GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

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A SPECIAL MEETING REVIEW EDITION

Highlights in Hepatocellular Carcinoma From the 2021 European Society for Medical Oncology Congress

A Review of Selected Presentations From the ESMO Congress • September 16-21, 2021

Special Reporting on:

- IMbrave150: Exploratory Efficacy and Safety Results in Patients With Hepatocellular Carcinoma Without Macrovascular Invasion or Extrahepatic Spread Treated With Atezolizumab + Bevacizumab or Sorafenib
- IMMUTACE: A Phase 2 Single-Arm, Open-Label Study of Transarterial Chemoembolization in Combination With Nivolumab Performed for Intermediate-Stage Hepatocellular Carcinoma
- Prognostic Factor Analysis of Atezolizumab-Bevacizumab in Unresectable Hepatocellular Carcinoma: Korean Cancer Study Group Study
- Updated Survival and Secondary Safety and Efficacy Analyses From CA 209-678: A Phase 2, Open-Label, Single-Center Study of Y90-Radioembolization in Combination With Nivolumab in Asian Patients With Advanced Hepatocellular Carcinoma
- A Phase 2 Clinical Trial of the Phosphatidylserine-Targeting Antibody Bavituximab in Combination With Pembrolizumab in Patients With Advanced Hepatocellular Carcinoma

PLUS Meeting Abstract Summaries

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IN 1L UNRESECTABLE OR mHCC

THE STRENGTH OF SUPERIOR SURVIVAL

The first and only cancer immunotherapy combination to demonstrate sustained survival benefit vs sorafenib, **with updated data available**

- Primary analysis: median OS was not reached with TECENTRIQ + Avastin vs 13.2 months with sorafenib (HR=0.58; 95% CI, 0.42, 0.79; *P*=0.0006)[1]

See pivotal data and updated OS results based on follow-up analysis.

NCCN CATEGORY 1, PREFERRED OPTION

Atezolizumab (TECENTRIQ) + bevacizumab (Avastin) is the only preferred first-line systemic therapy option (Category 1) for patients with unresectable or metastatic hepatocellular carcinoma (Child-Pugh Class A) in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[2*†]

*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 Guidelines® for detailed recommendations.

†Category 1: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

1L=first line; CI=confidence interval; HR=hazard ratio; mHCC=metastatic hepatocellular carcinoma; NCCN=National Comprehensive Cancer Network; OS=overall survival.

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

Indication

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

Important Safety Information

Serious Adverse Reactions

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

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 a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, they can also manifest after discontinuation of treatment.

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 additional Important Safety Information and Brief Summary of Prescribing Information on following pages.

Median follow-up of 8.6 months

UNPRECEDENTED OVERALL SURVIVAL IN 1L UNRESECTABLE OR mHCC[1]

TECENTRIQ + Avastin (bevacizumab) (n=336)		Sorafenib (n=165)
MEDIAN OS NOT REACHED (95% CI, NE, NE)	VS	**13.2 MONTHS** (95% CI, 10.4, NE)

HR=0.58 (95% CI, 0.42, 0.79; *P*=0.0006)

- OS was a coprimary endpoint

Coprimary endpoint: significantly improved progression-free survival[1]

- 6.8 months median PFS with TECENTRIQ + Avastin (95% CI, 5.8, 8.3) vs 4.3 months with sorafenib (95% CI, 4.0, 5.6) (HR=0.59; 95% CI, 0.47, 0.76; *P*<0.0001)*

Secondary endpoint: more than double the overall response rate vs sorafenib[1*†]

- 28% ORR with TECENTRIQ + Avastin (n=93/336; 95% CI, 23, 33) vs 12% with sorafenib (n=19/165; 95% CI, 7, 17) (*P*<0.0001)
  - 7% of patients demonstrated a complete response vs 0% with sorafenib, while 21% of patients demonstrated a partial response vs 12% with sorafenib

IMbrave150 was a Phase III, multicenter, international, open-label, randomized trial that compared TECENTRIQ + Avastin to sorafenib in 501 patients with locally advanced unresectable and/or metastatic HCC who had not received prior systemic therapy. Patients were randomized (2:1) to receive either TECENTRIQ 1200 mg IV followed by Avastin 15 mg/kg IV on the same day q3w or 400 mg sorafenib given orally twice daily, until disease progression or unacceptable toxicity. The major efficacy outcome measures were OS and IRF-assessed PFS per RECIST v1.1 in the ITT population. Key secondary endpoints included ORR‡ and DoR.[1,3‡]

ADA=antidrug antibody; 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; PFS=progression-free survival; q3w=every 3 weeks; RECIST=Response Evaluation Criteria In Solid Tumors.

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

Additional OS analysis[1]

- Exploratory analyses showed that the subset of patients (20%) who were ADA positive by Week 6 appeared to have reduced efficacy as compared to patients (80%) who tested negative for treatment-emergent ADA by Week 6. ADA-positive patients by Week 6 appeared to have similar OS compared to sorafenib-treated patients. However, the analyses were inconclusive due to the low number of events in ADA subgroups

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 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

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 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

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 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 1 patient and withholding of TECENTRIQ in 1 patient. Systemic corticosteroids were required in 81% (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

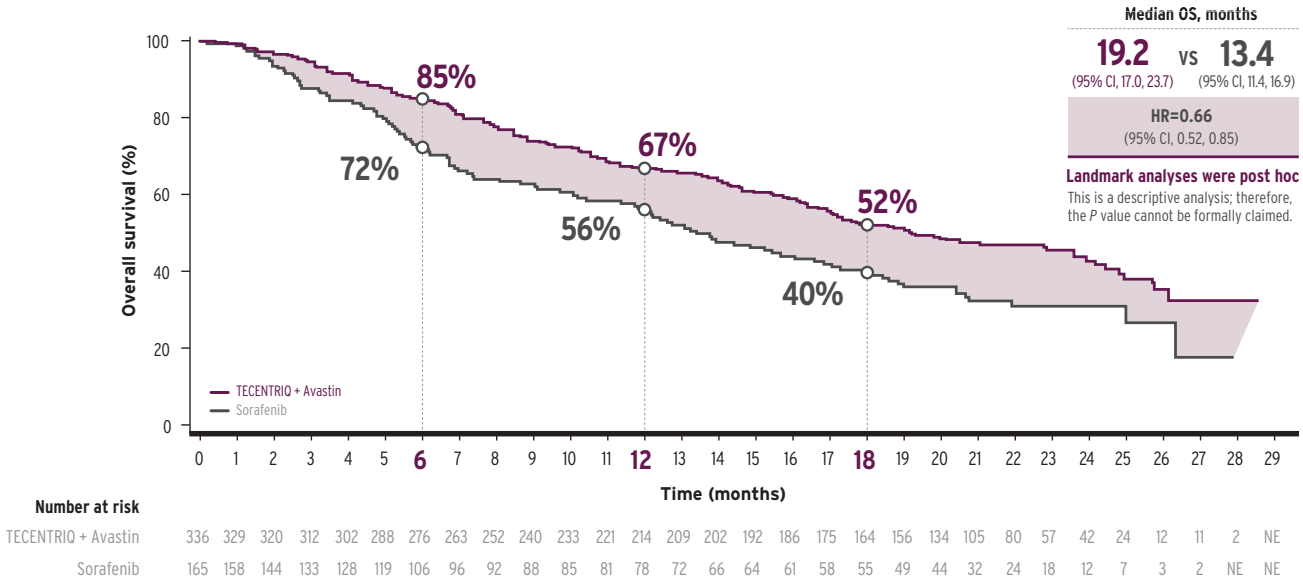
- TECENTRIQ can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated
- Hypophysitis occurred in <0.1% (2/2616) of patients receiving TECENTRIQ as a single agent, including Grade 2 (1 patient, <0.1%) adverse reactions.

