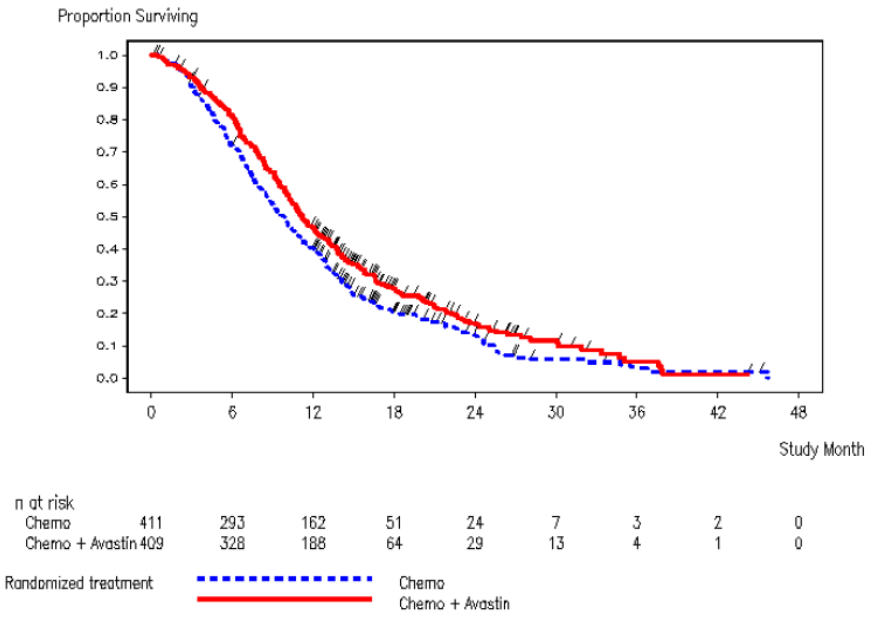
Table 12: Efficacy Results in Study ML18147

Efficacy Parameter	Avastin with Chemotherapy (N=409)	Chemotherapy (N=411)
Overall Survival[a]		
Median, in months	11.2	9.8
Hazard ratio (95% CI)	0.81 (0.69, 0.94)	
Progression-Free Survival[b]		
Median, in months	5.7	4.0
Hazard ratio (95% CI)	0.68 (0.59, 0.78)	

[a] p=0.0057 by unstratified log-rank test.

[b] p-value < 0.0001 by unstratified log-rank test.

Figure 2: Kaplan-Meier Curves for Duration of Survival in Metastatic Colorectal Cancer in Study ML18147



14.2 Lack of Efficacy in Adjuvant Treatment of Colon Cancer

Lack of efficacy of Avastin as an adjunct to standard chemotherapy for the adjuvant treatment of colon cancer was determined in two randomized, open-label, multicenter clinical studies.

The first study [BO17920 (NCT00112918)] was conducted in 3451 patients with high-risk stage II and III colon cancer, who had undergone surgery for colon cancer with curative intent. Patients were randomized to receive Avastin at a dose equivalent to 2.5 mg/kg/week on either a 2-weekly schedule with FOLFOX4 (N=1155) or on a 3-weekly schedule with XELOX (N=1145) or FOLFOX4 alone (N=1151). The main outcome measure was disease free survival (DFS) in patients with stage III colon cancer.

The median age was 58 years; 54% were male, 84% were White and 29% were ≥ 65 years. Eighty-three percent had stage III disease.

The addition of Avastin to chemotherapy did not improve DFS. As compared to FOLFOX4 alone, the proportion of stage III patients with disease recurrence or with death due to disease progression were numerically higher for patients receiving Avastin with FOLFOX4 or with XELOX. The hazard ratios for DFS were 1.17 (95% CI: 0.98,1.39) for Avastin with FOLFOX4 versus FOLFOX4 alone and 1.07 (95% CI: 0.90, 1.28) for Avastin with XELOX versus FOLFOX4 alone. The hazard ratios for OS were 1.31 (95% CI: 1.03, 1.67) and 1.27 (95% CI: 1, 1.62) for the comparison of Avastin with FOLFOX4 versus FOLFOX4 alone and Avastin with XELOX versus FOLFOX4 alone, respectively. Similar lack of efficacy for DFS was observed in the Avastin-containing arms compared to FOLFOX4 alone in the high-risk stage II cohort.

In a second study [NSABP-C-08 (NCT00096278)], patients with stage II and III colon cancer who had undergone surgery with curative intent, were randomized to receive either Avastin administered at a dose equivalent to 2.5 mg/kg/week with mFOLFOX6 (N=1354) or mFOLFOX6 alone (N=1356). The median age was 57 years, 50% were male and 87% White. Seventy-five percent had stage III disease. The main outcome was DFS among stage III patients. The HR for DFS was 0.92 (95% CI: 0.77, 1.10). OS was not significantly improved with the addition of Avastin to mFOLFOX6 [HR 0.96 (95% CI: 0.75,1.22)].

14.3 First-Line Non–Squamous Non–Small Cell Lung Cancer

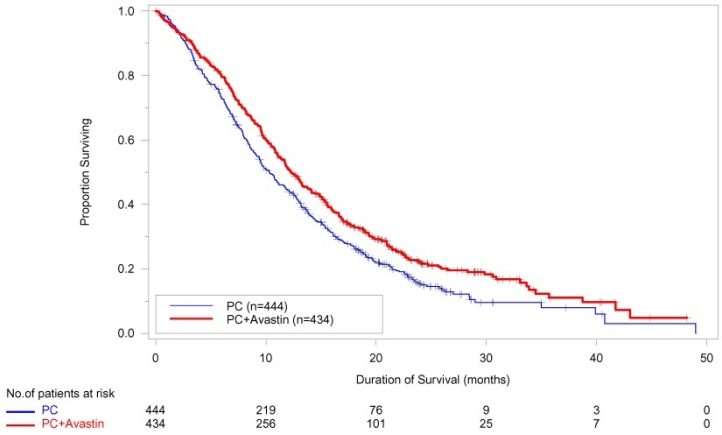
Study E4599

The safety and efficacy of Avastin as first-line treatment of patients with locally advanced, metastatic, or recurrent non–squamous NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study [E4599 (NCT00021060)]. A total of 878 chemotherapy-naïve patients with locally advanced, metastatic or recurrent non–squamous NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel (200 mg/m^2) and carboplatin (AUC 6) with or without Avastin 15 mg/kg. After completing or discontinuing chemotherapy, patients randomized to receive Avastin continued to receive Avastin alone until disease progression or until unacceptable toxicity. The trial excluded patients with predominant squamous histology (mixed cell type tumors only), CNS metastasis, gross hemoptysis (1/2 teaspoon or more of red blood), unstable angina, or receiving therapeutic anticoagulation. The main outcome measure was duration of survival.

