1L unresectable or metastatic hepatocellular carcinoma

TECENTRIQ + Avastin® (bevacizumab)

SURVIVAL. EXPERIENCE. CONFIDENCE.

The first and only approved immunotherapy combination with superior OS and PFS vs sorafenib[1]

Coprimary endpoints

- 42% reduction in risk of death achieved with TECENTRIQ + Avastin vs sorafenib (median OS was not reached vs 13.2 months; HR=0.58; 95% CI, 0.42, 0.79; *P*=0.0006)
- 41% reduction in disease progression or death demonstrated with TECENTRIQ + Avastin vs sorafenib (median PFS was 6.8 months vs 4.3 months; HR=0.59; 95% CI, 0.47, 0.76; *P*<0.0001)

Learn more about the #1 most prescribed regimen in 1L unresectable or mHCC[1,2]*

Visit **TECENTRIQ.COM/uHCC**

1L=first line; CI=confidence interval; EMR=electronic medical record; HR=hazard ratio; HSCT=hematopoietic stem cell transplantation; mHCC=metastatic hepatocellular carcinoma; OS=overall survival; PFS=progression-free survival.

*Flatiron EMR data ending Q4 '23.

Indication

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

Select Important Safety Information

Serious and sometimes fatal adverse reactions occurred with TECENTRIQ treatment. Warnings and precautions include severe and fatal immune-mediated adverse reactions, including pneumonitis, colitis, hepatitis, endocrinopathies, dermatologic adverse reactions, nephritis with renal dysfunction, and solid organ transplant rejection. Other warnings and precautions include infusion-related reactions, complications of allogeneic HSCT, and embryo-fetal toxicity.

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

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

Median follow-up of 8.6 months

UNPRECEDENTED PIVOTAL SURVIVAL DATA IN 1L UNRESECTABLE OR mHCC[1,3]

The major efficacy outcome measures were OS and IRF-assessed PFS vs sorafenib per RECIST v1.1 in the ITT population. Key secondary endpoints included ORR* and DoR.*

	TECENTRIQ + Avastin (bevacizumab) (n=336)	Sorafenib (n=165)	Reduction in risk
OS	**MEDIAN OS NOT REACHED** (95% CI, NE, NE)	**13.2 MONTHS** (95% CI, 10.4, NE)	**42%** HR=0.58 (95% CI, 0.42, 0.79; *P*=0.0006)
PFS†	**6.8 MONTHS** (95% CI, 5.8, 8.3)	**4.3 MONTHS** (95% CI, 4.0, 5.6)	**41%** HR=0.59 (95% CI, 0.47, 0.76; *P*<0.0001)
ORR†‡ (*P*<0.0001)	**28%** (n=93; 95% CI, 23, 33)	**12%** (n=19; 95% CI, 7, 17)	

- ORR as assessed by HCC mRECIST was 33% with TECENTRIQ + Avastin (n=112/336; 95% CI, 28, 39) vs 13% with sorafenib (n=21/165; 95% CI, 8, 19)‡

7% of patients demonstrated a complete response with TECENTRIQ + Avastin compared to 0% with sorafenib, while 21% of patients demonstrated a partial response compared to 12% with sorafenib

DoR=duration of response; HCC mRECIST=hepatocellular carcinoma modified Response Evaluation Criteria In Solid Tumors; IRF=independent review facility; ITT=intent to treat; IV=intravenous; NE=not estimable; ORR=overall response rate; q3w=every 3 weeks; RECIST=Response Evaluation Criteria In Solid Tumors.

*Assessed by IRF per RECIST v1.1 and HCC mRECIST.

†Assessed by IRF per RECIST v1.1.

‡Confirmed responses.

Study design: 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.

Important Safety Information

Severe and Fatal Immune-Mediated Adverse Reactions

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

Immune-mediated adverse reactions can occur in any organ system or tissue and at any time after starting TECENTRIQ. While immune-mediated adverse reactions usually manifest during treatment with TECENTRIQ, they can also manifest after discontinuation of treatment. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of TECENTRIQ.

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

Median follow-up of 15.6 months

OS WHEN ACCOUNTING FOR RISK STATUS

Prespecified descriptive follow-up analysis of OS in the ITT population[4]

	TECENTRIQ + Avastin (bevacizumab)	Sorafenib	Reduction in risk
ITT population	**19.2 MONTHS** (95% CI, 17.0, 23.7; n=336)	**13.4 MONTHS** (95% CI, 11.4, 16.9; n=165)	**34%** **HR=0.66** (95% CI, 0.52, 0.85)

Exploratory post hoc analysis of OS based on risk status[5]

- 20% of the ITT population in the IMbrave150 study consisted of patients with high-risk characteristics, including Vp4* MVI, the most extensive form of MVI portal vein involvement (15%); bile duct invasion (2%); and tumor ≥50% of the liver (6%)

	TECENTRIQ + Avastin	Sorafenib	Reduction in risk
Excluding high-risk patients	**22.8 MONTHS** (95% CI, 19.1, 24.9; n=272)	**15.7 MONTHS** (95% CI, 13.2, 19.0; n=128)	**32%** **HR=0.68** (95% CI, 0.51, 0.91)
High-risk patients only	**7.6 MONTHS** (95% CI, 6.6, 12.8; n=64)	**5.5 MONTHS** (95% CI, 4.1, 6.7; n=37)	**38%** **HR=0.62** (95% CI, 0.39, 1.00)

These are descriptive analyses; therefore, the *P* values cannot be formally claimed.

Post hoc analyses were not powered to demonstrate statistically significant differences and no conclusions can be drawn from these analyses.

The baseline characteristics of each subgroup were in line with their respective risk level.

Observed safety events were in line with the known safety profile of each drug and the complications of the underlying malignancy.

MVI=macrovascular invasion.

*Vp4 is defined as tumor invasion of the main trunk of the portal vein and/or a portal vein branch contralateral to the primarily involved lobe.

Important Safety Information (cont'd)

Severe and Fatal Immune-Mediated Adverse Reactions (cont'd)

Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

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

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

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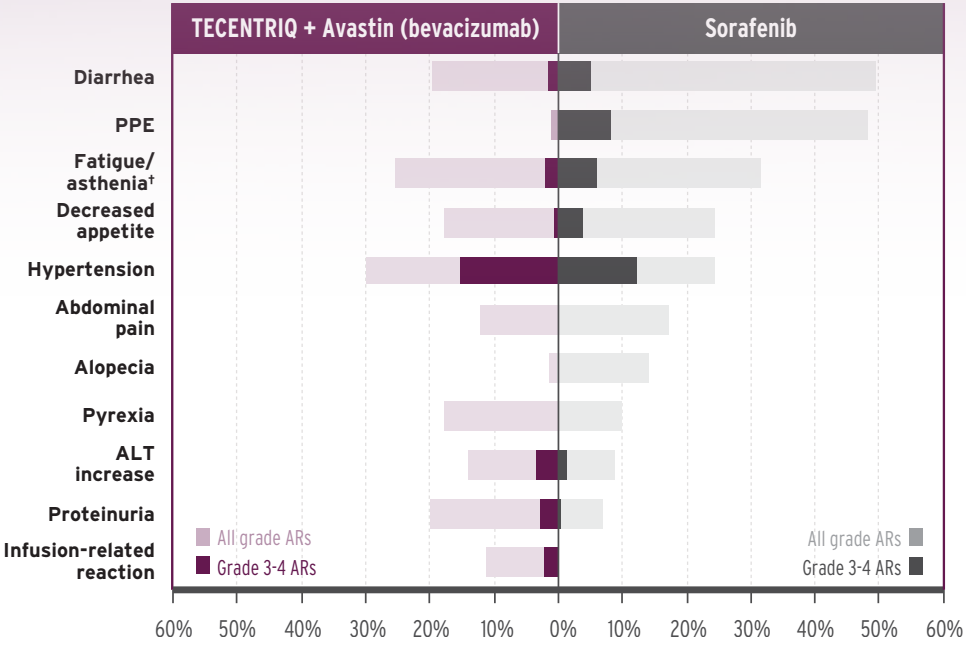
OBSERVED DIFFERENCES OF SELECT ARs

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



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 patients with 1L unresectable or mHCC

- The most common grade 3 to 4 ARs (≥2%) were hypertension, proteinuria, infusion-related reaction, and fatigue/asthenia[1]
- Treatment-related serious ARs were 17% with TECENTRIQ + Avastin and 15% with sorafenib[6]
- The most common ARs (rate ≥10%) in patients who received TECENTRIQ in combination with bevacizumab for HCC were hypertension (30%), fatigue/asthenia (26%), proteinuria (20%), diarrhea (19%), pruritus (19%), decreased appetite (18%), pyrexia (18%), constipation (13%), abdominal pain (12%), cough (12%), nausea (12%), rash (12%), infusion-related reactions (11%), weight decreased (11%), epistaxis (10%), and vomiting (10%)[1]

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

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ADDITIONAL SAFETY DATA REPORTED IN IMBRAVE150[1,3]

- 4.6% of patients who were treated with TECENTRIQ + Avastin (bevacizumab) experienced fatal ARs. The most common ARs leading to death were GI 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 GI hemorrhage (7%), infections (6%), and pyrexia (2.1%)
- ARs leading to discontinuation of TECENTRIQ occurred in 9% of patients in the TECENTRIQ + Avastin arm; the discontinuation rate due to ARs was 10% in the sorafenib arm
  - The most common ARs leading to discontinuation of TECENTRIQ were hemorrhages (1.2%), including GI, 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 phosphatase (8%); infections (6%); GI 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

Select safety data related to bleeding events[3,6,7]

- The majority (73%) of bleeding/hemorrhage AEs were grade 1 to 2
- The proportion of patients experiencing grade 3 to 4 bleed rates was 6.4% with TECENTRIQ + Avastin and 5.8% with sorafenib
- All IMbrave150 patients were required to receive an EGD within 6 months prior to treatment initiation. Per the Avastin USPI, an evaluation for the presence of varices is recommended within 6 months prior to initiation of Avastin in patients with HCC

AE=adverse event; EGD=esophagogastroduodenoscopy; GI=gastrointestinal.