Please see additional Important Safety Information and Brief Summary of Prescribing Information on following pages.

Median follow-up of 15.6 months

DESCRIPTIVE FOLLOW-UP ANALYSIS: NUMERICAL IMPROVEMENT OF 5.8 MONTHS IN MEDIAN OS

TECENTRIQ + Avastin OS data vs sorafenib[4]



Number at risk

TECENTRIQ + Avastin	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

Landmark analyses were not powered to demonstrate statistically significant differences and no conclusions can be drawn from these analyses. The OS rates at 6, 12, and 18 months were estimated with the use of Kaplan-Meier methodology for each treatment arm.

Important Safety Information (cont'd)

Immune-Mediated Endocrinopathies (cont'd)

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

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 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 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 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, 1 patient reinitiated TECENTRIQ; this patient did not have recurrence of hyperthyroidism
- 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

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 as a single agent, 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

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

IMPORTANT SAFETY INFORMATION (CONT'D)

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 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

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
- 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 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

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 as a single agent, 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 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 Brief Summary of TECENTRIQ Prescribing Information on following pages, and full Avastin Prescribing Information for additional Important Safety Information.

References: 1. TECENTRIQ Prescribing Information. Genentech, Inc. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hepatobiliary Cancers V.2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed April 16, 2021. To view the most recent and complete version of the guideline, go online to www.NCCN.org. **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.** Data on file. Genentech, Inc.

TECENTRIQ® [atezolizumab]

Initial U.S. Approval: 2016

This is a brief summary of information about TECENTRIQ. Before prescribing, please see full Prescribing Information.

1 INDICATIONS AND USAGE

1.1 Urothelial Carcinoma

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

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

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

1.2 Non-Small Cell Lung Cancer

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

1.3 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).

1.4 Hepatocellular Carcinoma

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

1.5 Melanoma

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

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.

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 81% (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. 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.

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.

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.

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.

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)]*

6.1 Clinical Trials Experience

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

The data described in WARNINGS AND PRECAUTIONS reflect exposure to TECENTRIQ as a single-agent in 2616 patients in two randomized, active-controlled studies (POPLAR, OAK) and four open-label, single arm studies (PCD4989g, IMvigor210, BIRCH, FIR) which enrolled 524 patients with metastatic urothelial carcinoma, 1636 patients with metastatic NSCLC, and 456 patients with other tumor types. TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks in all studies except PCD4989g. Among the 2616 patients who received a single-agent TECENTRIQ, 36% were exposed for longer than 6 months and 20% were exposed for longer than 12 months. Using the dataset described for patients who received TECENTRIQ as a single-agent, the most common adverse reactions in ≥ 20% of patients were fatigue/asthenia (48%), decreased appetite (25%), nausea (24%), cough (22%), and dyspnea (22%).

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

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.

Urothelial Carcinoma

Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

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

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

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

TECENTRIQ was discontinued for adverse reactions in 4.2% of patients. The adverse reactions leading to discontinuation were diarrhea/colitis (1.7%), fatigue (0.8%), hypersensitivity (0.8%), and dyspnea (0.8%). Adverse reactions leading to interruption occurred in 35% of patients; the most common (≥ 1%) were intestinal obstruction, fatigue, diarrhea, urinary tract infection, infusion-related reaction, cough, abdominal pain, peripheral edema, pyrexia, respiratory tract infection, upper respiratory tract infection, creatinine increase, decreased appetite, hyponatremia, back pain, pruritus, and venous thromboembolism.

Tables 4 and 5 summarize the adverse reactions and Grades 3–4 selected laboratory abnormalities, respectively, in patients who received TECENTRIQ in IMvigor210 (Cohort 1).

Table 4: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

Adverse Reaction	TECENTRIQ N = 119	
	All Grades (%)	Grades 3–4 (%)
General		
Fatigue[1]	52	8
Peripheral edema[2]	17	2
Pyrexia	14	0.8
Gastrointestinal		
Diarrhea[3]	24	5
Nausea	22	2
Vomiting	16	0.8
Constipation	15	2
Abdominal pain[4]	15	0.8
Metabolism and Nutrition		
Decreased appetite[5]	24	3
Musculoskeletal and Connective Tissue		
Back/Neck pain	18	3
Arthralgia	13	0
Skin and Subcutaneous Tissue		
Pruritus	18	0.8
Rash[6]	17	0.8
Infections		
Urinary tract infection[7]	17	5
Respiratory, Thoracic, and Mediastinal		
Cough[8]	14	0
Dyspnea[9]	12	0

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

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

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

Graded per NCI CTCAE v4.0.

Non-Small Cell Lung Cancer (NSCLC)

IMpower110

The safety of TECENTRIQ was evaluated in IMpower110, a multicenter, international, randomized, open-label study in 549 chemotherapy-naïve patients with stage IV NSCLC, including those with EGFR or ALK genomic tumor aberrations. Patients received TECENTRIQ 1200 mg every 3 weeks (n=286) or platinum-based chemotherapy consisting of carboplatin or cisplatin with either pemetrexed or gemcitabine (n=263) until disease progression or unacceptable toxicity *[see Clinical Studies (14.2)]*. IMpower110 enrolled patients whose tumors express PD-L1 (PD-L1 stained ≥ 1% of tumor cells [TC] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 1% of the tumor area). The median duration of exposure to TECENTRIQ was 5.3 months (0 to 33 months).

Fatal adverse reactions occurred in 3.8% of patients receiving TECENTRIQ; these included death (reported as unexplained death and death of unknown cause), aspiration, chronic obstructive pulmonary disease, pulmonary embolism, acute myocardial infarction, cardiac arrest, mechanical ileus, sepsis, cerebral 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 (14.2)]*. The median duration of exposure to TECENTRIQ was 8.3 months in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin.

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

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

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

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

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

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

Adverse Reaction	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin N = 393		Bevacizumab, Paclitaxel and Carboplatin N = 394	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Nervous System				
Neuropathy[1]	56	3	47	3
Headache	16	0.8	13	0
General				
Fatigue/Asthenia	50	6	46	6
Pyrexia	19	0.3	9	0.5
Skin and Subcutaneous Tissue				
Alopecia	48	0	46	0
Rash[2]	23	2	10	0.3
Musculoskeletal and Connective Tissue				
Myalgia/Pain[3]	42	3	34	2
Arthralgia	26	1	22	1
Gastrointestinal				
Nausea	39	4	32	2
Diarrhea[4]	33	6	25	0.5
Constipation	30	0.3	23	0.3
Vomiting	19	2	18	1
Metabolism and Nutrition				
Decreased appetite	29	4	21	0.8
Vascular				
Hypertension	25	9	22	8
Respiratory				
Cough	20	0.8	19	0.3
Epistaxis	17	1	22	0.3
Renal				
Proteinuria[5]	16	3	15	3

Graded per NCI CTCAE v4.0

[1] Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, 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
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 (14.2)]*. Among patients receiving TECENTRIQ, 55% were exposed for 6 months or longer and 3.5% were exposed for greater than one year.