The median age was 63 years; 54% were male, 43% were ≥ 65 years, and 28% had ≥ 5% weight loss at study entry. Eleven percent had recurrent disease. Of the 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease.

OS was statistically significantly longer for patients receiving Avastin with paclitaxel and carboplatin compared with those receiving chemotherapy alone. Median OS was 12.3 months vs. 10.3 months [HR 0.80 (95% CI: 0.68, 0.94), final p-value of 0.013, stratified log-rank test]. Based on investigator assessment which was not independently verified, patients were reported to have longer PFS with Avastin with paclitaxel and carboplatin compared to chemotherapy alone. Results are presented in Figure 3.

Figure 3: Kaplan-Meier Curves for Duration of Survival in First-Line Non-Squamous Non-Small Cell Lung Cancer in Study E4599



In an exploratory analysis across patient subgroups, the impact of Avastin on OS was less robust in the following subgroups: women [HR 0.99 (95% CI: 0.79, 1.25)], patients ≥ 65 years [HR 0.91 (95% CI: 0.72, 1.14)] and patients with ≥ 5% weight loss at study entry [HR 0.96 (95% CI: 0.73, 1.26)].

Study BO17704

The safety and efficacy of Avastin in patients with locally advanced, metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy was studied in another randomized, double-blind, placebo-controlled study [BO17704 (NCT00806923)]. A total of 1043 patients were randomized (1:1:1) to receive cisplatin and gemcitabine with placebo, Avastin 7.5 mg/kg or Avastin 15 mg/kg. The main outcome measure was PFS. Secondary outcome measure was OS.

The median age was 58 years; 36% were female and 29% were ≥ 65 years. Eight percent had recurrent disease and 77% had Stage IV disease.

PFS was significantly higher in both Avastin-containing arms compared to the placebo arm [HR 0.75 (95% CI: 0.62, 0.91), p-value of 0.0026 for Avastin 7.5 mg/kg and HR 0.82 (95% CI: 0.68; 0.98), p-value of 0.0301 for Avastin 15 mg/kg]. The addition of Avastin to cisplatin and gemcitabine failed to demonstrate an improvement in the duration of OS [HR 0.93 (95% CI: 0.78; 1.11), p-value of 0.420 for Avastin 7.5 mg/kg and HR 1.03 (95% CI: 0.86, 1.23), p-value of 0.761 for Avastin 15 mg/kg].

14.4 Recurrent Glioblastoma

Study EORTC 26101

The safety and efficacy of Avastin were evaluated in a multicenter, randomized (2:1), open-label study in patients with recurrent GBM (EORTC 26101, NCT01290939). Patients with first progression following radiotherapy and temozolomide were randomized (2:1) to receive Avastin (10 mg/kg every 2 weeks) with lomustine (90 mg/m^2 every 6 weeks) or lomustine (110 mg/m^2 every 6 weeks) alone until disease progression or unacceptable toxicity. Randomization was stratified by World Health Organization performance status (0 vs. >0), steroid use (yes vs. no), largest tumor diameter (≤ 40 vs. > 40 mm), and institution. The main outcome measure was OS. Secondary outcome measures were investigator-assessed PFS and ORR per the modified Response Assessment in Neuro-oncology (RANO) criteria, health related quality of life (HRQoL), cognitive function, and corticosteroid use.

A total of 432 patients were randomized to receive lomustine alone (N=149) or Avastin with lomustine (N=283). The median age was 57 years; 24.8% of patients were ≥ 65 years. The majority of patients with were male (61%); 66% had a WHO performance status score > 0; and in 56% the largest tumor diameter was ≤ 40 mm. Approximately 33% of patients randomized to receive lomustine received Avastin following documented progression.

No difference in OS (HR 0.91, p-value of 0.4578) was observed between arms; therefore, all secondary outcome measures are descriptive only. PFS was longer in the Avastin with lomustine arm [HR 0.52 (95% CI: 0.41, 0.64)] with a median PFS of 4.2 months in the Avastin with lomustine arm and 1.5 months in the lomustine arm. Among the 50% of patients receiving corticosteroids at the time of randomization, a higher percentage of patients in the Avastin with lomustine arm discontinued corticosteroids (23% vs. 12%).

Study AVF3708g and Study NCI 06-C-0064E

The efficacy and safety of Avastin 10 mg/kg every 2 weeks in patients with previously treated GBM were evaluated in one single arm single center study (NCI 06-C-0064E) and a randomized noncomparative multicenter study [AVF3708g (NCT00345163)]. Response rates in both studies were evaluated based on modified WHO criteria that considered corticosteroid use. In AVF3708g, the response rate was 25.9% (95% CI: 17%, 36.1%) with a median duration of response of 4.2 months (95% CI: 3, 5.7). In Study NCI 06-C-0064E, the response rate was 19.6% (95% CI: 10.9%, 31.3%) with a median duration of response of 3.9 months (95% CI: 2.4, 17.4).