Important Safety Information (cont'd)

Immune-Mediated Pneumonitis

- TECENTRIQ can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation
- Immune-mediated pneumonitis occurred in 3% (83/2616) of patients receiving TECENTRIQ alone, including fatal (<0.1%), Grade 4 (0.2%), Grade 3 (0.8%), and Grade 2 (1.1%) adverse reactions. Pneumonitis led to permanent discontinuation of TECENTRIQ in 0.5% and withholding of TECENTRIQ in 1.5% of patients

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IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-Mediated Pneumonitis (cont'd)

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

Immune-Mediated Colitis

- TECENTRIQ can cause immune-mediated colitis. Colitis can present with diarrhea, abdominal pain, and lower gastrointestinal (GI) bleeding. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies
- Immune-mediated colitis occurred in 1% (26/2616) of patients receiving TECENTRIQ alone, including Grade 3 (0.5%) and Grade 2 (0.3%) adverse reactions. Colitis led to permanent discontinuation of TECENTRIQ in 0.2% and withholding of TECENTRIQ in 0.5% of patients. Systemic corticosteroids were required in 50% (13/26) of patients with colitis. Colitis resolved in 73% of the 26 patients. Of the 12 patients in whom TECENTRIQ was withheld for colitis, 8 reinitiated TECENTRIQ after symptom improvement; of these, 25% had recurrence of colitis

Immune-Mediated Hepatitis

- TECENTRIQ can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 1.8% (48/2616) of patients receiving TECENTRIQ alone, including fatal (<0.1%), Grade 4 (0.2%), Grade 3 (0.5%), and Grade 2 (0.5%) adverse reactions. Hepatitis led to permanent discontinuation of TECENTRIQ in 0.2% and withholding of TECENTRIQ in 0.2% of patients. Systemic corticosteroids were required in 25% (12/48) of patients with hepatitis. Hepatitis resolved in 50% of the 48 patients. Of the 6 patients in whom TECENTRIQ was withheld for hepatitis, 4 reinitiated TECENTRIQ after symptom improvement; of these, none had recurrence of hepatitis

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

- TECENTRIQ can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated
- Adrenal insufficiency occurred in 0.4% (11/2616) of patients receiving TECENTRIQ alone, including Grade 3 (<0.1%) and Grade 2 (0.2%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of TECENTRIQ in 1 patient and withholding of TECENTRIQ in 1 patient. Systemic corticosteroids were required in 82% (9/11) of patients with adrenal insufficiency; of these, 3 patients remained on systemic corticosteroids. The single patient in whom TECENTRIQ was withheld for adrenal insufficiency did not reinitiate TECENTRIQ

Hypophysitis

- TECENTRIQ can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated
- Hypophysitis occurred in <0.1% (2/2616) of patients receiving TECENTRIQ alone, including Grade 2 (1 patient, <0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of TECENTRIQ in 1 patient and no patients required withholding of TECENTRIQ. Systemic corticosteroids were required in 50% (1/2) of patients with hypophysitis. Hypophysitis did not resolve in these 2 patients

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IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-Mediated Endocrinopathies (cont'd)

Thyroid Disorders

- TECENTRIQ can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or medical management for hyperthyroidism as clinically indicated
- Thyroiditis occurred in 0.2% (4/2616) of patients receiving TECENTRIQ alone, including Grade 2 (<0.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 1 patient. Hormone replacement therapy was required in 75% (3/4) of patients with thyroiditis. Systemic corticosteroids were required in 25% (1/4) of patients with thyroiditis. Thyroiditis resolved in 50% of patients. The single patient in whom TECENTRIQ was withheld for thyroiditis reinitiated TECENTRIQ; this patient did not have recurrence of thyroiditis
- Hyperthyroidism occurred in 0.8% (21/2616) of patients receiving TECENTRIQ alone, including Grade 2 (0.4%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 0.1% of patients. Antithyroid therapy was required in 29% (6/21) of patients with hyperthyroidism. Of these 6 patients, the majority remained on antithyroid treatment. Of the 3 patients in whom TECENTRIQ was withheld for hyperthyroidism, 1 patient reinitiated TECENTRIQ; this patient did not have recurrence of hyperthyroidism
- Hypothyroidism occurred in 4.9% (128/2616) of patients receiving TECENTRIQ alone, including Grade 3 (0.2%) and Grade 2 (3.4%) adverse reactions. Hypothyroidism did not lead to permanent discontinuation of TECENTRIQ in any of these patients, but led to withholding of TECENTRIQ in 0.6% of patients. Hormone replacement therapy was required in 81% (104/128) of patients with hypothyroidism. The majority of patients with hypothyroidism remained on thyroid hormone replacement. Of the 17 patients in whom TECENTRIQ was withheld for hypothyroidism, 8 reinitiated TECENTRIQ after symptom improvement

Type 1 Diabetes Mellitus, Which Can Present With Diabetic Ketoacidosis

- Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated
- Type 1 diabetes mellitus occurred in 0.3% (7/2616) of patients receiving TECENTRIQ alone, including Grade 3 (0.2%) and Grade 2 (<0.1%) adverse reactions. Type 1 diabetes mellitus led to permanent discontinuation of TECENTRIQ in 1 patient and withholding of TECENTRIQ in 2 patients. Treatment with insulin was required for all patients with confirmed Type 1 diabetes mellitus and insulin therapy was continued long-term. Of the 2 patients in whom TECENTRIQ was withheld for Type 1 diabetes mellitus, both reinitiated TECENTRIQ treatment

Immune-Mediated Nephritis With Renal Dysfunction

- TECENTRIQ can cause immune-mediated nephritis
- Immune-mediated nephritis with renal dysfunction occurred in <0.1% (1/2616) of patients receiving TECENTRIQ alone, and this adverse reaction was a Grade 3 (<0.1%) adverse reaction. Nephritis led to permanent discontinuation of TECENTRIQ in this patient. This patient required systemic corticosteroids. In this patient, nephritis did not resolve

Immune-Mediated Dermatologic Adverse Reactions

- TECENTRIQ can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes

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IMPORTANT SAFETY INFORMATION (CONT'D)

Immune-Mediated Dermatologic Adverse Reactions (cont'd)

- Immune-mediated dermatologic adverse reactions occurred in 0.6% (15/2616) of patients receiving TECENTRIQ alone, including Grade 3 (<0.1%) and Grade 2 (0.2%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of TECENTRIQ in 0.1% and withholding of TECENTRIQ in 0.2% of patients. Systemic corticosteroids were required in 20% (3/15) of patients with dermatologic adverse reactions. Dermatologic adverse reactions resolved in 87% of the 15 patients. Of the 4 patients in whom TECENTRIQ was withheld for immune-mediated dermatologic adverse reactions, none reinitiated TECENTRIQ

Other Immune-Mediated Adverse Reactions

- The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received TECENTRIQ or were reported with the use of other PD-1/PD-L1 blocking antibodies
  - *Cardiac/Vascular*: Myocarditis, pericarditis, vasculitis
  - *Nervous System*: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy
  - *Ocular*: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss
  - *Gastrointestinal*: Pancreatitis to include increases in serum amylase and lipase levels, gastritis, duodenitis
  - *Musculoskeletal and Connective Tissue*: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatic
  - *Endocrine*: Hypoparathyroidism
  - *Other (Hematologic/Immune)*: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection, other transplant (including corneal graft) rejection

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. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses
- Infusion-related reactions occurred in 1.3% of patients receiving TECENTRIQ alone, including Grade 3 (0.2%) reactions
- The frequency and severity of infusion-related reactions were similar across the recommended dose range

Complications of Allogeneic HSCT After PD-1/PD-L1 Inhibitors

- Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody
- Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring

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IMPORTANT SAFETY INFORMATION (CONT'D)

Complications of Allogeneic HSCT After PD-1/PD-L1 Inhibitors (cont'd)

febrile syndrome (without an identified infectious cause)

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

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 and to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose

Use in Specific Populations

Nursing Mothers

- There is no information regarding the presence of TECENTRIQ 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 female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose

Fertility

- 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 full TECENTRIQ Prescribing Information and full Avastin Prescribing Information for additional Important Safety Information.

References: 1. TECENTRIQ Prescribing Information. Genentech, Inc. **2.** Data on file. Genentech, Inc. **3.** 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. **4.** Cheng A-L, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. 2022;76:862-873. **5.** Finn RS, Qin S, Ikeda M, et al. IMbrave150: updated efficacy and safety by risk status in patients (pts) receiving atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (sor) as first-line treatment for unresectable hepatocellular carcinoma (HCC). Paper presented at: Annual Meeting of the American Association for Cancer Research; April 10-15, 2021; virtual conference. **6.** Data on file. Clinical Study Report YO40245. Genentech, Inc. **7.** Avastin (bevacizumab) Prescribing Information. Genentech, Inc. **8.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatocellular Carcinoma V.1.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed April 9, 2024. To view the most recent and complete version of the guideline, go online to www.NCCN.org.

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NCCN RECOMMENDS | CATEGORY 1, PREFERRED OPTION

Atezolizumab (TECENTRIQ) + bevacizumab (Avastin) is an NCCN **Category 1, preferred** first-line systemic therapy option for patients with unresectable* or metastatic† hepatocellular carcinoma‡ according to the National Comprehensive Cancer Network® (NCCN®).[8§‖¶]

Child-Pugh Class removed from HCC Systemic Therapy Guidelines.

*In patients with liver-confined, unresectable disease, and deemed ineligible for transplant.
†Extrahepatic/metastatic disease; and deemed ineligible for resection, transplant, or locoregional therapy.
‡Caution: systemic therapies listed for advanced HCC may have limited safety data available for Child-Pugh Class B or C liver function. Use with extreme caution in patients with elevated bilirubin levels and consult the Prescribing Information for individual agents.
§NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for their application or use in any way. See the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for detailed recommendations.
‖Category 1: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
¶Preferred intervention: interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

Indication

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

Select Important Safety Information

Serious and sometimes fatal adverse reactions occurred with TECENTRIQ treatment. Warnings and precautions include severe and fatal immune-mediated adverse reactions, including pneumonitis, colitis, hepatitis, endocrinopathies, dermatologic adverse reactions, nephritis with renal dysfunction, and solid organ transplant rejection. Other warnings and precautions include infusion-related reactions, complications of allogeneic HSCT, and embryo-fetal toxicity.

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M-US-00010761(v4.0)

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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

Dosage and Administration (2.3)	04/2023
Warnings and Precautions (5.1)	04/2024

INDICATIONS AND USAGE

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

Non-Small Cell Lung Cancer (NSCLC)

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

Small Cell Lung Cancer (SCLC)

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

Hepatocellular Carcinoma (HCC)

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

Melanoma

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

Alveolar Soft Part Sarcoma (ASPS)

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

DOSAGE AND ADMINISTRATION

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

NSCLC

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

Small Cell Lung Cancer

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

Hepatocellular Carcinoma

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

Melanoma

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

ASPS

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

TECENTRIQ as a single-agent

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

TECENTRIQ in combination with other antineoplastic drugs

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

TECENTRIQ in combination with bevacizumab

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

TECENTRIQ in combination with cobimetinib and vemurafenib

- Most common adverse reactions (≥ 20%) with TECENTRIQ in patients with melanoma are rash, musculoskeletal pain, fatigue, hepatotoxicity, pyrexia, nausea, pruritus, edema, stomatitis, hypothyroidism, and photosensitivity reaction. (6.1)

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

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2024

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 Non-Small Cell Lung Cancer

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

1.2 Small Cell Lung Cancer

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

1.3 Hepatocellular Carcinoma

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

1.4 Melanoma

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

1.5 Alveolar Soft Part Sarcoma

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

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

2.2 Recommended Dosage

The recommended dosages of TECENTRIQ administered intravenously as a single agent are presented in Table 1.