Fatal adverse reactions occurred in 5.3% of patients receiving TECENTRIQ; these included 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 (14.2)]*. A total of 609 patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel (n=578) 75 mg/m^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 (14.4)]*. Among 198 patients receiving TECENTRIQ, 32% were exposed for 6 months or longer and 12% were exposed for 12 months or longer.

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

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

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

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

Tables 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 (14.5)]*. Patients received 1,200 mg of TECENTRIQ intravenously followed by 15 mg/kg bevacizumab (n=329) every 3 weeks, or 400 mg of sorafenib (n=156) given orally twice daily, until disease progression or unacceptable toxicity. The median duration of exposure to TECENTRIQ was 7.4 months (range: 0-16 months) and to bevacizumab was 6.9 months (range: 0-16 months).

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

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

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

Adverse reactions leading to interruption of TECENTRIQ occurred in 41% of patients in the TECENTRIQ and bevacizumab arm; the most common (≥ 2%) were liver function laboratory abnormalities including increased transaminases, bilirubin, or alkaline 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				
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 (14.5)]*. 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 (%)	Grades 3–4 (%)	All Grades (%)	Grades 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 (%)	Grades 3–4 (%)	All Grades (%)	Grades 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.

6.2 Immunogenicity

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

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

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

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

Among 315 ADA-evaluable patients with HCC who received TECENTRIQ and bevacizumab in IMbrave150, 28% (n=88) tested positive for treatment-emergent ADA at one or more post-dose time points and 66% (58/88) of these 88 patients tested ADA-positive prior to receiving the third dose of TECENTRIQ. The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA had lower systemic atezolizumab exposure as compared to patients who were ADA-negative *[see Clinical Pharmacology (12.3)]*. Exploratory analyses showed that the subset of patients who were ADA-positive by week 6 (20%; 58/288) appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 6; *[see Clinical Studies (14.5)]*. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 218 ADA-evaluable patients with melanoma who received TECENTRIQ in combination with cobimetinib and vemurafenib in IMspire150, 13% (n=29) tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA had decreased systemic atezolizumab exposure *[see Clinical Pharmacology (12.3)]*. There are insufficient numbers of patients with positive ADA to determine whether ADA alters the efficacy or incidence or severity of adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

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

Infertility

Females

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

8.4 Pediatric Use

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

The safety and antitumor activity 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.

In pediatric patients who received TECENTRIQ 15 mg/kg with a maximum dose of 1200 mg every 3 weeks, the steady-state exposure (AUC) of atezolizumab in pediatric patients aged 12 years or older was comparable to that in adult patients who received TECENTRIQ 1200 mg every 3 weeks, while the exposure trended lower in pediatric patients less than 12 years old.

8.5 Geriatric Use

Of 2616 patients with metastatic urothelial carcinoma, 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.

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)]*.

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IMbrave150: Exploratory Efficacy and Safety Results in Patients With Hepatocellular Carcinoma Without Macrovascular Invasion or Extrahepatic Spread Treated With Atezolizumab + Bevacizumab or Sorafenib

The global, open-label phase 3 IMbrave150 trial evaluated the combination of atezolizumab, a programmed death ligand-1 inhibitor, plus bevacizumab among patients with previously untreated, unresectable hepatocellular carcinoma (HCC).[1] The combination of atezolizumab (1200 mg) plus bevacizumab (15 mg/kg) was administered every 3 weeks, and sorafenib (400 mg) was administered twice daily. The primary endpoints were overall survival (OS) and progression-free survival (PFS), evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[2]

The intention-to-treat population consisted of 336 patients in the atezolizumab/bevacizumab arm and 165 in the sorafenib arm. The primary analysis revealed a superior survival benefit with atezolizumab plus bevacizumab vs sorafenib (hazard ratio [HR] for death, 0.58; 95% CI, 0.42-0.70; *P*<.001).[1] The 12-month OS was 67.2% with atezolizumab plus bevacizumab vs 54.6% with sorafenib. The median PFS was 6.8 months vs 4.3 months, respectively (HR, 0.59; 95% CI, 0.47-0.76; *P*<.001). After an additional 12 months of follow-up, the median OS was 19.2 months with atezolizumab plus bevacizumab vs 13.4 months with sorafenib.[3] The median PFS was 6.9 months vs 4.3 months, respectively.

The rates of grade 3/4 adverse events (AEs) were similar in the 2 treatment arms. Grade 3/4 hypertension was observed in 15.2% of patients in the atezolizumab/bevacizumab arm vs 12.2% of those in the sorafenib arm. The trial established the combination of atezolizumab plus bevacizumab as the standard of care for the first-line treatment of unresectable HCC.

An exploratory analysis of the updated data from the IMbrave150 study compared the safety and efficacy of atezolizumab plus bevacizumab vs sorafenib in the subgroup of patients with Barcelona Clinic Liver Cancer (BCLC) stage B or C disease who did not have extrahepatic spread or macrovascular invasion.[4] The study evaluated data for 70 patients in the atezolizumab/bevacizumab arm and 38 patients in the sorafenib arm. The efficacy analysis included 66 patients and 37 patients, respectively. The base-