14.5 Metastatic Renal Cell Carcinoma

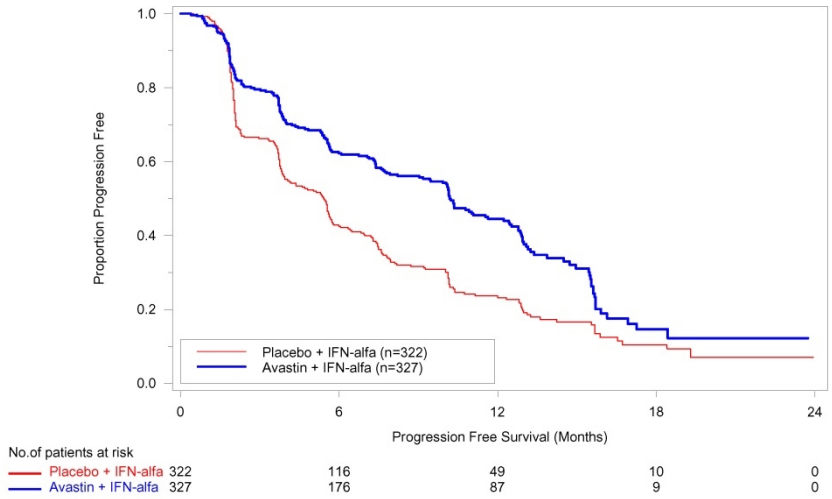
Study BO17705

The safety and efficacy of Avastin were evaluated in patients with treatment-naïve mRCC in a multicenter, randomized, double-blind, international study [BO17705 (NCT00738530)] comparing interferon alfa and Avastin versus interferon alfa and placebo. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10 mg/kg every 2 weeks; N = 327) or placebo (every 2 weeks; N = 322) with interferon alfa (9 MIU subcutaneously three times weekly for a maximum of 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main outcome measure was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 60 years (18 to 82 years); 70% were male and 96% were White. The study population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate (1-2), 8% poor (3–5), and 7% missing.

PFS was statistically significantly prolonged among patients receiving Avastin compared to placebo; median PFS was 10.2 months vs. 5.4 months [HR 0.60 (95% CI: 0.49, 0.72), p-value < 0.0001, stratified log-rank test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs. 12%, p-value < 0.0001, stratified CMH test). There was no improvement in OS based on the final analysis conducted after 444 deaths, with a median OS of 23 months in the patients receiving Avastin with interferon alfa and 21 months in patients receiving interferon alone [HR 0.86, (95% CI: 0.72, 1.04)]. Results are presented in Figure 4.

Figure 4: Kaplan-Meier Curves for Progression-Free Survival in Metastatic Renal Cell Carcinoma in Study BO17705



14.6 Persistent, Recurrent, or Metastatic Cervical Cancer

Study GOG-0240

The safety and efficacy of Avastin were evaluated in patients with persistent, recurrent, or metastatic cervical cancer in a randomized, four-arm, multicenter study comparing Avastin with chemotherapy versus chemotherapy alone [GOG-0240 (NCT00803062)]. A total of 452 patients were randomized (1:1:1:1) to receive paclitaxel and cisplatin with or without Avastin, or paclitaxel and topotecan with or without Avastin.

The dosing regimens for Avastin, paclitaxel, cisplatin and topotecan were as follows:

- Day 1: Paclitaxel 135 mg/m^2 over 24 hours, Day 2: cisplatin 50 mg/m^2 with Avastin;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours, Day 2: cisplatin 50 mg/m^2 with Avastin;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours with cisplatin 50 mg/m^2 with Avastin;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours with Avastin, Days 1-3: topotecan IV 0.75 mg/m^2 over 30 minutes

Patients were treated until disease progression or unacceptable adverse reactions. The main outcome measure was OS. Secondary outcome measures included ORR.

The median age was 48 years (20 to 85 years). Of the 452 patients randomized at baseline, 78% of patients were White, 80% had received prior radiation, 74% had received prior chemotherapy concurrent with radiation, and 32% had a platinum-free interval of less than 6 months. Patients had a GOG performance status of 0 (58%) or 1 (42%). Demographic and disease characteristics were balanced across arms.

Results are presented in Figure 5 and Table 13.

Figure 5: Kaplan-Meier Curves for Overall Survival in Persistent, Recurrent, or Metastatic Cervical Cancer in Study GOG-0240