Table 1: Recommended Dosage of TECENTRIQ as a Single Agent

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

* 60-minute intravenous infusion. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

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

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

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

* 60-minute intravenous infusion. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

2.3 Dosage Modifications for Adverse Reactions

No dose reduction for TECENTRIQ is recommended. In general, withhold TECENTRIQ for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue TECENTRIQ for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

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

Table 3: Recommended Dosage Modifications for Adverse Reactions

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

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

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

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

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

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

2.4 Preparation and Administration

Preparation

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

Prepare the solution for infusion as follows:

- Select the appropriate vial(s) based on the prescribed dose.
- Withdraw the required volume of TECENTRIQ from the vial(s) using sterile needle and syringe.
- Dilute to a final concentration between 3.2 mg/mL and 16.8 mg/mL in a polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% Sodium Chloride Injection, USP.
- Dilute with only 0.9% Sodium Chloride Injection, USP.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard used or empty vials of TECENTRIQ.

Storage of Infusion Solution

This product does not contain a preservative.

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

- At room temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration of the infusion, or
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from time of preparation.

Do not freeze.

Do not shake.

Administration

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

Do not coadminister other drugs through the same intravenous line.

Do not administer as an intravenous push or bolus.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

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

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

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

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

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

Immune-Mediated Pneumonitis

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

TECENTRIQ as a Single Agent:

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

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

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

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

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

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

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

Immune-Mediated Colitis

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

TECENTRIQ as a Single Agent:

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

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

Immune-Mediated Hepatitis

TECENTRIQ can cause immune-mediated hepatitis.

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

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

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

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

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

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

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

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

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

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

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

Hypophysitis

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

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

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

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

Thyroid disorders

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

Thyroiditis:

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

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

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

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

Hyperthyroidism:

TECENTRIQ as a Single Agent:

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

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

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

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

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

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

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

Hypothyroidism:

TECENTRIQ as a Single Agent:

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

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

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

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

TECENTRIQ in Combination with Platinum-based Chemotherapy:

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

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

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

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

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

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

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

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

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

Immune-Mediated Nephritis with Renal Dysfunction

TECENTRIQ can cause immune-mediated nephritis.

TECENTRIQ as a Single Agent:

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

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

TECENTRIQ in Combination with Cobimetinib and Vemurafenib:

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

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

Immune-Mediated Dermatologic Adverse Reactions

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

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

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

Other Immune-Mediated Adverse Reactions

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

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

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis.

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

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

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

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

Endocrine: Hypoparathyroidism.

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

5.2 Infusion-Related Reactions

TECENTRIQ can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.3)]*. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent *[see Adverse Reactions (6.1)]*, infusion-related reactions occurred in 1.3% of patients, including Grade 3 (0.2%). The frequency and severity of infusion-related reactions were similar whether TECENTRIQ was given as a single-agent in patients with various cancers, in combination with other antineoplastic drugs in NSCLC and SCLC, and across the recommended dose range (840 mg Q2W to 1680 mg Q4W).

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

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

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

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women.

Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death.

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

The data described in WARNINGS AND PRECAUTIONS reflect exposure to TECENTRIQ as a single-agent in 2616 patients in two randomized, active-controlled studies (POPLAR, OAK) and three open-label, single arm studies (PCD4989g, BIRCH, FIR) which enrolled 1636 patients with metastatic NSCLC, and 980 patients with other tumor types. TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks in all studies except PCD4989g. Among the 2616 patients who received a single-agent TECENTRIQ, 36% were exposed for longer than 6 months and 20% were exposed for longer than 12 months. Using the dataset described for patients who received TECENTRIQ as a single-agent, the most common adverse reactions in ≥ 20% of patients were fatigue/asthenia (48%), decreased appetite (25%), nausea (24%), cough (22%), and dyspnea (22%). In addition, the data reflect exposure to TECENTRIQ as a single agent as adjuvant therapy in 495 patients with early stage NSCLC enrolled in a randomized study (IMpower010).

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

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

Non-Small Cell Lung Cancer (NSCLC)

Adjuvant Treatment of Early-stage NSCLC

IMpower010

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

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

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

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

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

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

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

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

*Graded per NCI CTCAE v4.0

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

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

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

[4] Includes pyrexia, body temperature increased, hyperthermia

[5] Includes fatigue, asthenia

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

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

[8] Includes arthralgia, arthritis

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

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

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

Metastatic Chemotherapy-Naïve NSCLC

IMpower110

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

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

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

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

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

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

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

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

Graded per NCI CTCAE v4.0

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

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

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

IMpower150

The safety of TECENTRIQ with bevacizumab, paclitaxel and carboplatin was evaluated in IMpower150, a multicenter, international, randomized, open-label trial in which 393 chemotherapy-naïve patients with metastatic non-squamous NSCLC received TECENTRIQ 1200 mg with bevacizumab 15 mg/kg, paclitaxel 175 mg/m^2 or 200 mg/m^2, and carboplatin AUC 6 mg/mL/min intravenously every 3 weeks for a maximum of 4 or 6 cycles, followed by TECENTRIQ 1200 mg with bevacizumab 15 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.1)]*. The median duration of exposure to TECENTRIQ was 8.3 months in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin.

Fatal adverse reactions occurred in 6% of patients receiving TECENTRIQ; these included hemoptysis, febrile neutropenia, pulmonary embolism, pulmonary hemorrhage, death, cardiac arrest, cerebrovascular accident, pneumonia, aspiration pneumonia, chronic obstructive pulmonary disease, intracranial hemorrhage, intestinal angina, intestinal ischemia, intestinal obstruction and aortic dissection.

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

TECENTRIQ was discontinued due to adverse reactions in 15% of patients; the most common adverse reaction leading to discontinuation was pneumonitis (1.8%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 48%; the most common (>1%) were neutropenia, thrombocytopenia, fatigue/asthenia, diarrhea, hypothyroidism, anemia, pneumonia, pyrexia, hyperthyroidism, febrile neutropenia, increased ALT, dyspnea, dehydration and proteinuria.

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

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

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

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

Graded per NCI CTCAE v4.0

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

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

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

[4] Includes diarrhea, gastroenteritis, colitis, enterocolitis

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

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

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

Laboratory Abnormality	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin		Bevacizumab, Paclitaxel and Carboplatin	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Increased Alkaline Phosphatase	37	2	32	1
Increased ALT	37	6	28	0.5
Increased TSH	30	NA[1]	20	NA[1]
Hyperkalemia	28	3	25	2
Increased Creatinine	28	1	19	2
Hypocalcemia	26	3	21	3
Hypophosphatemia	25	4	18	4
Hypokalemia	23	7	14	4
Hyperphosphatemia	25	NA[1]	19	NA[1]

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

IMpower130

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

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

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

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

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

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

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

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

Graded per NCI CTCAE v4.0

[1] Includes diarrhea, colitis, and gastroenteritis

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

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

[4] Includes dyspnea, dyspnea exertional and wheezing

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

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

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

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ with paclitaxel protein-bound and carboplatin (range: 423 - 467); paclitaxel protein-bound and carboplatin (range: 218 - 229). Graded per NCI CTCAE v4.0.
[1] NA = Not applicable. NCI CTCAE does not provide a Grades 3-4 definition for these laboratory abnormalities

Previously Treated Metastatic NSCLC

The safety of TECENTRIQ was evaluated in OAK, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression *[see Clinical Studies (14.1)]*. A total of 609 patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel (n=578) 75 mg/m^2 intravenously every 3 weeks until unacceptable toxicity or disease progression. The study excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids. The median duration of exposure was 3.4 months (0 to 26 months) in TECENTRIQ-treated patients and 2.1 months (0 to 23 months) in docetaxel-treated patients.

The study population characteristics were: median age of 63 years (25 to 85 years), 46% age 65 years or older, 62% male, 71% White, 20% Asian, 68% former smoker, 16% current smoker, and 63% had ECOG performance status of 1.

Fatal adverse reactions occurred in 1.6% of patients; these included pneumonia, sepsis, septic shock, dyspnea, pulmonary hemorrhage, sudden death, myocardial ischemia or renal failure.

Serious adverse reactions occurred in 33.5% of patients. The most frequent serious adverse reactions (>1%) were pneumonia, sepsis, dyspnea, pleural effusion, pulmonary embolism, pyrexia and respiratory tract infection.

TECENTRIQ was discontinued due to adverse reactions in 8% of patients. The most common adverse reactions leading to TECENTRIQ discontinuation were fatigue, infections and dyspnea. Adverse reactions leading to interruption of TECENTRIQ occurred in 25% of patients; the most common (>1%) were pneumonia, liver function test abnormality, dyspnea, fatigue, pyrexia, and back pain.

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

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

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

Graded per NCI CTCAE v4.0

[1] Includes fatigue and asthenia

[2] Includes cough and exertional cough

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

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

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

Laboratory Abnormality	TECENTRIQ		Docetaxel	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
Anemia	67	3	82	7
Lymphocytopenia	49	14	60	21
Chemistry				
Hypoalbuminemia	48	4	50	3
Hyponatremia	42	7	31	6
Increased Alkaline Phosphatase	39	2	25	1
Increased AST	31	3	16	0.5
Increased ALT	27	3	14	0.5
Hypophosphatemia	27	5	23	4
Hypomagnesemia	26	1	21	1
Increased Creatinine	23	2	16	1

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ (range: 546–585) and docetaxel (range: 532–560). Graded according to NCI CTCAE version 4.0

Small Cell Lung Cancer (SCLC)

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

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

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

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

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

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

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

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

Graded per NCI CTCAE v4.0

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

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

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ (range: 181-193); Placebo (range: 181-196). Graded per NCI CTCAE v4.0

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

Hepatocellular Carcinoma (HCC)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[1] Graded per NCI CTCAE v4.0

Melanoma

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

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

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

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

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

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

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

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

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

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

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

[2] Includes fatigue, asthenia and malaise

[3] Includes pyrexia and hyperpyrexia

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

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

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

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

[8] Includes hypothyroidism and blood thyroid stimulating hormone increased

[9] Includes infusion related reaction and hypersensitivity

[10] Includes pneumonitis and interstitial lung disease

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

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

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

Eye Disorders: Uveitis

Gastrointestinal disorders: Pancreatitis

Infections and infestations: Pneumonia, urinary tract infection

Metabolism and nutrition disorders: Hyperglycemia

Nervous system Disorders: Dizziness, dysgeusia, syncope

Respiratory, thoracic and mediastinal disorders: Dyspnea, oropharyngeal pain

Skin and Subcutaneous Tissue Disorders: Vitiligo

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

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

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

Unresectable or Metastatic Alveolar Soft Part Sarcoma (ASPS)

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

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

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

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

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

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

Weight increased	16	6

Graded per NCI CTCAE v4.0

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

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

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

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

6.2 Postmarketing Experience

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

- Cardiac: pericarditis, pericardial effusion, cardiac tamponade

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

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

Infertility

Females

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

8.4 Pediatric Use

Alveolar Soft Part Sarcoma

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

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

Solid Tumors and Lymphomas

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

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

8.5 Geriatric Use

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

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

No overall differences in safety or effectiveness were observed between patients aged 65 years or older and younger patients.

11 DESCRIPTION

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

TECENTRIQ (atezolizumab) injection for intravenous use is a sterile, preservative-free, colorless to slightly yellow solution in single-dose vials. Each 20 mL vial contains 1200 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), polysorbate 20 (8 mg), and sucrose (821.6 mg), with a pH of 5.8. Each 14 mL vial contains 840 mg of atezolizumab and is formulated in glacial acetic acid (11.5 mg), L-histidine (43.4 mg), polysorbate 20 (5.6 mg), and sucrose (575.1 mg) with a pH of 5.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

Distribution

The volume of distribution at steady state is 6.9 L.