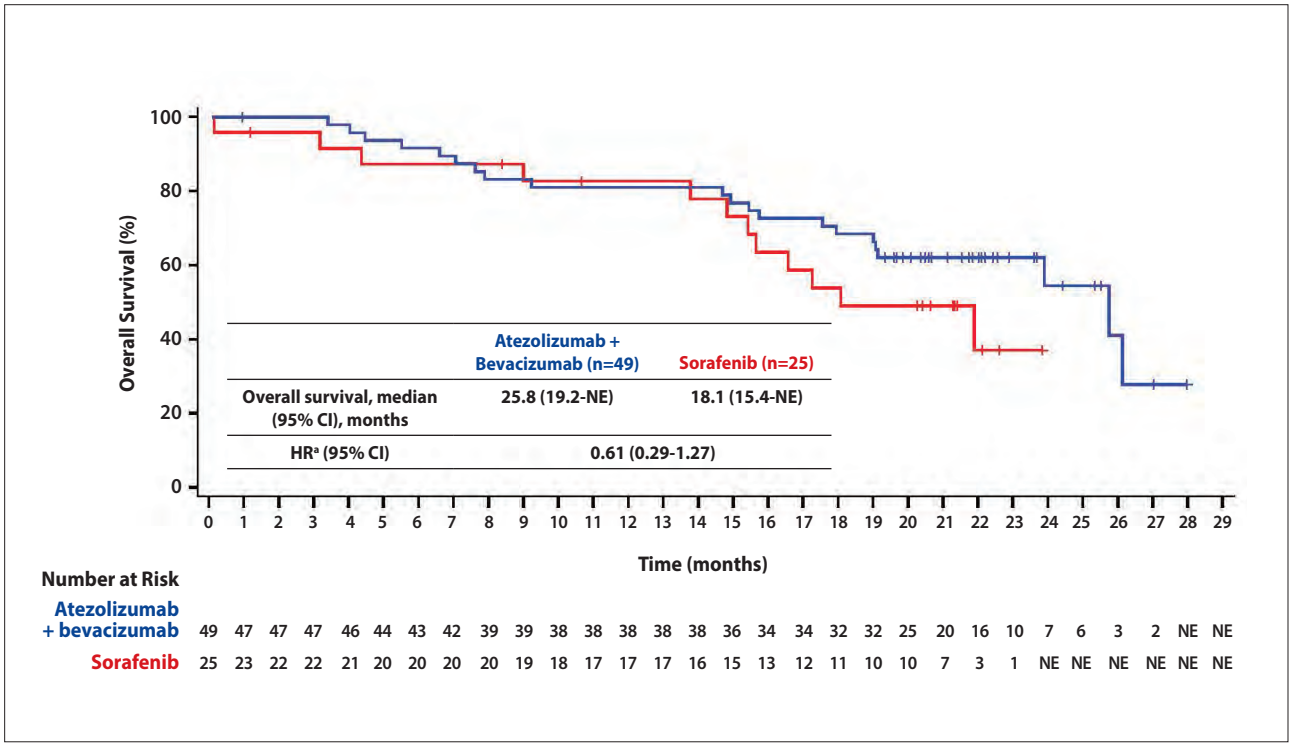

Figure 1. Overall survival among patients with BCLC stage B disease, in a subgroup analysis of the phase 3 IMbrave150 trial, which evaluated atezolizumab plus bevacizumab in patients with previously untreated, unresectable hepatocellular carcinoma. [a]The HR is unstratified.
BCLC, Barcelona Clinic Liver Cancer; HR, hazard ratio; NE, not evaluable. Adapted from Kudo M et al. ESMO abstract 932P. *Ann Oncol.* 2021;32(suppl 5).[4]

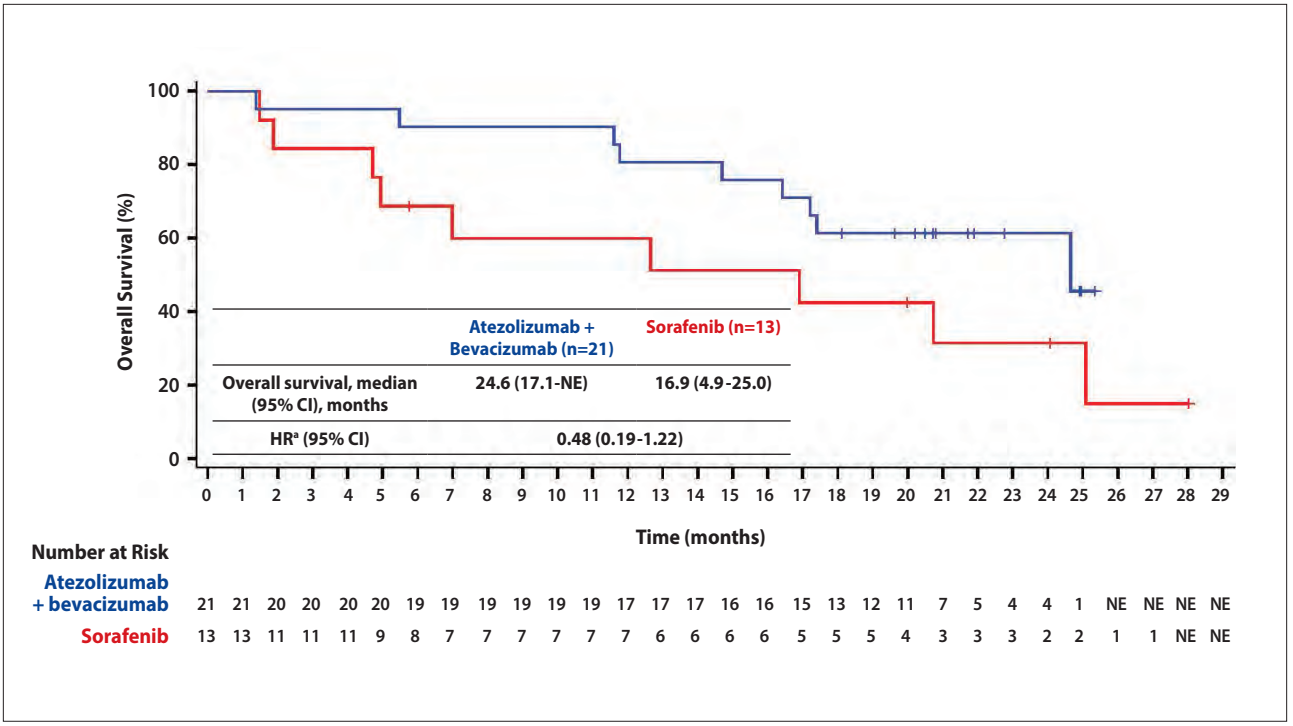

Figure 2. Overall survival among patients with BCLC stage C disease, in a subgroup analysis of the phase 3 IMbrave150 trial, which evaluated atezolizumab plus bevacizumab in patients with previously untreated, unresectable hepatocellular carcinoma. [a]The HR is unstratified. BCLC, Barcelona Clinic Liver Cancer; HR, hazard ratio; NE, not evaluable. Adapted from Kudo M et al. ESMO abstract 932P. *Ann Oncol.* 2021;32(suppl 5).[4]

line characteristics were generally well-balanced across the 2 arms. Among patients treated with atezolizumab plus bevacizumab, the etiology of HCC was nonviral in 46% of patients, associated with hepatitis B virus in 29% of patients, and associated with hepatitis C virus in 26% of patients. BCLC stage B disease was reported in 70% of patients, and 30% had BCLC stage C disease. In the sorafenib arm, the etiology of HCC was nonviral in 42% of patients, linked to hepatitis B virus in 24%, and linked to hepatitis C virus in 34% of patients. Two-thirds of patients had BCLC stage B disease, and one-third had BCLC stage C disease. Previous treatment with transarterial chemoembolization (TACE) was reported in 44% of patients in the atezolizumab/bevacizumab arm vs 53% in the sorafenib arm.

Among patients with BCLC stage B disease, the exploratory analysis yielded a median OS of 25.8 months with atezolizumab plus bevacizumab vs 18.1 months with sorafenib (HR, 0.61; 95% CI, 0.29-1.27; Figure 1).[4] Among patients with BCLC stage C disease, the median OS was 24.6 months vs 16.9 months, respectively (HR, 0.48; 95% CI, 0.19-1.22; Figure 2). Among patients with BCLC stage B disease, the median PFS was 12.6 months vs 8.6 months, respectively (HR, 0.63; 95% CI, 0.36-1.10). In patients with BCLC stage C disease, the median PFS was 7.0 months vs 4.8 months (HR, 0.83; 95% CI, 0.36-1.88). Based on RECIST 1.1, the confirmed objective response rate (ORR) was 43% with atezolizumab/bevacizumab vs 25% with sorafenib in patients with BCLC stage B HCC. The confirmed ORR was 15% in both cohorts of patients with BCLC stage C disease.

The safety profile of the atezolizumab/bevacizumab regimen was consistent with the known safety profiles of the individual antibodies. Grade 3/4 AEs were reported in 70% of patients treated with atezolizumab plus bevacizumab and 65% of those treated with sorafenib. AEs led to dose modification or interruption of any study treatment among 65% of patients in both treatment arms.

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IMMUTACE: A Phase 2 Single-Arm, Open-Label Study of Transarterial Chemoembolization in Combination With Nivolumab Performed for Intermediate-Stage Hepatocellular Carcinoma

Real-world data show that 60% of patients with intermediate-stage HCC are treated with TACE.[1] The treatment is not curative, and the median OS is less than 20 months.[1] Local treatment increases the release of antigens, and therefore the addition of nivolumab to TACE could provide synergistic antitumor activity. The open-label, single-arm phase 2 IMMUTACE study investigated the safety and efficacy of TACE combined with nivolumab among patients with intermediate-stage HCC.[2] The trial enrolled patients with histologically confirmed, intermediate-stage HCC, an Eastern Cooperative Oncology Group (ECOG) score of 0 to 2, and a Child-Pugh score of A. The patients could have limited metastatic disease. The primary objective was the ORR, with an ORR of 55% or greater considered promising enough for further investigation. The secondary objectives included PFS, time to failed strategy, OS, quality of life, and safety. Patients received an initial TACE treatment, followed by nivolumab within 2 to 3 days. Nivolumab (240 mg) was administered every 2 weeks until the patient developed progressive disease. A second TACE procedure was permitted, based on the investigator's decision. PFS was evaluated after the first indication of disease progression.