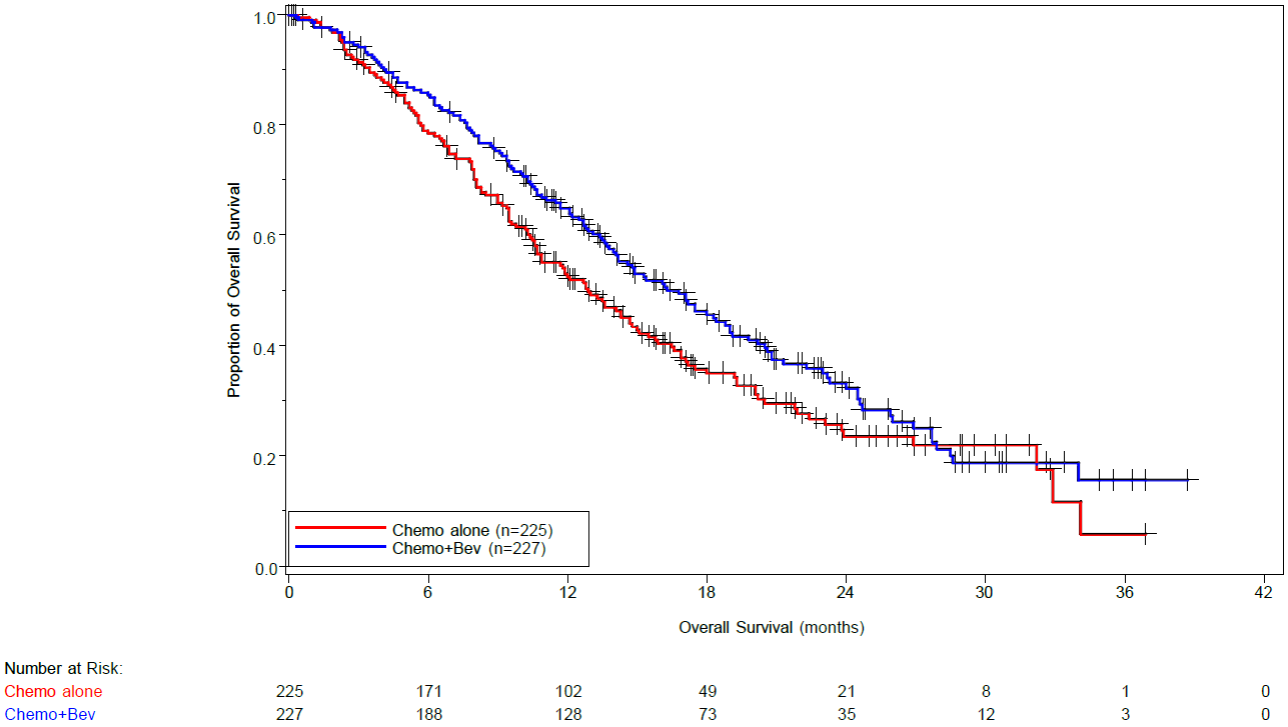


Table 13: Efficacy Results in Study GOG-0240

Efficacy Parameter	Avastin with Chemotherapy (N=227)	Chemotherapy (N=225)
Overall Survival		
Median, in months[a]	16.8	12.9
Hazard ratio (95% CI)	0.74 (0.58, 0.94)	
p-value[b]	0.0132	

[a] Kaplan-Meier estimates.
[b] log-rank test (stratified).

The ORR was higher in patients who received Avastin with chemotherapy [45% (95% CI: 39, 52)] compared to patients who received chemotherapy alone [34% (95% CI: 28,40)].

Table 14: Efficacy Results in Study GOG-0240

Efficacy Parameter	Topotecan and Paclitaxel with or without Avastin (N=223)	Cisplatin and Paclitaxel with or without Avastin (N=229)
Overall Survival		
Median, in months[a]	13.3	15.5
Hazard ratio (95% CI)	1.15 (0.91, 1.46)	
p-value	0.23	

[a] Kaplan-Meier estimates.

The HR for OS with Avastin with cisplatin and paclitaxel as compared to cisplatin and paclitaxel alone was 0.72 (95% CI: 0.51,1.02). The HR for OS with Avastin with topotecan and paclitaxel as compared to topotecan and paclitaxel alone was 0.76 (95% CI: 0.55, 1.06).

14.7 Stage III or IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Following Initial Surgical Resection

Study GOG-0218

The safety and efficacy of Avastin were evaluated in a multicenter, randomized, double-blind, placebo controlled, three arm study [Study GOG-0218 (NCT00262847)] evaluating the effect of adding Avastin to carboplatin and paclitaxel for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer (N=1873) following initial surgical resection. Patients were randomized (1:1:1) to one of the following arms:

- CPP: carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for six cycles, with concurrent placebo started at cycle 2, followed by placebo alone every three weeks for a total of up to 22 cycles of therapy (n=625) or
- CPB15: carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for six cycles, with concurrent Avastin started at cycle 2, followed by placebo alone every three weeks for a total of up to 22 cycles of therapy (n=625) or
- CPB15+: carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for six cycles, with concurrent Avastin started at cycle 2, followed by Avastin as a single agent every three weeks for a total of up to 22 cycles of therapy (n=623).

The main outcome measure was investigator-assessed PFS. OS was a secondary outcome measure.

The median age was 60 years (range 22-89 years) and 28% of patients were >65 years of age.
Overall, approximately 50% of patients had a GOG PS of 0 at baseline, and 43% a GOG PS score of 1. Patients had either epithelial ovarian cancer (83%), primary peritoneal cancer (15%), or fallopian tube cancer (2%). Serous adenocarcinoma was the most common histologic type (85% in CPP and CPB15 arms, 86% in CPB15+ arm). Overall, approximately 34% of patients had resected FIGO Stage III with residual disease < 1 cm, 40% had resected Stage III with residual disease >1 cm, and 26% had resected Stage IV disease.

The majority of patients in all three treatment arms received subsequent antineoplastic treatment, 78.1% in the CPP arm, 78.6% in the CPB15 arm, and 73.2% in the CPB15+ arm. A higher proportion of patients in the CPP arm (25.3%) and CPB15 arm (26.6%) received at least one anti-angiogenic (including bevacizumab) treatment after discontinuing from study compared with the CPB15+ arm (15.6%).

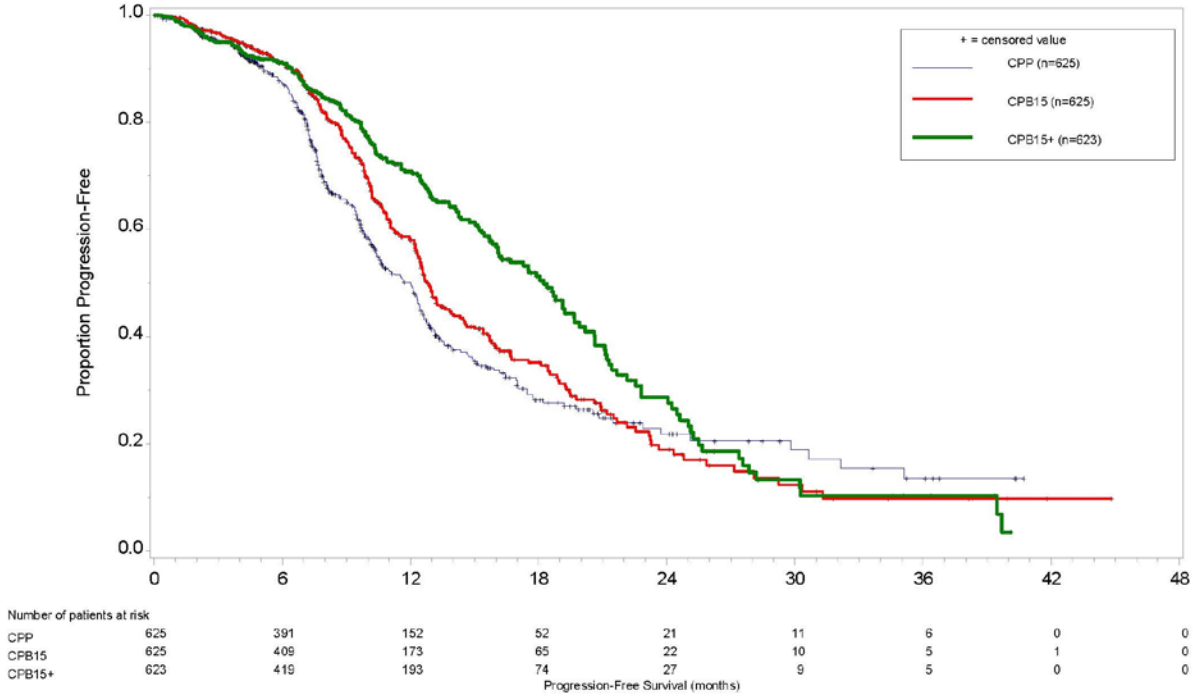
Study results are presented in Table 15 and Figure 6.