Elimination

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

Specific Populations

The following factors had no clinically significant effect on the systemic exposure of atezolizumab: age (2 to 89 years), body weight, sex, albumin levels, tumor burden, region or race, mild or moderate renal impairment [estimated glomerular filtration rate (eGFR) 30 to 89 mL/min/1.73 m^2], mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1 to 1.5 × ULN and any AST), moderate hepatic impairment (bilirubin >1.5 to 3x ULN and any AST), level of PD-L1 expression, or performance status.

Pediatric Patients

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

12.6 Immunogenicity

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

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

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Non-Small Cell Lung Cancer

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

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

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

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

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

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

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

Efficacy results are presented in Table 22 and Figure 1.

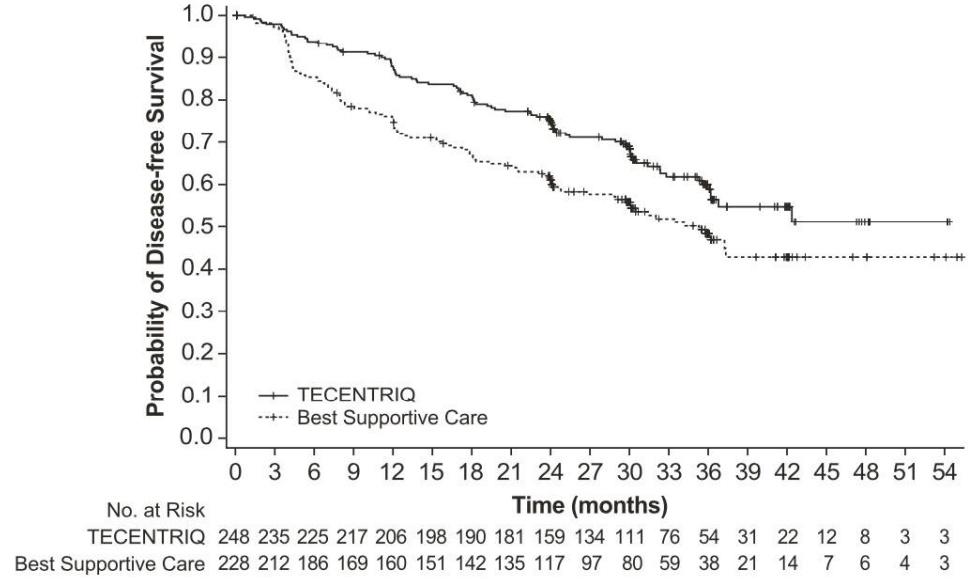
Table 22 Efficacy Results from IMpower010 in Patients with Stage II - IIIA NSCLC with PD-L1 expression ≥ 1% TC

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

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

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

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



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

Metastatic Chemotherapy-Naïve NSCLC with High PD-L1 Expression

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

express PD-L1 (PD-L1 stained ≥ 1% of tumor cells [TC ≥ 1%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 1% of the tumor area [IC ≥ 1%]), who had received no prior chemotherapy for metastatic disease. PD-L1 tumor status was determined based on immunohistochemistry (IHC) testing using the VENTANA PD-L1 (SP142) Assay. The evaluation of efficacy is based on the subgroup of patients with high PD-L1 expression (TC ≥ 50% or IC ≥ 10%), excluding those with EGFR or ALK genomic tumor aberrations. The trial excluded patients with a history of autoimmune disease, administration of a live attenuated vaccine within 28 days prior to randomization, active or untreated CNS metastases, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization.

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

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

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

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

Administration of TECENTRIQ was permitted beyond RECIST-defined disease progression. Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define subgroups for pre-specified analyses.

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

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

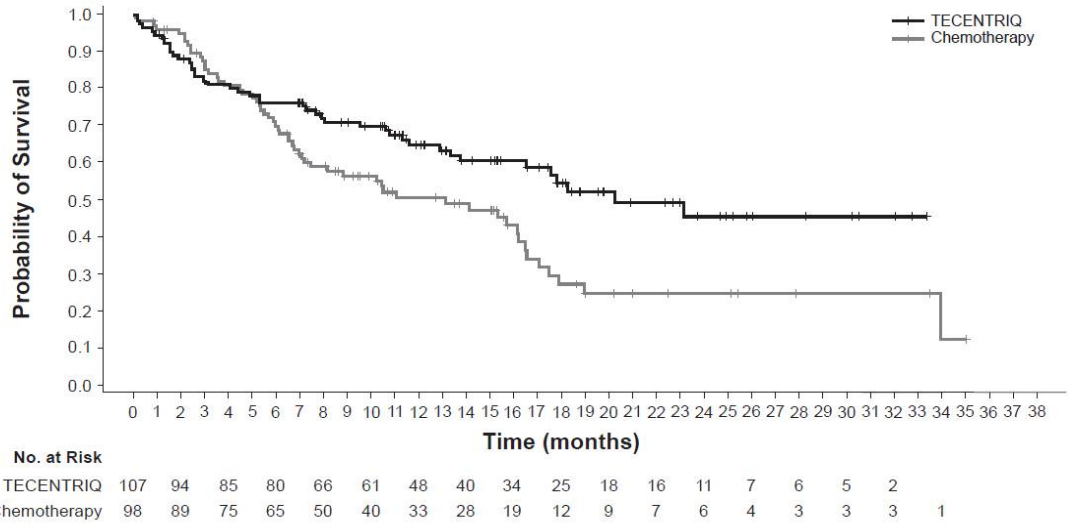
The trial demonstrated a statistically significant improvement in OS for patients with high PD-L1 expression (TC ≥50% or IC ≥10%) at the time of the OS interim analysis. There was no statistically significant difference in OS for the other two PD-L1 subgroups (TC ≥5% or IC ≥5%; and TC ≥1% or IC ≥1%)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

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

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

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

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



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

Metastatic Chemotherapy-Naive Non-Squamous NSCLC

IMpower150

The efficacy of TECENTRIQ with bevacizumab, paclitaxel, and carboplatin was evaluated in IMpower150 (NCT02366143), a multicenter, international, randomized (1:1:1), open-label trial in patients with metastatic non-squamous NSCLC. Patients with stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease but could have received prior EGFR or ALK kinase inhibitor if appropriate, regardless of PD-L1 or T-effector gene (tGE)

status and ECOG performance status 0 or 1 were eligible. The trial excluded patients with a history of autoimmune disease, administration of a live attenuated vaccine within 28 days prior to randomization, active or untreated CNS metastases, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization, or clear tumor infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions as seen on imaging. Randomization was stratified by sex, presence of liver metastases, and PD-L1 expression status on tumor cells (TC) and tumor-infiltrating immune cells (IC) as follows: TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1. Patients were randomized to one of the following three treatment arms:

- Arm A: TECENTRIQ 1200 mg, paclitaxel 175 mg/m² or 200 mg/m² and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles
- Arm B: TECENTRIQ 1200 mg, bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles
- Arm C: bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles

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

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

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

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

A total of 1202 patients were enrolled across the three arms of whom 1045 were in the ITT-WT subpopulation and 447 were in the tGE-WT subpopulation. The demographic information is limited to the 800 patients enrolled in Arms B and C where efficacy has been demonstrated. The median age was 63 years (range: 31 to 90), and 60% of patients were male. The majority of patients were White (82%), 13% of patients were Asian, 10% were Hispanic, and 2% of patients were Black. Clinical sites in Asia (enrolling 13% of the study population) received paclitaxel at a dose of 175 mg/m^2 while the remaining 87% received paclitaxel at a dose of 200 mg/m^2. Approximately 14% of patients had liver metastases at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%). PD-L1 was TC3 and any IC in 12%, TC0/1/2 and IC2/3 in 13%, and TC0/1/2 and IC0/1 in 75%. The

demographics for the 696 patients in the ITT-WT subpopulation were similar to the ITT population except for the absence of patients with EGFR- or ALK- positive NSCLC.

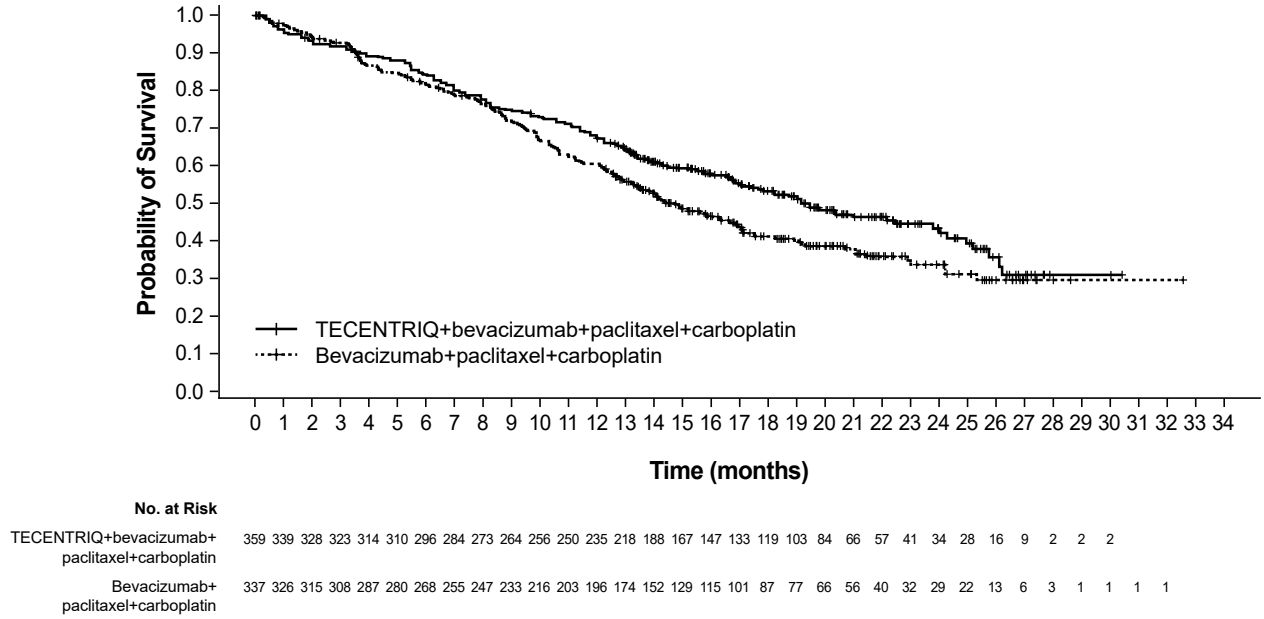
The trial demonstrated a statistically significant improvement in PFS between Arms B and C in both the tGE-WT and ITT-WT subpopulations, but did not demonstrate a significant difference for either subpopulation between Arms A and C based on the final PFS analyses. In the interim analysis of OS, a statistically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

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

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

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

Figure 3: Kaplan-Meier Curves for Overall Survival in ITT-WT Population in IMpower150



Exploratory analyses showed that the subset of patients in the four drug regimen arm who were ADA positive by week 4 (30%) appeared to have similar efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 (70%) *[see, Clinical Pharmacology (12.6)]*. In an exploratory analysis, propensity score matching was conducted to compare ADA positive patients in the TECENTRIQ, bevacizumab, paclitaxel, and carboplatin arm with a matched population in the bevacizumab, paclitaxel, and carboplatin arm. Similarly ADA negative patients in the TECENTRIQ, bevacizumab, paclitaxel, and carboplatin arm were compared with a matched population in the bevacizumab, paclitaxel, and carboplatin arm. Propensity score matching factors were: baseline sum of longest tumor size (BSLD), baseline ECOG, baseline albumin, baseline LDH, sex, tobacco history, metastatic site, TC level, and IC level. The hazard ratio comparing the ADA-positive subgroup with its matched control was 0.69 (95% CI: 0.44, 1.07). The hazard ratio comparing the ADA-negative subgroup with its matched control was 0.64 (95% CI: 0.46, 0.90).