The patients were a median age of 66 years (range, 42-83 years), and 81.6% were male.[2] The ECOG performance status was 0 in 85.7% of

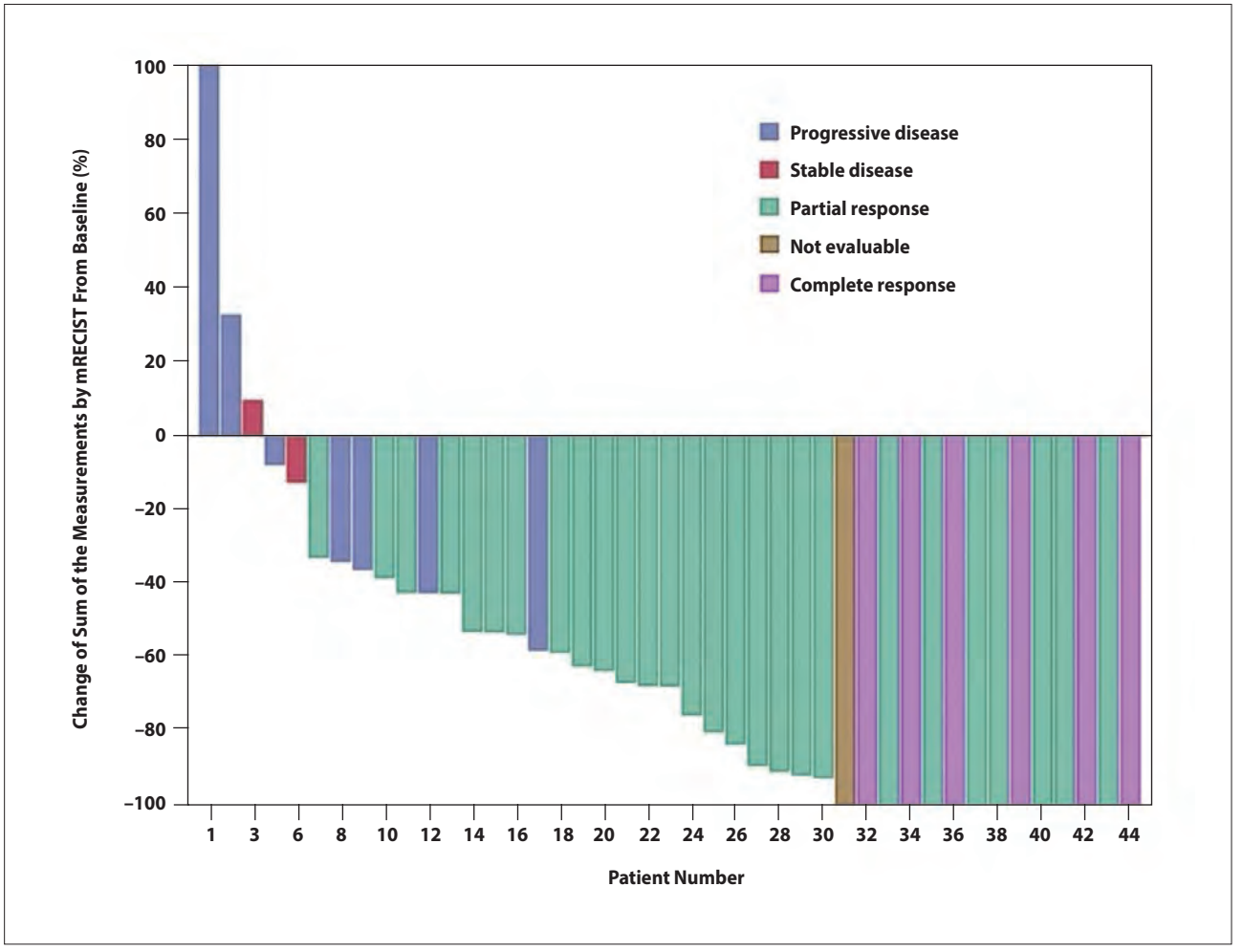

Figure 3. Response in the open-label, single-arm, phase 2 IMMUTACE study, which evaluated TACE combined with nivolumab in patients with intermediate-stage hepatocellular carcinoma. mRECIST, modified Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization. Adapted from Vogel A et al. ESMO abstract LBA37. *Ann Oncol.* 2021;32(suppl 5).[2]

patients and 1 in 14.3%. Nonviral etiology was reported in 69.4% of patients. HCC was associated with hepatitis B virus in 8.2% of patients and hepatitis C virus in 14.3% of patients. Previous therapies included resection (22%) and radiotherapy (2%). The patients had a median of 3 tumors (range, 1-12), and the median tumor size was 3 cm (range, 0.6-14.7). The BCLC stage was A in 18.4%, B in 59.2%, and C in 2.0%.

The ORR was 71.4% (95% CI, 56.8%-83.4%), which consisted of complete responses (CRs) in 16.3% and partial responses (PRs) in 55.1% (Figure 3). A subgroup analysis did not identify any differences in treatment response, although the number of patients in each group was small.

Treatment was generally well tolerated.[2] The most common AEs of any grade were fatigue (30.6%), increase in aspartate aminotransferase (24.5%), and increase in alanine aminotransferase (22.4%). The most common AEs of grade 3 or higher were increases in aspartate aminotransferase (14.3%), gamma-glutamyl transferase (10.2%), and alanine aminotransferase (8.2%). An ongoing correlative analysis is evaluating whether treatment efficacy corresponds with genetic alterations, gene expression patterns, and/or changes in immune cell populations.

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Prognostic Factor Analysis of Atezolizumab-Bevacizumab in Unresectable Hepatocellular Carcinoma: Korean Cancer Study Group Study

In the phase 3 IMbrave150 trial, atezolizumab plus bevacizumab improved PFS and OS in patients with previously untreated, unresectable HCC.[1] A retrospective, multicenter analysis by the Korean Cancer Study Group evaluated real-world data to identify prognostic factors among patients with advanced HCC treated with first-line atezolizumab plus bevacizumab.[2]

The trial enrolled 121 patients with a Child-Pugh score of A5 (74.4%) or A6 (25.6%) and BCLC stage B (20.7%) or C (79.3%) disease.[2] Their median age was 61 years, and most patients (84%) were male. Macrovascular invasion was reported in 37.2% of patients, and 70.2% of patients had extrahepatic spread. The cause of HCC was hepatitis B in 76.9% and hepatitis C in 5%. Prior treatment included TACE in 57.9% of patients, radiotherapy in 37.2%, surgery in 31.4%, and radiofrequency ablation in 14.9%.

The ORR was 24.0%, with a CR rate of 1.7%.[2] The median OS was not reached (95% CI, not evaluable; Figure 4), and the median PFS was 6.5 months (95% CI, 4.1-9.0). Based on multivariate analysis, the PFS and OS were significantly better in patients with a neutrophil-to-lymphocyte ratio of less than 5 (Figure 5). The hazard ratio for the neutrophil-to-lymphocyte ratio (≥5 vs <5) was 2.23 (95% CI, 1.12-4.45; *P*=.023) for PFS and 4.68 (95% CI, 1.87-11.73; *P*<.001) for OS. The median PFS was superior in patients who achieved a CR or PR vs those with stable or progressive disease (*P*<.001), as well as in those with an increase in alpha-fetoprotein vs those with a decrease (*P*=.002).