Table 15: Efficacy Results in Study GOG-0218

Efficacy Parameter	**Avastin with carboplatin and paclitaxel followed by Avastin alone (N=623)**	**Avastin with carboplatin and paclitaxel (N=625)**	**Carboplatin and paclitaxel (N= 625)**
Progression-Free Survival per Investigator			
Median, in months	18.2	12.8	12.0
Hazard ratio (95% CI)[a]	0.62 (0.52, 0.75)	0.83 (0.70, 0.98)	
p –value[b]	< 0.0001	NS	
Overall Survival[c]			
Median, in months	43.8	38.8	40.6
Hazard ratio (95% CI)[a]	0.89 (0.76, 1.05)	1.06 (0.90, 1.24)	

NS=not significant
[a] Relative to the control arm; stratified hazard ratio
[b] Two-sided p-value based on re-randomization test
[c] Final overall survival analysis

Figure 6: Kaplan-Meier Curves for Investigator-Assessed Progression-Free Survival in Stage III or IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Following Initial Surgical Resection in Study GOG-0218



14.8 Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study MO22224

The safety and efficacy of Avastin were evaluated in a multicenter, open-label, randomized study [MO22224 (NCT00976911)] comparing Avastin with chemotherapy versus chemotherapy alone in patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that recurred within <6 months from the most recent platinum-based therapy (N=361). Patients had received no more than 2 prior chemotherapy regimens. Patients received one of the following chemotherapy regimens at the discretion of the investigator: paclitaxel (80 mg/m^2 on days 1, 8, 15 and 22 every 4 weeks; pegylated liposomal doxorubicin 40 mg/m^2 on day 1 every 4 weeks; or topotecan 4 mg/m^2 on days 1, 8 and 15 every 4 weeks or 1.25 mg/m^2 on days 1-5 every 3 weeks). Patients were treated until disease progression, unacceptable toxicity, or withdrawal. Forty percent of patients on the chemotherapy alone arm received Avastin alone upon progression. The main outcome measure was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 61 years (25 to 84 years) and 37% of patients were ≥65 years. Seventy-nine percent had measurable disease at baseline, 87% had baseline CA-125 levels ≥2 times ULN and 31% had ascites at baseline. Seventy-three percent had a platinum-free interval (PFI) of 3 months to 6 months and 27% had PFI of <3 months. ECOG performance status was 0 for 59%, 1 for 34% and 2 for 7% of the patients.

The addition of Avastin to chemotherapy demonstrated a statistically significant improvement in investigator-assessed PFS, which was supported by a retrospective independent review analysis. Results for the ITT population are presented in Table 16 and Figure 7. Results for the separate chemotherapy cohorts are presented in Table 17.

Table 16: Efficacy Results in Study MO22224

Efficacy Parameter	Avastin with Chemotherapy (N=179)	Chemotherapy (N=182)
Progression-Free Survival per Investigator		
Median (95% CI), in months	6.8 (5.6, 7.8)	3.4 (2.1, 3.8)
HR (95% CI)[a]	0.38 (0.30, 0.49)	
p-value[b]	<0.0001	
Overall Survival		
Median (95% CI), in months	16.6 (13.7, 19.0)	13.3 (11.9, 16.4)
HR (95% CI)[a]	0.89 (0.69, 1.14)	
Overall Response Rate		
Number of Patients with Measurable Disease at Baseline	142	144
Rate, % (95% CI)	28% (21%, 36%)	13% (7%, 18%)
Duration of Response		
Median, in months	9.4	5.4

[a] per stratified Cox proportional hazards model
[b] per stratified log-rank test

Figure 7: Kaplan-Meier Curves for Investigator-Assessed Progression-Free Survival in Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study MO22224