IMpower130

The efficacy of TECENTRIQ with paclitaxel protein-bound and carboplatin was evaluated in IMpower130 (NCT02367781), a multicenter, randomized (2:1), open-label trial in patients with stage IV non-squamous NSCLC. Patients with Stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease, but could have received prior EGFR or ALK kinase inhibitor, if appropriate, were eligible. The trial excluded patients with history of autoimmune disease, administration of live attenuated vaccine within 28 days prior to randomization, administration of immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization, and active or untreated CNS metastases. Randomization was stratified by sex, presence of liver metastases, and PD-L1 tumor expression according to the VENTANA PD-L1 (SP142) assay as follows: TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1. Patients were randomized to one of the following treatment regimens:

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

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

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

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

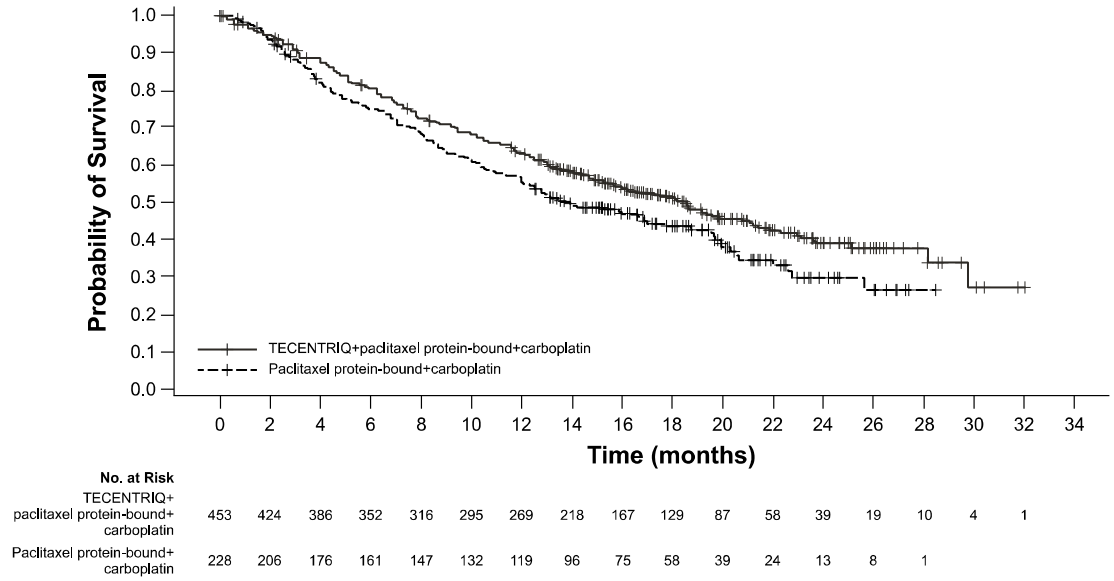
Table 25: Efficacy Results from IMpower130

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

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

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

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



Previously Treated Metastatic NSCLC

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

Patients were randomized to receive TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel 75 mg/m^2 intravenously every 3 weeks until unacceptable toxicity or disease progression. Tumor assessments were conducted every 6 weeks for the first 36 weeks and every 9 weeks thereafter. Major efficacy outcome measure was overall survival (OS) in the first 850 randomized patients and OS in the subgroup of patients with PD-L1-expressing tumors (defined as ≥ 1% PD-L1 expression on tumor cells [TC] or immune cells [IC]). Additional efficacy outcome measures were OS in all randomized patients (n = 1225), OS in subgroups based on PD-L1 expression, overall response rate (ORR), and progression free survival as assessed by the investigator per RECIST v.1.1.

Among the first 850 randomized patients, the median age was 64 years (33 to 85 years) and 47% were ≥ 65 years old; 61% were male; 70% were White and 21% were Asian; 15% were current smokers and 67% were former smokers; and 37% had baseline ECOG PS of 0 and 63% had a baseline ECOG PS of 1. Nearly all (94%) had metastatic disease, 74% had non-squamous

histology, 75% had received only one prior platinum-based chemotherapy regimen, and 55% of patients had PD-L1-expressing tumors.

Efficacy results are presented in Table 26 and Figure 5.

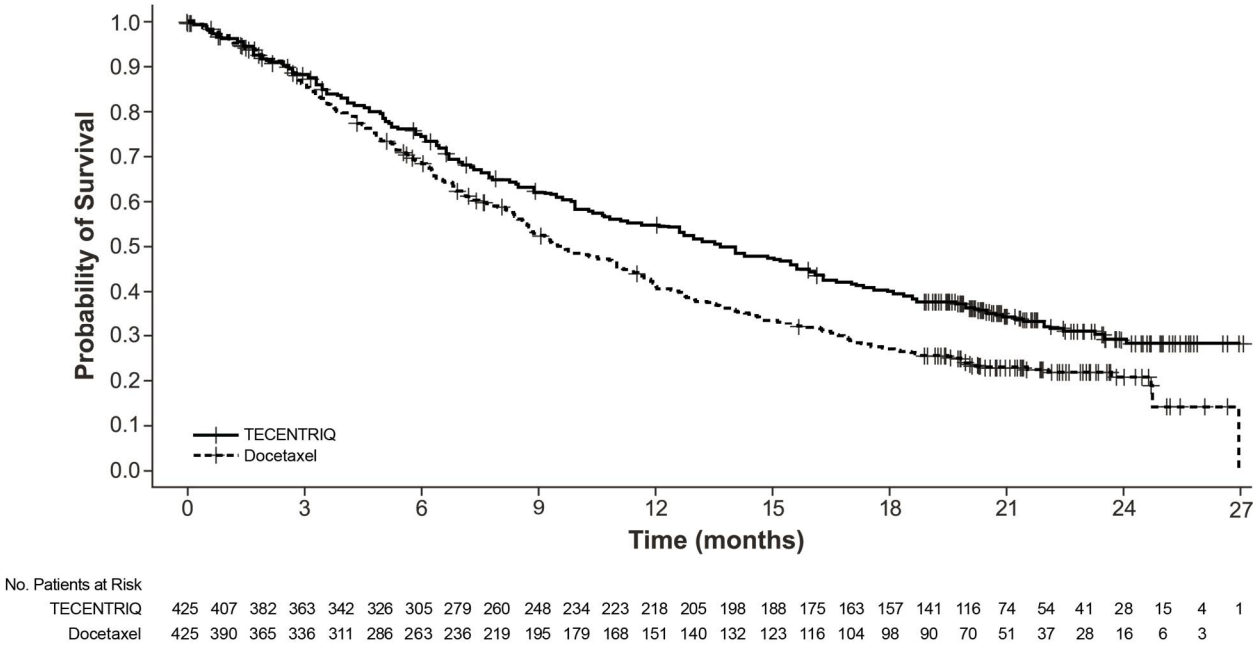
Table 26: Efficacy Results in OAK

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

[1] Stratified by PD-L1 expression in tumor infiltrating immune cells, the number of prior chemotherapy regimens, and histology
[2] Based on the stratified log-rank test
[3] Compared to the pre-specified allocated α of 0.03 for this analysis
[4] Per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)

	TECENTRIQ	Docetaxel
[5] Compared to the allocated α of 0.0177 for this interim analysis based on 86% information using O'Brien-Fleming boundary CI=confidence interval; NE=not estimable		

Figure 5: Kaplan-Meier Curves of Overall Survival in the First 850 Patients Randomized in OAK



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

Exploratory analyses showed that the subset of patients who were ADA positive by week 4 (21%) appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 (79%) *[see Clinical Pharmacology (12.6)]*. ADA positive patients by week 4 appeared to have similar OS compared to docetaxel-treated patients. In an exploratory analysis, propensity score matching was conducted to compare ADA positive patients in the 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).

14.2 Small Cell Lung Cancer

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

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

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

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

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

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

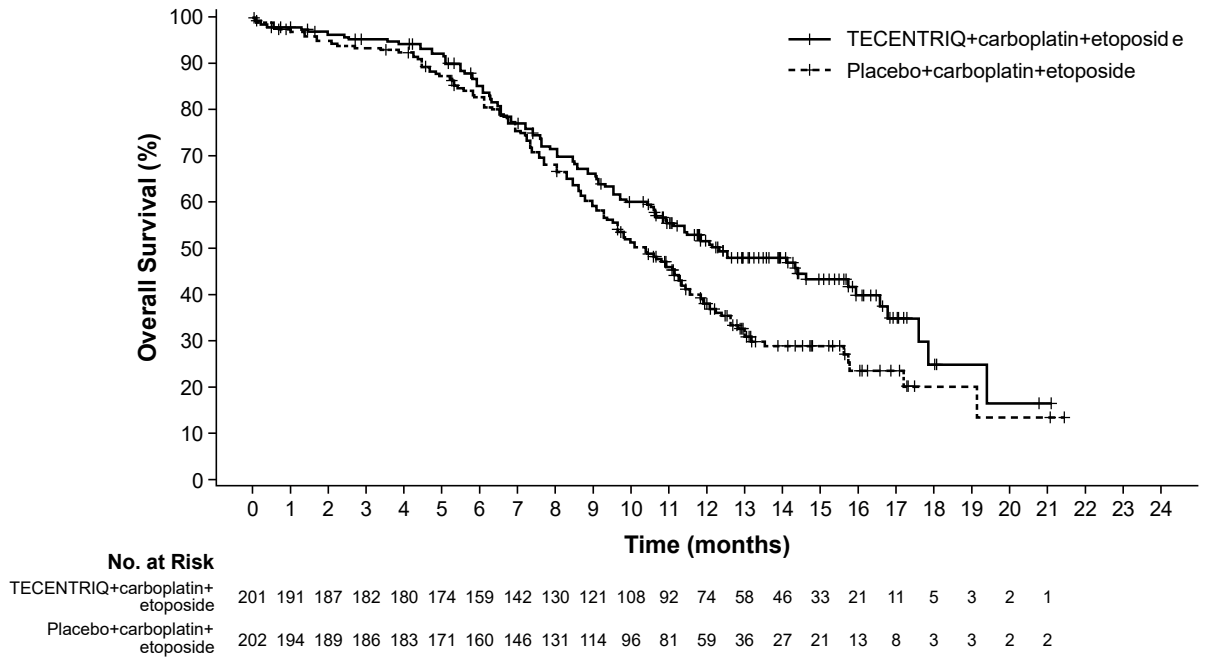
Efficacy results are presented in Table 27 and Figure 6.