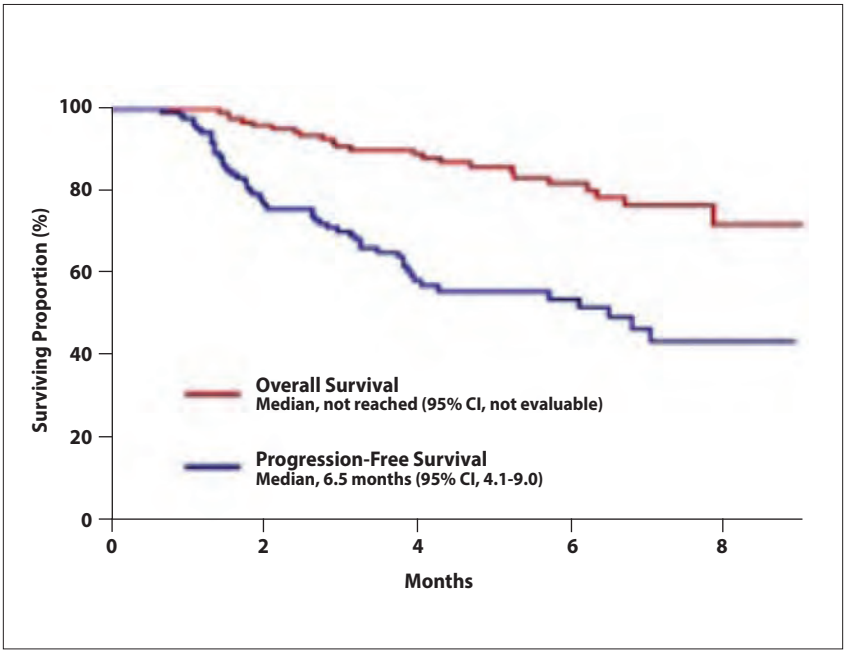

Figure 4. Overall and progression-free survival in a retrospective, multicenter analysis of patients with advanced hepatocellular carcinoma treated with first-line atezolizumab plus bevacizumab. Adapted from Cheon J et al. ESMO abstract 955P. *Ann Oncol*. 2021;32(suppl 5).[2]

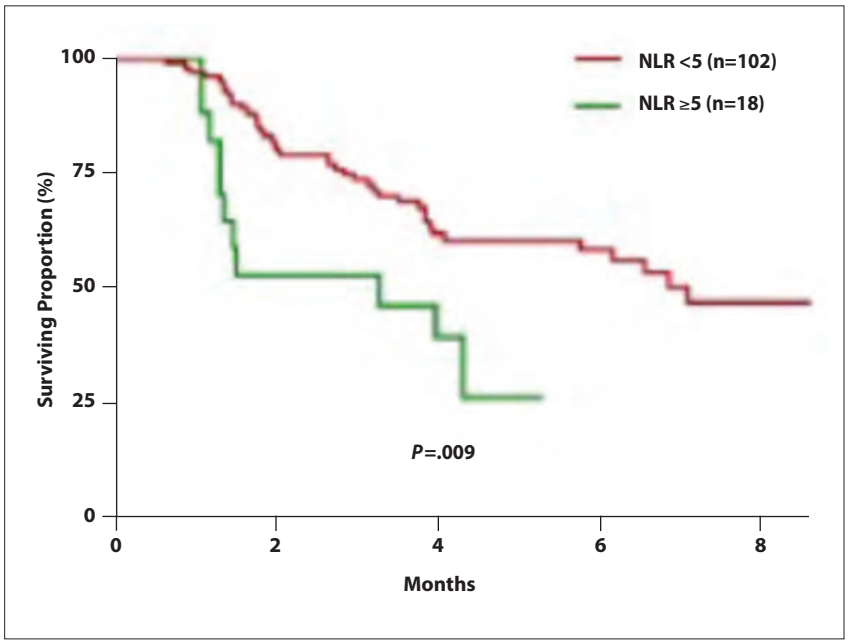

Figure 5. Median progression-free survival according to the NLR in a retrospective, multicenter analysis of patients with advanced hepatocellular carcinoma treated with first-line atezolizumab plus bevacizumab. NLR, neutrophil-to-lymphocyte ratio. Adapted from Cheon J et al. ESMO abstract 955P. *Ann Oncol.* 2021;32(suppl 5).[2]

A grade 3/4 AE was reported in 28.9%. The most common grade 3/4 AEs were elevated aspartate aminotransferase in 10.7%, hypertension in 6.6%, and thrombocytopenia in 4.9%.

The study investigators concluded that the results of their real-world analysis were similar to those reported in the IMbrave150 trial.[1,2] They noted that careful assessment of treatment response is needed in patients with an elevated neutrophil-to-lymphocyte ratio, who had lower survival outcomes in this analysis.

References

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Updated Survival and Secondary Safety and Efficacy Analyses From CA 209-678: A Phase 2, Open-Label, Single-Center Study of Y90-Radioembolization in Combination With Nivolumab in Asian Patients With Advanced Hepatocellular Carcinoma

As separate therapies, nivolumab and Yttrium-90 (Y90) are effective in patients with advanced HCC.[1,2] Previous data have suggested that there may be synergy between these 2 treatments.[3] The open-label, single-center phase 2 CA 209-678 trial investigated Y90 embolization combined with nivolumab in patients with advanced HCC.[4]

The trial enrolled 40 patients, of whom 36 were evaluable.[4] All patients had a Child-Pugh score of A and were not candidates for curative surgery. The patients' median age was 64 years (range, 23-79 years), 78% were male, and 69% were of Chinese ethnicity.

The patients received a median of 7 cycles (range, 1-66+) of nivolumab. After a median follow-up of 24.8

Table. Responses in CA 209-678, a Phase 2 Study of Y90 Embolization Combined With Nivolumab in Patients With Advanced Hepatocellular Carcinoma

	Response Rate (95% CI)	Disease Control Rate (95% CI)
Overall population	30.6% (16.4%-48.1%)	61.1% (43.5%-76.9%)
Hepatitis B+ (n=22)	27.3% (10.7%-50.2%)	50.0% (28.2%-71.8%)
Hepatitis B– (n=14)	35.7% (12.8%-64.9%)	78.6% (49.2%-95.3%)
AFP ≤400 ng/mL (n=18)	27.8% (9.7%-53.5%)	66.7% (41.0%-96.7%)
AFP >400 ng/mL (n=18)	33.3% (13.3%-59.0%)	55.6% (30.8%-78.5%)

AFP, alpha-fetoprotein; Y90, Yttrium-90.
Adapted from Lee J et al. ESMO abstract 947P. *Ann Oncol.* 2021;32(suppl 5).[4]

months, the ORR according to RECIST 1.1 was 30.6% and the disease control rate was 61.1%. The median time to response was 3.8 months. The median PFS was 3.6 months (95% CI, 2.1-8.8 months), and the median OS was 16.9 months (95% CI, 8.1-27.6 months). Outcomes differed according to the patient's baseline hepatitis B status and level of alpha-fetoprotein (Table).