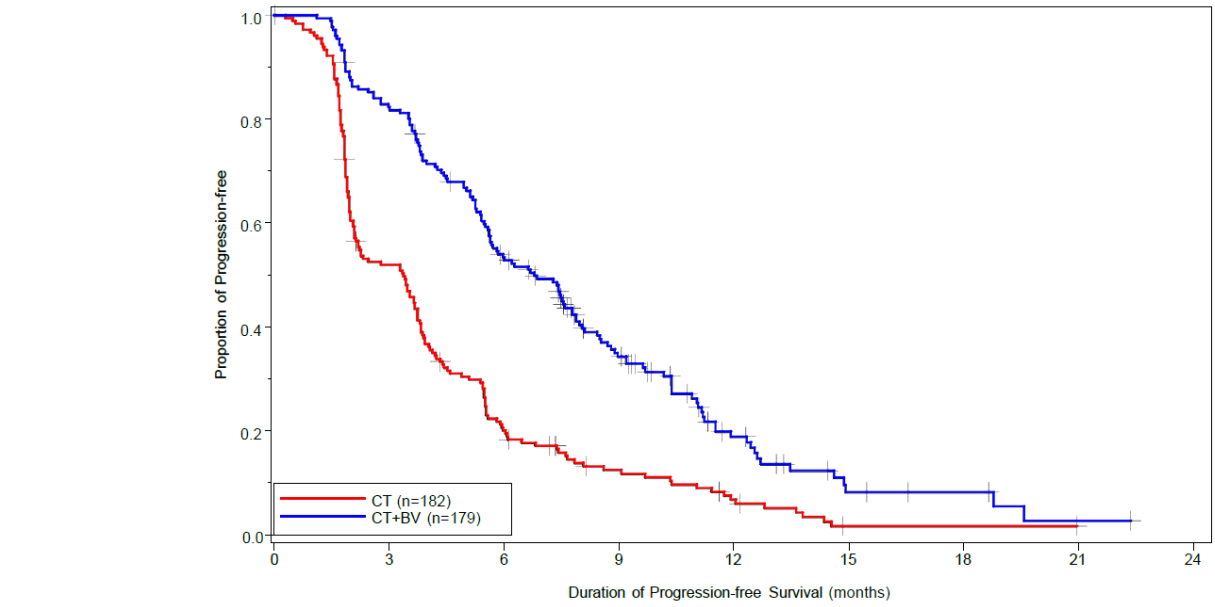


Table 17: Efficacy Results in Study MO22224 by Chemotherapy

Efficacy Parameter	Paclitaxel		Topotecan		Pegylated Liposomal Doxorubicin	
	Avastin with Chemotherapy (N=60)	Chemotherapy (N=55)	Avastin with Chemotherapy (N=57)	Chemotherapy (N=63)	Avastin with Chemotherapy (N=62)	Chemotherapy (N=64)
Progression-Free Survival per Investigator						
Median, in months (95% CI)	9.6 (7.8, 11.5)	3.9 (3.5, 5.5)	6.2 (5.3, 7.6)	2.1 (1.9, 2.3)	5.1 (3.9, 6.3)	3.5 (1.9, 3.9)
Hazard ratio[a] (95% CI)	0.47 (0.31, 0.72)		0.24 (0.15, 0.38)		0.47 (0.32, 0.71)	
Overall Survival						
Median, in months (95% CI)	22.4 (16.7, 26.7)	13.2 (8.2, 19.7)	13.8 (11.0, 18.3)	13.3 (10.4, 18.3)	13.7 (11.0, 18.3)	14.1 (9.9, 17.8)
Hazard ratio [a] (95% CI)	0.64 (0.41, 1.01)		1.12 (0.73, 1.73)		0.94 (0.63, 1.42)	
Overall Response Rate						
Number of patients with measurable disease at baseline	45	43	46	50	51	51
Rate, % (95% CI)	53 (39, 68)	30 (17, 44)	17 (6, 28)	2 (0, 6)	16 (6, 26)	8 (0, 15)
Duration of Response						
Median, in months	11.6	6.8	5.2	NE	8.0	4.6

[a] per stratified Cox proportional hazards model
NE=Not Estimable

14.9 Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study AVF4095g

The safety and efficacy of Avastin were evaluated in a randomized, double-blind, placebo-controlled study [AVF4095g (NCT00434642)] studying Avastin with chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior chemotherapy in the recurrent setting or prior bevacizumab treatment (N=484). Patients were randomized (1:1) to receive Avastin (15 mg/kg day 1) or placebo every 3 weeks with carboplatin (AUC 4, day 1) and gemcitabine (1000 mg/m^2 on days 1 and 8) a for 6 to 10 cycles followed by Avastin or placebo alone until disease progression or unacceptable toxicity. The main outcome measures were investigator-assessed PFS. Secondary outcome measures were ORR and OS.

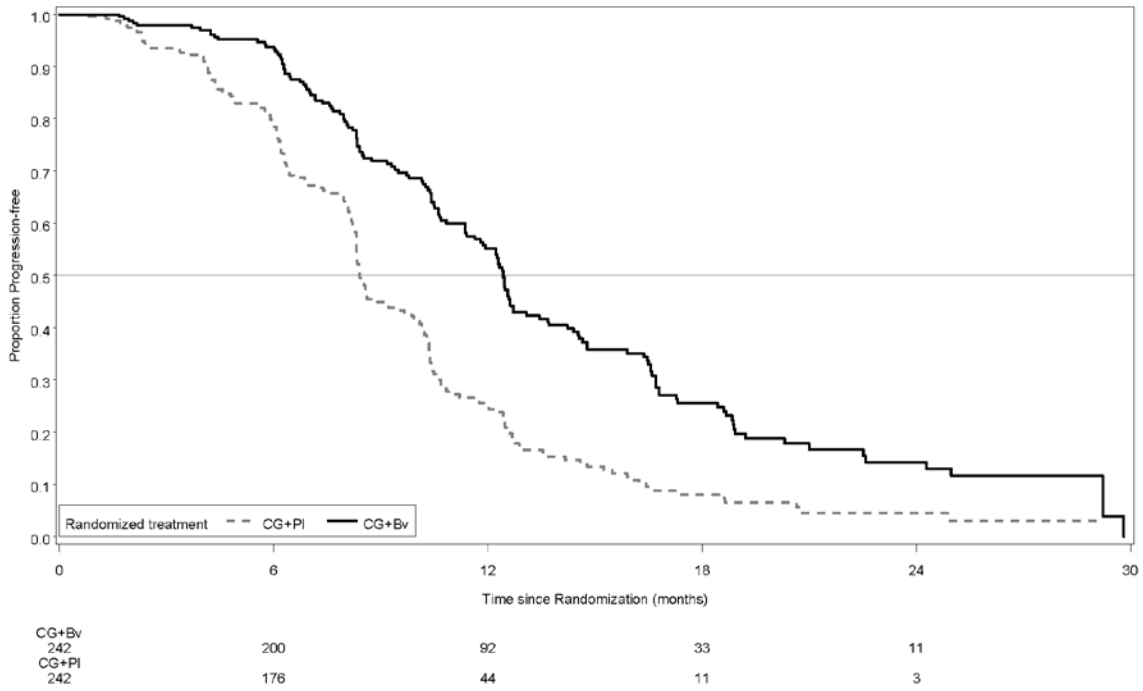
The median age was 61 years (28 to 87 years) and 37% of patients were ≥65 years. All patients had measurable disease at baseline, 74% had baseline CA-125 levels >ULN (35 U/mL). The platinum-free interval (PFI) was 6 months to 12 months in 42 % of patients and >12 months in 58% of patients. The ECOG performance status was 0 or 1 for 99.8% of patients.