Table 27: Efficacy Results from IMpower133

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

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

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



14.3 Hepatocellular Carcinoma

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

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

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

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

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

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

Efficacy results are presented in Table 28 and Figure 7.

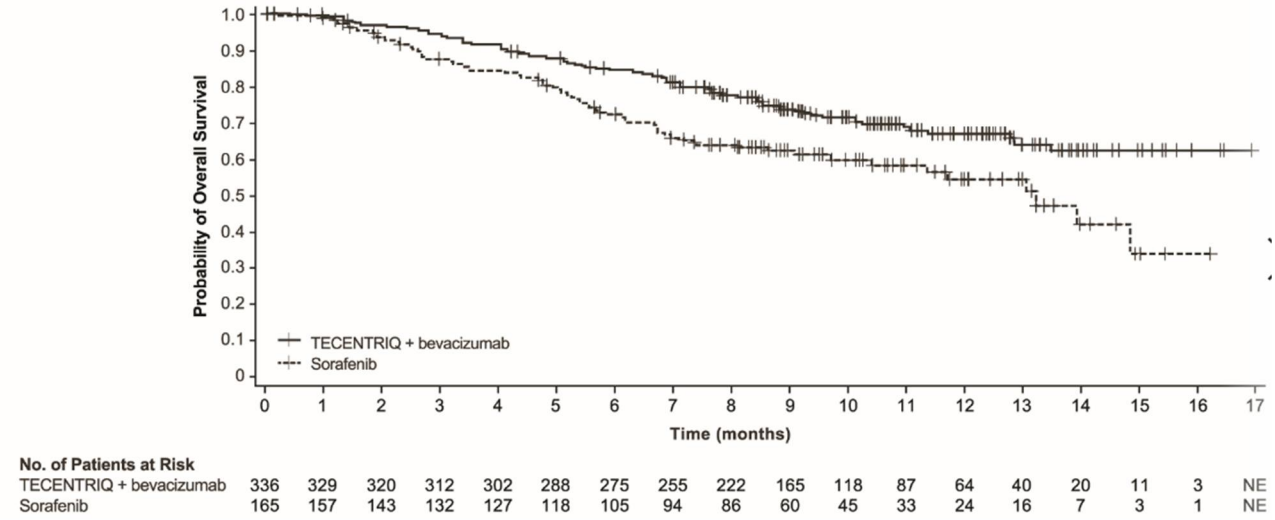
Table 28: Efficacy Results from IMbrave150

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

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

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

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



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

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

14.4 Melanoma

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

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

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

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

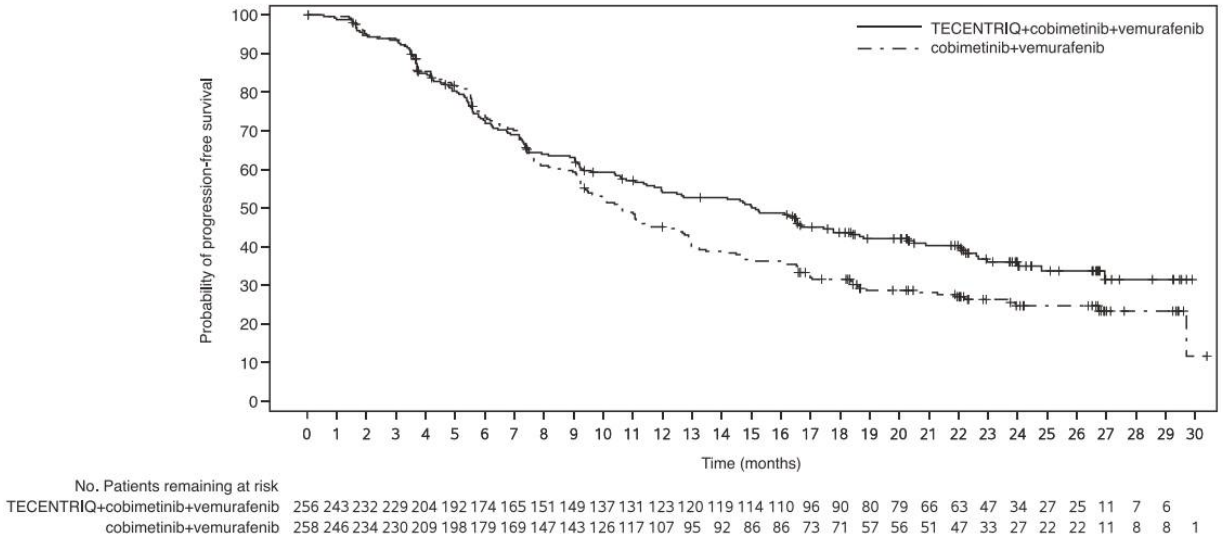
Efficacy results are summarized in Table 29 and Figure 8. Patients had a median survival follow up time of 18.9 months.

Table 29 Efficacy Results from IMspire150

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

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

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



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

14.5 Alveolar soft part sarcoma (ASPS)

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

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

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

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

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

Efficacy results of this study are summarized in Table 30.

Table 30: Efficacy Results from Study ML39345

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

TECENTRIQ injection is a sterile, preservative-free, and colorless to slightly yellow solution for intravenous infusion supplied as a carton containing one 840 mg/14 mL single-dose vial (NDC 50242-918-01) or 1,200 mg/20 mL single-dose vial (NDC 50242-917-01).

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

17 PATIENT COUNSELING INFORMATION

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

Immune-Mediated Adverse Reactions

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

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

Infusion-Related Reactions

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

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

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

Embryo-Fetal Toxicity

Advise females of reproductive potential that TECENTRIQ can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

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

Lactation

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

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

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 in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You can have more than one of these problems at the same time. These problems may happen anytime during your treatment or even after your treatment has ended.

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

Lung problems.

- cough
- shortness of breath
- chest pain

Intestinal problems.

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

Liver problems.

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

Hormone gland problems.

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

Kidney problems.

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

Skin problems.

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

Problems can also happen in other organs.

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

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

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

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

Complications, including graft-versus-host disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be serious and can lead to death. These

complications may happen if you underwent transplantation either before or after being treated with TECENTRIQ. Your healthcare provider will monitor you for these complications.

Getting medical treatment right away may help keep these problems from becoming more serious.
Your healthcare provider will check you for these problems during your treatment with TECENTRIQ. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with TECENTRIQ if you have severe side effects.

What is TECENTRIQ?

TECENTRIQ is a prescription medicine used to treat adults with:

- **a type of lung cancer called non-small cell lung cancer (NSCLC).**
  - **TECENTRIQ may be used alone as a treatment for your lung cancer:**
    - to help prevent your lung cancer from coming back after your tumor(s) has been removed by surgery and you have received platinum-based chemotherapy, **and**
    - you have stage 2 to stage 3A NSCLC (talk to your healthcare provider about what these stages mean), **and**
    - your cancer tests positive for “PD-L1”.
  - **TECENTRIQ may be used alone as your first treatment when your lung cancer:**
    - has spread or grown, **and**
    - your cancer tests positive for “high PD-L1”, **and**
    - your tumor does not have an abnormal “EGFR” or “ALK” gene.
  - **TECENTRIQ may be used with the medicines bevacizumab, paclitaxel, and carboplatin as your first treatment when your lung cancer:**
    - has spread or grown, **and**
    - is a type called “non-squamous NSCLC”, **and**
    - your tumor does not have an abnormal “EGFR” or “ALK” gene.
  - **TECENTRIQ may be used with the medicines paclitaxel protein-bound and carboplatin as your first treatment when your lung cancer:**
    - has spread or grown, **and**
    - is a type called “non-squamous NSCLC”, **and**
    - your tumor does not have an abnormal “EGFR” or “ALK” gene.
  - **TECENTRIQ may also be used alone when your lung cancer:**
    - has spread or grown, **and**
    - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
    - if your tumor has an abnormal “EGFR” or “ALK” gene, you should have also tried an FDA-approved therapy for tumors with these abnormal genes, and it did not work or is no longer working.
- **adults with a type of lung cancer called small cell lung cancer (SCLC). TECENTRIQ may be used with the chemotherapy medicines carboplatin and etoposide as your first treatment when your lung cancer**
  - is a type called “extensive-stage SCLC,” which means that it has spread or grown.
- **adults with a type of liver cancer called hepatocellular carcinoma (HCC). TECENTRIQ may be used with the medicine bevacizumab when your liver cancer:**
  - has spread or cannot be removed by surgery, **and**
  - you have not received other medicines by mouth or injection through your vein (IV) to treat your cancer.
- **adults with a type of skin cancer called melanoma. TECENTRIQ may be used with the medicines cobimetinib and vemurafenib when your melanoma:**
  - has spread to other parts of the body or cannot be removed by surgery, **and**
  - has a certain type of abnormal “BRAF” gene. Your healthcare provider will perform a test to make sure this TECENTRIQ combination is right for you.
- **adults and children 2 years of age and older with a type of soft tissue tumor (cancer) called alveolar soft part sarcoma (ASPS). TECENTRIQ may be used when your sarcoma:**
  - has spread to other parts of the body or cannot be removed by surgery.

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

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

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

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

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

How will I receive TECENTRIQ?

- Your healthcare provider will give you TECENTRIQ into your vein through an intravenous (IV) line over 30 to 60 minutes.
- TECENTRIQ is usually given every 2, 3, or 4 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will test your blood to check you for certain side effects.
- For treatment of a type of skin cancer called melanoma, your healthcare provider will also prescribe you cobimetinib and vemurafenib. Take cobimetinib and vemurafenib exactly as your healthcare provider tells you.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of TECENTRIQ?

TECENTRIQ can cause serious side effects, including:

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

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

- feeling tired or weak
- decreased appetite
- nausea
- cough
- shortness of breath

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

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

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

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

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

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

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

These are not all the possible side effects of TECENTRIQ.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TECENTRIQ.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about TECENTRIQ that is written for health professionals.

What are the ingredients in TECENTRIQ?

Active ingredient: atezolizumab

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

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

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:12/2022

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 (1.1)	9/2022
Dosage and Administration (2.2)	9/2022
Warnings and Precautions, Infusion-Related Reactions (5.9)	9/2022

----------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 bevacizumab product-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----------

Withhold for at least 28 days prior to elective surgery. Do not administer Avastin for 28 days following major surgery and until adequate wound healing. (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 bevacizumab product-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 after dilution. See full Prescribing Information for preparation and administration instructions and dosage modifications for adverse reactions (2.9, 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: In patients who experience wound healing complications during Avastin treatment, withhold Avastin until adequate wound healing. Withhold for at least 28 days prior to elective surgery. Do not administer Avastin for at least 28 days following a major surgery, and until adequate wound healing. The safety of resumption of AVASTIN after resolution of wound healing complication has not been established. Discontinue for wound healing complication of necrotizing fasciitis. (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: 9/2022

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 bevacizumab product-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

Withhold for at least 28 days prior to elective surgery. Do not administer Avastin until at least 28 days following major surgery and until adequate wound healing.