Treatment-related AEs occurred in 81% of patients. These events were grade 3/4 in 14% of patients. There were no grade 5 treatment-related AEs. The most common treatment-related AEs were pruritus, which occurred in 50% of patients, and rash, which occurred in 39%.

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A Phase 2 Clinical Trial of the Phosphatidylserine-Targeting Antibody Bavituximab in Combination With Pembrolizumab in Patients With Advanced Hepatocellular Carcinoma

Phosphatidylserine is expressed on the inner leaflet of the plasma membrane of normal cells.[1] However, phosphatidylserine becomes externalized on the outer leaflet of the plasma membrane of tumor cells and other cells in the tumor microenvironment, making it a potential target for therapy. Bavituximab is a chimeric antibody that binds to phosphatidylserine, thus increasing the antitumor immune response.[2] A single-arm, open-label phase 2 study evaluated the combination of bavituximab plus pembrolizumab among patients with advanced HCC.[3]

The trial enrolled patients with locally advanced or metastatic HCC that could not be treated with locoregional therapy. Patients received pembrolizumab (200 mg every 3 weeks) plus bavituximab (3 mg/kg weekly). The primary endpoint was the ORR according to RECIST 1.1, with secondary endpoints of OS, 6-month PFS, duration of response, and safety.[4]

The 25 study participants had a median age of 63.5 years, and 88% were male.[3] Among 16 evaluable patients, the ORR was 31%, with no CRs. PRs were confirmed by radiographic assessment performed at least 4 weeks after the initial assessment.

Pembrolizumab plus bavituximab was generally well tolerated. Most AEs were grade 1 or 2. Grade 1 increased alanine transaminase and grade 2 acute renal insufficiency each occurred in 1 patient. Grade 3/4 AEs included diarrhea and shortness of breath, observed in 1 patient each. The study has a planned enrollment of 28 patients.

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Multicenter Phase 2 Trial of Lenvatinib Plus Hepatic Intra-Arterial Infusion Chemotherapy With Cisplatin for Advanced Hepatocellular Carcinoma: LEOPARD

The phase 2 LEOPARD trial evaluated lenvatinib plus hepatic arterial infusion chemotherapy with cisplatin as first-line therapy in patients with HCC (Abstract 937P). The trial enrolled 36 patients with advanced HCC who were not eligible for TACE, surgical resection, liver transplant, or local ablation. The study therapy yielded an ORR of 64.7%, with a CR rate of 29.4%, based on modified RECIST and central assessment. Using RECIST 1.1 criteria, central assessment showed an ORR of 45.7%, with a CR rate of 8.6%. The median PFS was 6.3 months (95% CI, 5.1-7.9 months), and the median OS was 17.2 months (95% CI, 10.9 months to not evaluable). The most common grade 3/4 AEs were increased aspartate aminotransferase (33%), leukocytopenia (22%), increased alanine aminotransferase (19%), and neutropenia (19%).

Highlights in Hepatocellular Carcinoma From the 2021 European Society for Medical Oncology Congress: Commentary

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Several abstracts presented at the 2021 European Society for Medical Oncology (ESMO) congress provided important insights into the management of patients with hepatocellular carcinoma (HCC). Studies provided new data for treatments such as atezolizumab plus bevacizumab, systemic treatment plus locoregional therapy or resection, and novel regimens.

Atezolizumab Plus Bevacizumab

The combination of atezolizumab plus bevacizumab is at the forefront of recommendations for systemic first-line treatment of patients with HCC. At the 2021 ESMO congress, there were several abstracts that focused on the use of atezolizumab plus bevacizumab, including how this regimen works among various patient populations. Dr Masatoshi Kudo presented an analysis of the phase 3 IMbrave150 study, which compared atezolizumab plus bevacizumab vs sorafenib in patients with advanced HCC.[1,2] Updated results, which were presented at the 2021 American Society of Clinical Oncology Gastrointestinal Cancers symposium, showed that the median overall survival was 19.2 months with atezolizumab plus bevacizumab vs 13.4 months with sorafenib.[3] The median progression-free survival was 6.9 months vs 4.3 months, respectively. The analysis by Dr Kudo and colleagues focused on patients who had Barcelona Clinic Liver Cancer (BCLC) stage B or C disease without macrovascular invasion or extrahepatic spread, who are likely to be early in their disease course.[2] More than half of these patients had undergone locoregional therapy. The analysis showed that atezolizumab plus bevacizumab was still superior to sorafenib in this patient population for both overall survival and progression-free survival. The safety analysis was consistent with the previous data for atezolizumab plus bevacizumab,[1] which was reassuring.

The study separately analyzed outcome for patients with BCLC stage B vs stage C disease, which led to an interesting finding.[2] The benefit of atezolizumab/bevacizumab was greater in patients with BCLC stage C disease. The median overall survival was 24.6 months with atezolizumab/bevacizumab vs 16.9 months with sorafenib, for a hazard ratio of 0.48. It would be expected that patients with BCLC stage B disease are earlier in their disease course and therefore would have a better response to the investigative treatment. For these patients, however, the median overall survival was 25.8 months with atezolizumab/bevacizumab vs 18.1 months with sorafenib, for a hazard ratio of 0.61. The Kaplan-Meier curves crossed each other in this patient population. It should be noted that the population with BCLC stage B disease was small (n=74). For patients with BCLC stage B HCC, treatment often consists of locoregional therapy, which is recommended over systemic therapy in guidelines.[4] There is the possibility that patient characteristics may have impacted response to treatment in the IMbrave150 study. This subgroup analysis of the IMbrave150 trial supports the overall data previously reported for the combination of atezolizumab plus bevacizumab.

Dr Jaekyung Cheon presented results from a real-world study of atezolizumab plus bevacizumab in patients with unresectable HCC from the Korean Cancer Study Group.[5] This study aimed to identify prognostic factors for atezolizumab/bevacizumab. Currently, there are no specific prognostic factors that predict whether a patient will respond to systemic treatment. This multicenter, retrospective analysis included 138 patients. The median overall survival was not reached, and the median progression-free survival was 6.5 months. Many of these patients had viral hepatitis; 77% had hepatitis B and 5% had hepatitis C. There have been some data suggesting that immunotherapies are more effective in patients with viral hepatitis.[6] It was reassuring to see that atezolizumab/bevacizumab was beneficial in these patients. These data support the use of immunotherapy in patients with HCC and viral hepatitis.

This multivariate analysis identified several predictors of survival outcomes. Previous studies have evaluated the potential of the neutrophil-to-lymphocyte ratio (NLR) as a disease biomarker.[7,8] Currently, the application of the NLR is unclear. Patients with a high NLR generally have disease that is more aggressive and that progresses earlier. Studies have used different cutoff values for the NLR. The study by Dr Cheon and colleagues compared outcomes among patients with an NLR of less than 5 vs 5 or higher.[5] Patients with an NLR below 5 had much better overall survival and

progression-free survival. For overall survival, the hazard ratio for the NLR (≥5 vs <5) was 4.68 (95% CI, 1.87-11.73; *P*<.001). For progression-free survival, the hazard ratio was 2.23 (95% CI, 1.12-4.45; *P*=.023). Physicians might consider this finding when deciding whether to proceed with systemic therapy.

This analysis evaluated whether an increase or decrease of alpha-fetoprotein at the first evaluation after treatment could predict prognosis.[5] As expected, patients with a decrease in alpha-fetoprotein had better overall survival and progression-free survival. It might be possible to use this value as a marker early in the course of therapy. The investigators also evaluated prognosis according to best response by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[9] Patients who had a complete response or partial response after treatment with atezolizumab plus bevacizumab had much better overall survival and progression-free survival compared with those who had stable disease or progressive disease. Again, this marker cannot be used until after treatment is initiated.