A statistically significant prolongation in PFS was demonstrated among patients receiving Avastin with chemotherapy compared to those receiving placebo with chemotherapy (Table 18 and Figure 8). Independent radiology review of PFS was consistent with investigator assessment [HR 0.45 (95% CI: 0.35, 0.58)]. OS was not significantly improved with the addition of Avastin to chemotherapy [HR 0.95 (95% CI: 0.77, 1.17)].

Table 18: Efficacy Results in Study AVF4095g

Efficacy Parameter	**Avastin with Gemcitabine and Carboplatin (N=242)**	**Placebo with Gemcitabine and Carboplatin (N=242)**
Progression-Free Survival		
Median, in months	12.4	8.4
Hazard ratio (95% CI)	0.46 (0.37, 0.58)	
p-value	< 0.0001	
Overall Response Rate		
% patients with overall response	78%	57%
p-value	< 0.0001	

Figure 8: Kaplan-Meier Curves for Progression-Free Survival in Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study AVF4095g



Study GOG-0213

The safety and efficacy of Avastin were evaluated in a randomized, controlled, open-label study [Study GOG-0213 (NCT00565851)] of Avastin with chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have not received more than one previous regimen of chemotherapy (N=673). Patients were randomized (1:1) to receive carboplatin (AUC 5) and paclitaxel (175 mg/m^2 IV over 3 hours) every 3 weeks for 6 to 8 cycles (N=336) or Avastin (15 mg/kg) every 3 weeks with carboplatin (AUC 5) and paclitaxel (175 mg/m^2 IV over 3 hours) for 6 to 8 cycles followed by Avastin (15 mg/kg every 3 weeks) as a single agent until disease progression or unacceptable toxicity. The main outcome measure was OS. Other outcome measures were investigator-assessed PFS, and ORR.

The median age was 60 years (23 to 85 years) and 33% of patients were ≥ 65 years. Eighty-three percent had measurable disease at baseline and 74% had abnormal CA-125 levels at baseline. Ten percent of patients had received prior bevacizumab. Twenty-six percent had a PFI of 6 months to 12 months and 74% had a PFI of >12 months. GOG performance status was 0 or 1 for 99% of patients.

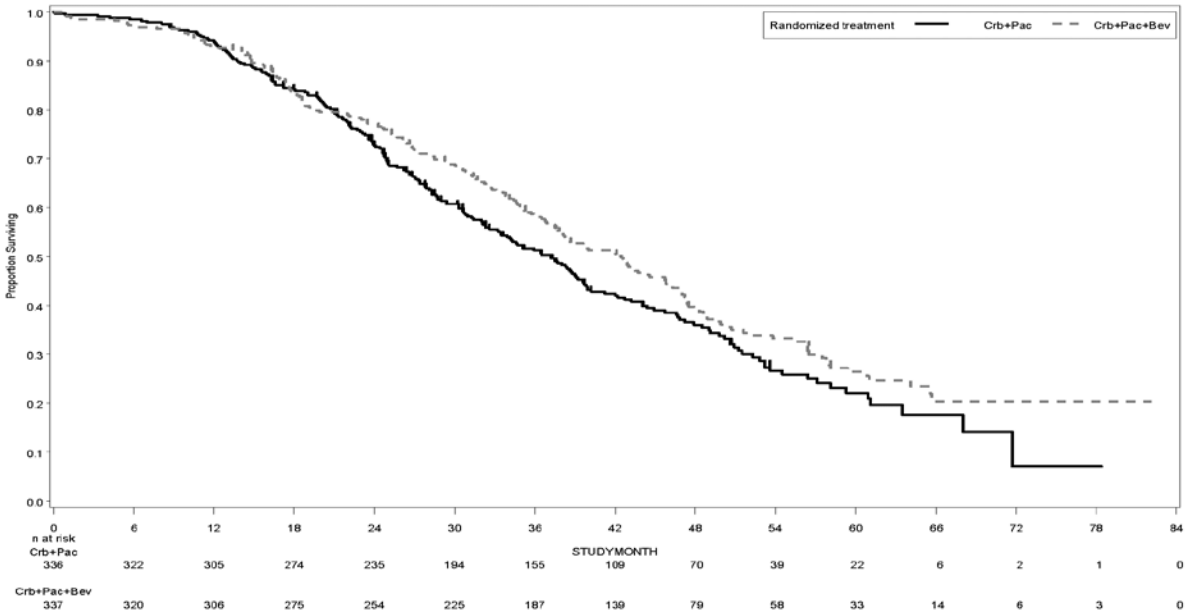
Results are presented in Table 19 and Figure 9.

Table 19: Efficacy Results in Study GOG-0213

Efficacy Parameter	**Avastin with Carboplatin and Paclitaxel (N=337)**	**Carboplatin and Paclitaxel (N=336)**
Overall Survival		
Median, in months	42.6	37.3
Hazard ratio (95% CI) (IVRS)[a]	0.84 (0.69, 1.01)	
Hazard ratio (95% CI) (eCRF)[b]	0.82 (0.68, 0.996)	
Progression-Free Survival		
Median, in months	13.8	10.4
Hazard ratio (95% CI) (IVRS)[a]	0.61 (0.51, 0.72)	
Overall Response Rate		
Number of patients with measurable disease at baseline	274	286
Rate, %	213 (78%)	159 (56%)

[a] HR was estimated from Cox proportional hazards models stratified by the duration of treatment free-interval prior to enrolling onto this study per IVRS (interactive voice response system) and secondary surgical debulking status.
[b] HR was estimated from Cox proportional hazards models stratified by the duration of platinum free-interval prior to enrolling onto this study per eCRF (electronic case report form) and secondary surgical debulking status.