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 bevacizumab product-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)]*.	• Any	Withhold AVASTIN until adequate wound healing.The safety of resumption of AVASTIN after resolution of wound healing complications has not been established.
	• 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.
- Use sterile needle and syringe to prepare Avastin.
- 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.
- Diluted Avastin solution may be stored at 2°C to 8°C (36°F to 46°F) for up to 8 hours, if not used immediately.
- 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)]*.

In patients who experience wound healing complications during Avastin treatment, withhold Avastin until adequate wound healing. Withhold for at least 28 days prior to elective surgery. Do not administer for at least 28 days following major surgery and until adequate wound healing. The safety of resumption of AVASTIN after resolution of wound healing complications has not been established *[see Dosage and Administration (2.9)]*.

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, anaphylactoid/anaphylactic reactions, 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%

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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%

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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%

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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 phosphatase (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
Vascular: Arterial (including aortic) aneurysms, dissections, and rupture

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 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.

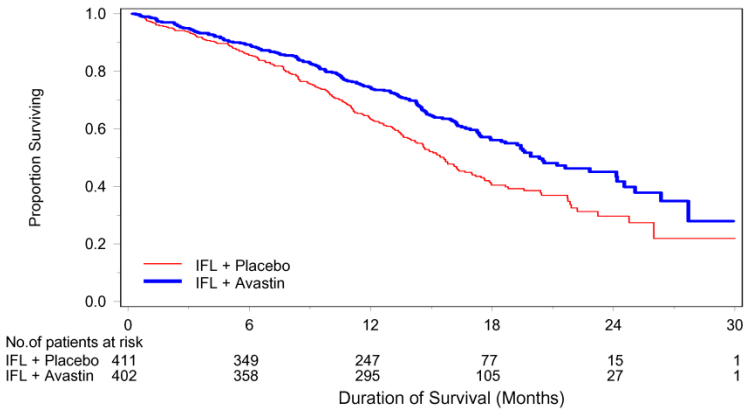
Table 11: Efficacy Results in Study AVF2107g

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.

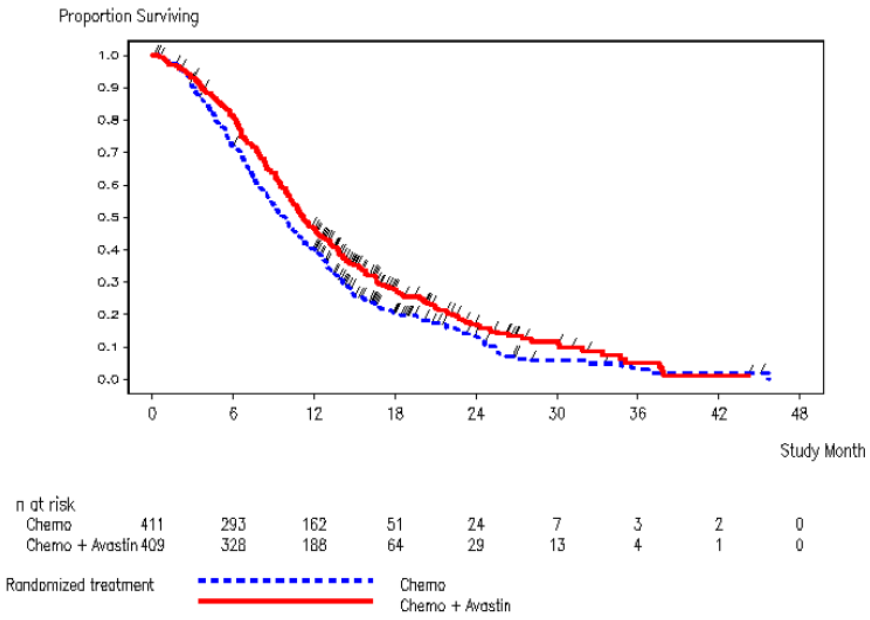
Table 12: Efficacy Results in Study ML18147

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

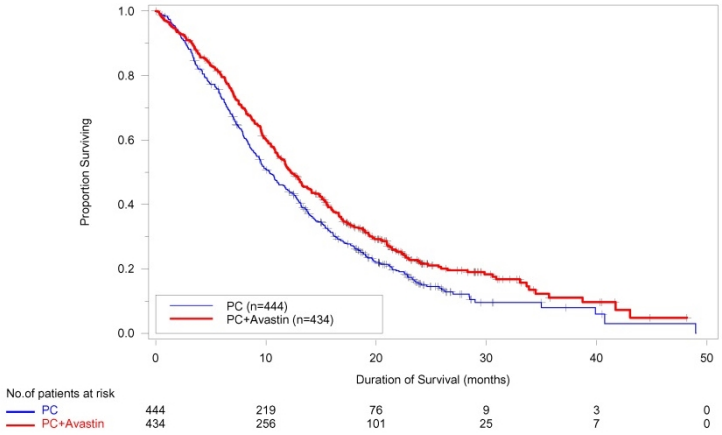
Study E4599

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

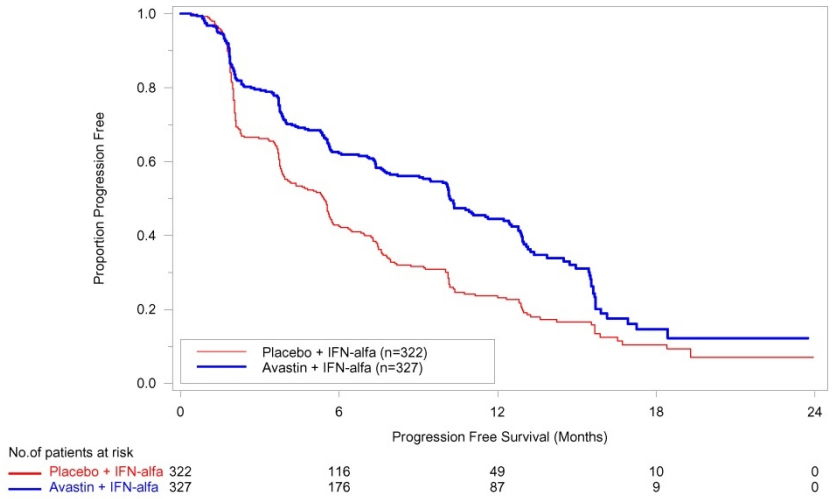
Study BO17705

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 (PFI) 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

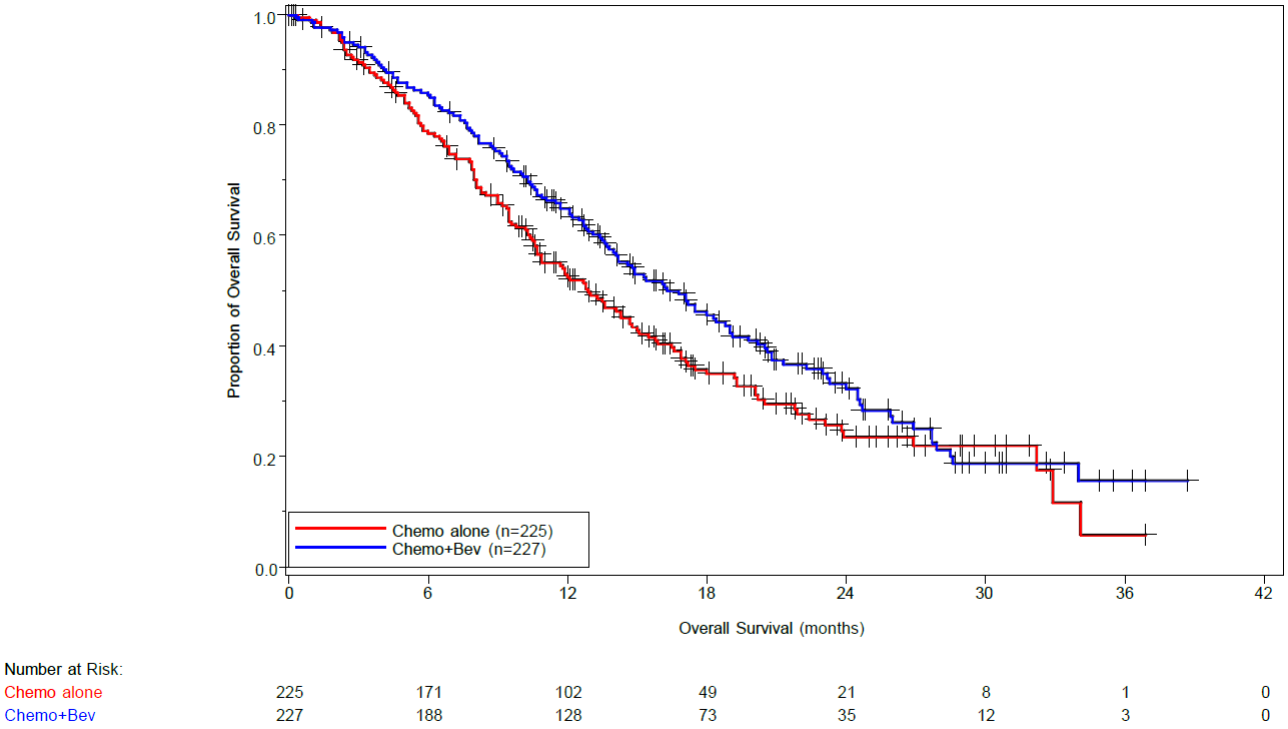


Table 13: Efficacy Results in Study GOG-0240

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.

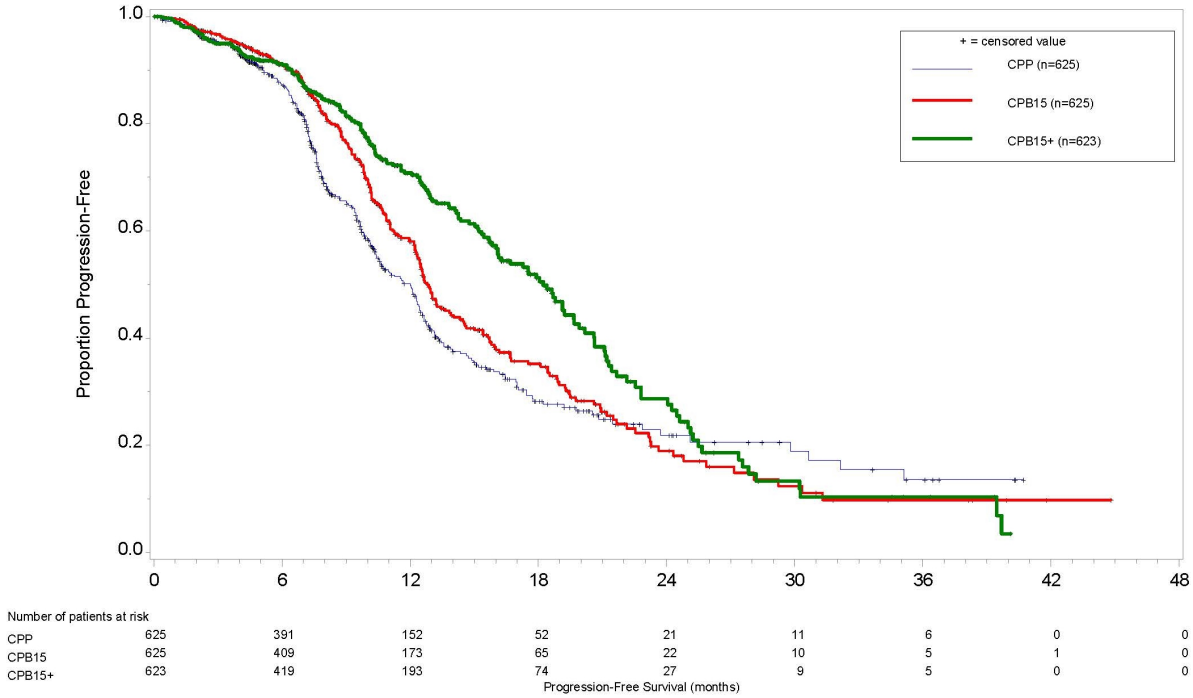
Table 15: Efficacy Results in Study GOG-0218