Figure 9: Kaplan Meier Curves for Overall Survival in Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study GOG-0213



14.10 Hepatocellular Carcinoma

The efficacy of Avastin in combination with atezolizumab 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 atezolizumab as an intravenous infusion of 1200 mg, followed by 15 mg/kg Avastin, 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 atezolizumab or Avastin (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.

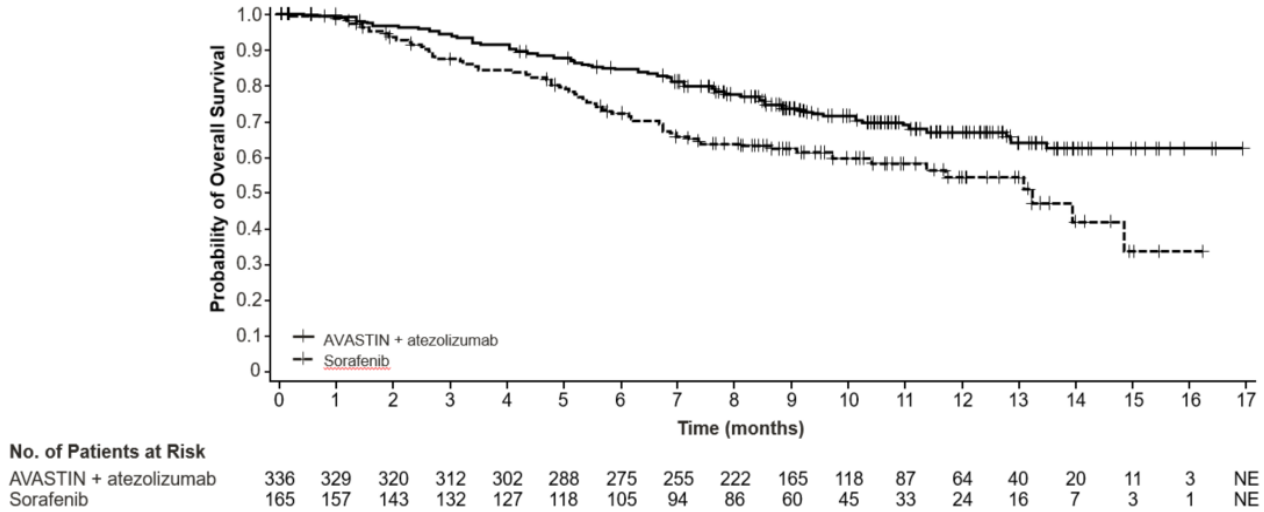
Efficacy results are presented in Table 20 and Figure 10.

Table 20: Efficacy Results from IMbrave150

	Avastin in combination with Atezolizumab (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; N/A=not applicable; RECIST 1.1= Response Evaluation Criteria in Solid Tumors v1.1

Figure 10: Kaplan-Meier Plot of Overall Survival in IMbrave150



16 HOW SUPPLIED/STORAGE AND HANDLING

Avastin (bevacizumab) injection is a clear to slightly opalescent, colorless to pale brown, sterile solution for intravenous infusion supplied as single-dose vials in the following strengths:

- 100 mg/4 mL: carton of one vial (NDC 50242-060-01); carton of 10 vials (NDC 50242-060-10).
- 400 mg/16 mL: carton of one vial (NDC 50242-061-01); carton of 10 vials (NDC 50242-061-10).

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton until time of use to protect from light. Do not freeze or shake the vial or carton.

17 PATIENT COUNSELING INFORMATION

Gastrointestinal Perforations and Fistulae: Avastin may increase the risk of developing gastrointestinal perforations and fistulae. Advise patients to immediately contact their health care provider for high fever, rigors, persistent or severe abdominal pain, severe constipation, or vomiting *[see Warnings and Precautions (5.1)]*.

Surgery and Wound Healing Complications: Avastin can increase the risk of wound healing complications. Advise patients that Avastin should not be used for at least 28 days before or after surgery and until surgical wounds are fully healed *[see Warnings and Precautions (5.2)]*.

Hemorrhage: Avastin can increase the risk of hemorrhage. Advise patients to immediately contact their health care provider for signs and symptoms of serious or unusual bleeding including coughing or spitting blood *[see Warnings and Precautions (5.3)]*.

Arterial and Venous Thromboembolic Events: Avastin increases the risk of arterial and venous thromboembolic events. Advise patients to immediately contact their health care provider for signs and symptoms of arterial or venous thromboembolism *[see Warnings and Precautions (5.4, 5.5)]*.

Hypertension: Avastin can increase blood pressure. Advise patients that they will undergo routine blood pressure monitoring and to contact their healthcare provider if they experience changes in blood pressure *[see Warnings and Precautions (5.6)]*.

Posterior Reversible Leukoencephalopathy Syndrome: Posterior reversible encephalopathy syndrome (PRES) has been associated with Avastin treatment. Advise patients to immediately contact their health care provider for new onset or worsening neurological function *[see Warnings and Precautions (5.7)]*.

Renal Injury and Proteinuria: Avastin increases the risk of proteinuria and renal injury, including nephrotic syndrome. Advise patients that treatment with Avastin requires regular monitoring of renal function and to contact their health care provider for proteinuria or signs and symptoms of nephrotic syndrome *[see Warnings and Precautions (5.8)]*.

Infusion-Related Reactions: Avastin can cause infusion-related reactions. Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.9)]*.

Congestive Heart Failure: Avastin can increase the risk of developing congestive heart failure. Advise patients to contact their healthcare provider immediately for signs and symptoms of CHF *[see Warnings and Precautions (5.12)]*.

Embryo-Fetal Toxicity: Advise female patients that Avastin may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Ovarian Failure: Avastin may lead to ovarian failure. Advise patients of potential options for preservation of ova prior to starting treatment *[see Warnings and Precautions (5.11)]*.

Lactation: Advise women not to breastfeed during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.2)]*.

Avastin® (bevacizumab)

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