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 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

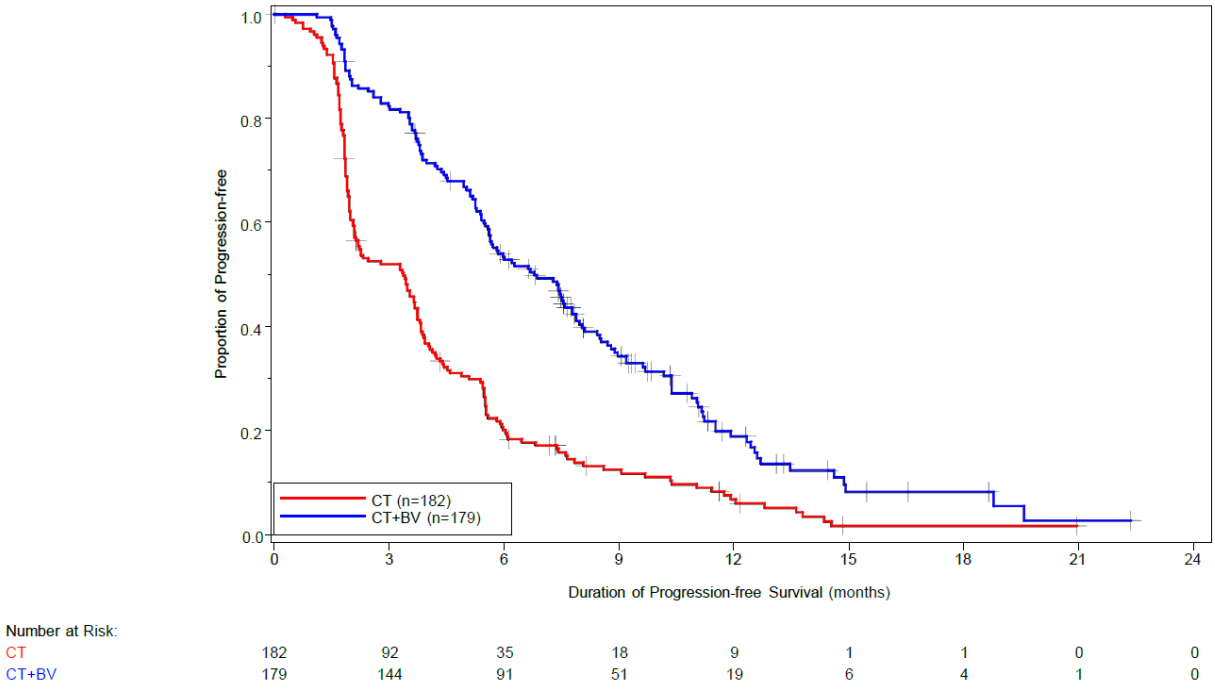


Table 17: Efficacy Results in Study MO22224 by Chemotherapy

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.

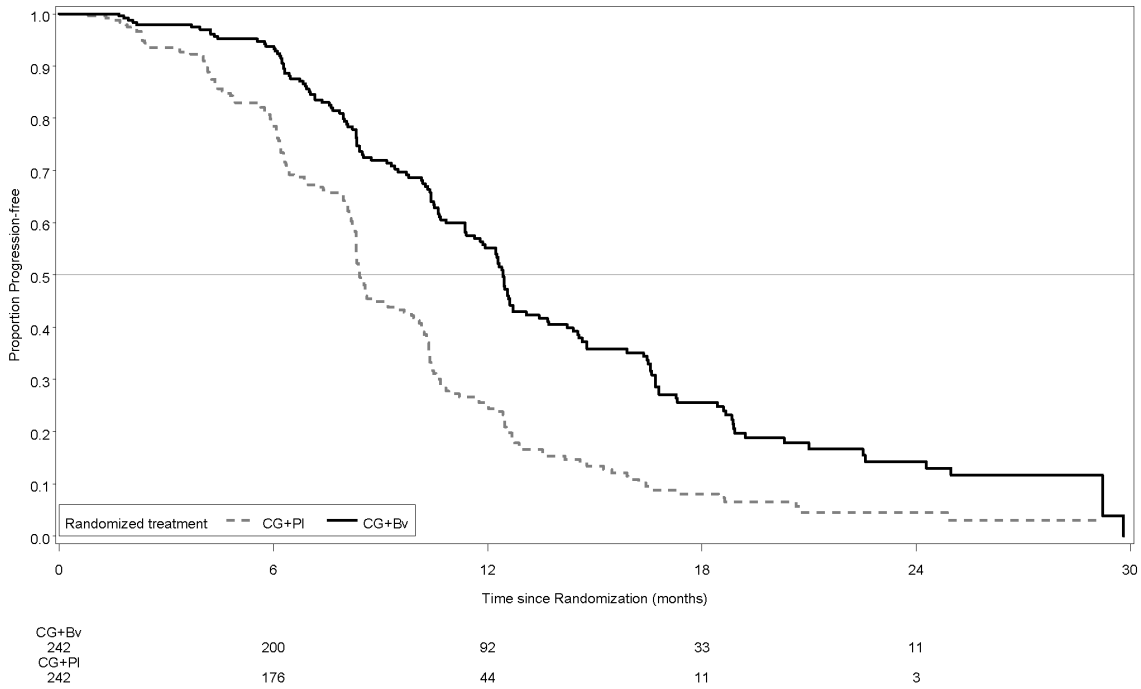
The median age was 61 years (28 to 87 years) and 37% of patients were ≥65 years. All patients had measurable disease at baseline, 74% had baseline CA-125 levels >ULN (35 U/mL). The platinum-free interval (PFI) was 6 months to 12 months in 42 % of patients and >12 months in 58% of patients. The ECOG performance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

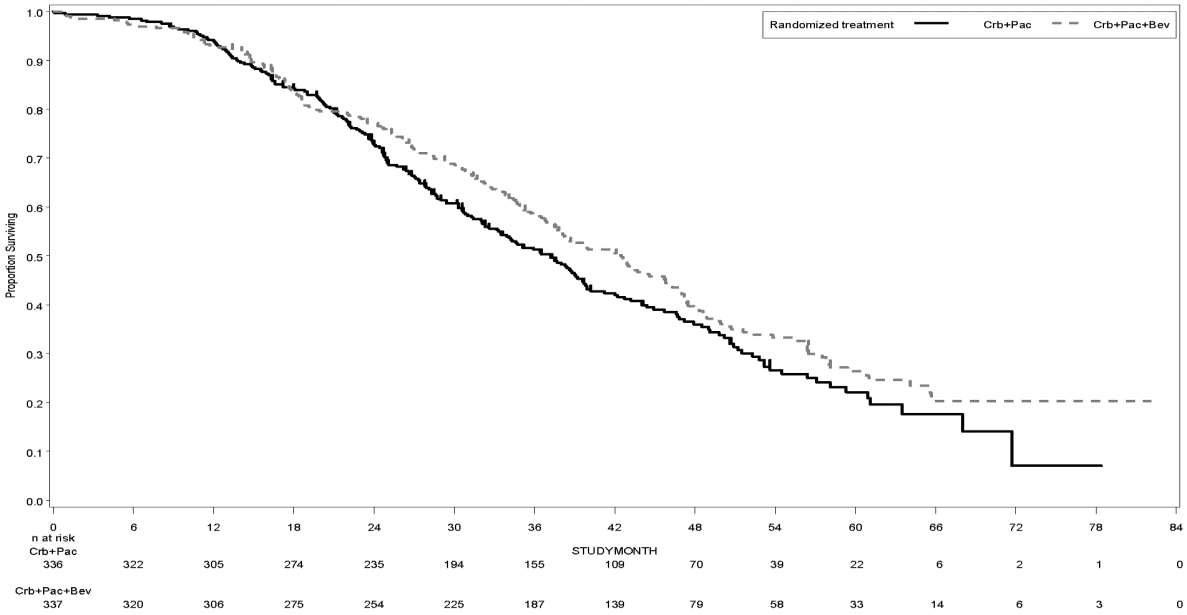
Results are presented in Table 19 and Figure 9.

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.

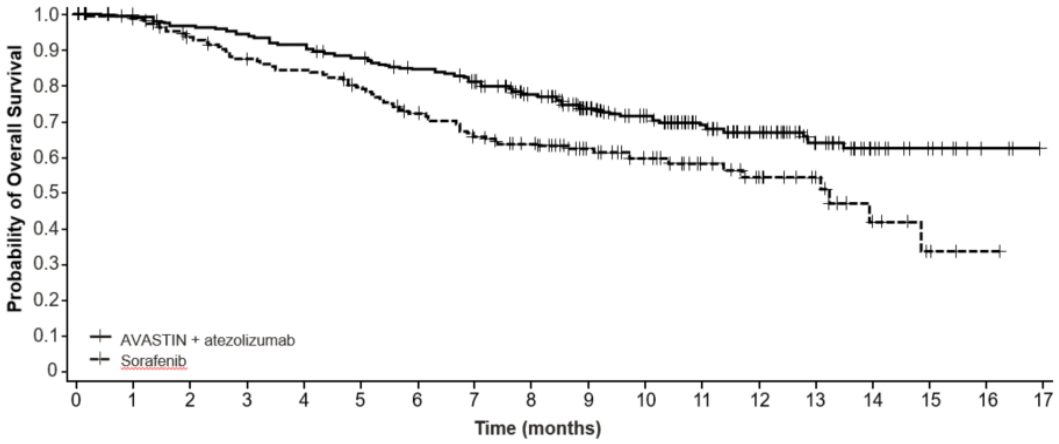
Efficacy results are presented in Table 20 and Figure 10.

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



No. of Patients at Risk

AVASTIN + atezolizumab	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

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 (25 mg/mL): carton of one vial (NDC 50242-060-01)
- 400 mg/16 mL (25 mg/mL): carton of one vial (NDC 50242-061-01)

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 healthcare 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. Instruct patients not to undergo surgery without first discussing this potential risk with their healthcare provider *[see Warnings and Precautions (5.2)]*.

Hemorrhage: Avastin can increase the risk of hemorrhage. Advise patients to immediately contact their healthcare 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 healthcare 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 healthcare 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 healthcare 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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