Systemic Treatment Plus Locoregional Therapy or Resection

Many studies of systemic therapy in HCC are evaluating the use of this treatment earlier in the course of the disease, before patients progress to BCLC stage C and are no longer candidates for more invasive treatments, such as resection or locoregional therapy with transarterial chemoembolization (TACE) or Yttrium-90 (Y90). Presentations at the 2021 ESMO congress included multiple studies that evaluated the combination of systemic treatments with locoregional therapy or resection. In a late-breaking oral abstract, Dr Arndt Vogel presented results from IMMUTACE, a single-arm, phase 2 study of TACE in combination with nivolumab for intermediate-stage HCC.[10] Immunotherapy is very helpful for advanced HCC.[11] The immune system is active earlier in the course of the disease, particularly after locoregional therapies, such as TACE. After local treatments, tumors release more neoantigens. The impact of immunotherapy might be increased if administered when these neoantigens are circulating. The premise behind this study was that a synergistic benefit might be seen if systemic therapies, such as immunotherapy, are combined with a locoregional therapy, such as TACE.

The trial enrolled 49 patients with intermediate-stage HCC. Patients were permitted to have limited metastatic disease. In the United States, locoregional therapy is generally not considered for patients with metastatic disease, except in rare instances. The study's primary objective was to assess the overall response rate. Progression-free survival was a secondary objective.

The patients underwent an initial course of TACE. After they recovered—which took anywhere from a few days to a few weeks—they began treatment with nivolumab. They were able to receive a second course of TACE if needed. Patients with a response to nivolumab continued treatment. Among patients with progressive disease, those who were candidates for further locoregional therapy were permitted to undergo a third course of TACE, ablation, or resection. The treatment strategy was deemed unsuccessful in patients who were not candidates for further locoregional therapy and those who did not respond to the third course of TACE.

The enrolled patients reflected the standard HCC population. Most patients were men, and the median age was 66 years. In general, the patients had a good performance status. Most patients had nonviral hepatitis. Given the concerns regarding the use of immunotherapy in patients with nonviral-related HCC, it was good to see data showing some benefit. The patients had relatively advanced disease. The median number of tumors was 3, with a range of 1 to 12. The median tumor size was 3 cm, and the range was 0.6 cm to almost 15 cm. Most patients had BCLC stage B disease. All patients had Child-Pugh class A disease. The albumin-bilirubin score was 1 in 61.2% of patients and 2 in 34.7% of patients.

The study investigators reported a promising overall response rate of 71.4%, which is better than that expected with either of these treatments alone.[10-12] A complete response was seen in 16.3% of patients, and a partial response occurred in 55.1%.

Adjuvant Camrelizumab Combined With Apatinib Treatment After Resection of Hepatocellular Carcinoma in CNLC II and III Stage: A Single-Center Prospective Phase 2 Trial

A single-center phase 2 trial evaluated adjuvant camrelizumab, which inhibits programmed cell death protein 1, plus apatinib following HCC resection in patients with Chinese National Liver Cancer stage 2 or 3 disease (Abstract 944P). Patients had a median alpha-fetoprotein level of 121.9 ng/mL (interquartile range, 11.3-3745.0 ng/mL) and a mean tumor size of 6.7±3.0 cm. After a median follow-up of 21.5 months, the median relapse-free survival was 11.7 months (95% CI, 5.8-17.6 months). The median OS was not reached. The 1-year relapse-free survival rate was 48.9%, and the 1-year OS was 97.8%. No patient withdrew owing to an AE, and no treatment-related deaths occurred. Grade 3/4 AEs of thrombocytopenia or leukopenia occurred in 1 patient each.

Stable disease was reported in 4.1% of patients, and progressive disease was reported in 14.3%. Safety was a secondary objective. The combination of TACE plus nivolumab was safe, with no unexpected adverse events based on the use of either treatment alone. A subgroup analysis did not identify any groups with particularly better or worse outcomes. However, the low number of enrolled patients may have limited the subgroup analysis. Overall, this study suggests that there may be some benefit to combining immunotherapy with TACE. The data will need to be confirmed in larger prospective, randomized controlled trials, but they are promising.

An open-label, single-center phase 2 trial evaluated the combination of Y90 plus nivolumab.[13] This small study enrolled 40 patients, and 36 were evaluable. Approximately 60% of patients had hepatitis B, so there was a large amount of viral hepatitis in this population. The time to response was 3.8 months. The median progression-free survival was 3.6 months, with a median overall survival of 16.9 months. The overall response rate was approximately 30.6%, and the in-field overall response rate according to RECIST 1.1 was 36.1%.[9] There were no new or unexpected treatment-related adverse events. This combination of locoregional and systemic therapy therefore appears to be safe and has the potential to improve responses in patients with HCC.

An interesting phase 2 study presented by Dr Xin-Rong Yang from Fudan University in Shanghai, China evaluated combination systemic therapy after resection in earlier-stage disease.[14] This study combined camrelizumab, a programmed cell death protein 1 (PD-1) immune checkpoint inhibitor, with apatinib, a tyrosine kinase inhibitor that is more selective to vascular endothelial growth factor receptor 2. These 2 drugs are not routinely used to treat HCC in the United States, although other agents from these classes are used frequently in this setting.

The study enrolled patients who were undergoing resection of HCC.[14] Resection is associated with recurrence rates as high as 70% at 5 years after the procedure. To make resection successful, and even curative, it would be helpful to have adjuvant therapy or neoadjuvant therapy that improves overall survival and recurrence rates. The enrolled patients had pathologically confirmed HCC, with no evidence of extrahepatic metastases. According to protocol, the trial excluded patients with peri-resection mortality, although the number of these patients was not reported. The investigators assessed 76 patients for eligibility and excluded 31 patients for a variety of reasons, including history of other tumor types and issues with baseline laboratory parameters, anticoagulation, and informed consent. A total of 45 patients were allocated to receive a combination of camrelizumab and apatinib after resection of their HCC.

The patients were a median age of 54 years, and most were men. This study also had a very strong viral hepatitis population; 40 out of 45 patients had hepatitis B. The patients had good laboratory parameters and good liver function, as would be expected given that they were undergoing resection. However, the patients had very aggressive disease, as reflected in their characteristics. Among countries in Asia, HCC resection is used much more liberally than in the United States. This is partly because the availability of transplant is more limited in Asia. In addition, many of these patients have hepatitis B and do not have cirrhosis. Their liver function is excellent, so resection can be considered more readily. Among the 45 patients in this study, 19 had portal vein invasion. In the United States, resection would not have been offered to many of these patients.

The median number of tumors was 2, and the mean tumor size was 6.7 cm. Only 13 patients had tumor encapsulation, which is a good prognostic indicator. Many of the patients had more advanced tumor differentiation and a more advanced stage of liver cancer. These patients had advanced HCC for a resection procedure, which provided a good opportunity for the use of a potentially curative therapy.

The median follow-up was 21.5 months.[14] The median recurrence-free survival was 11.7 months, with a recurrence-free survival rate of 48.9% at 1 year and a 1-year overall survival rate of 97.8%. These results are very promising in patients with such advanced tumors.

There were adverse events related to camrelizumab and apatinib, but they did not cause any patient to stop treatment. Adverse events were treated and controlled. This tolerability is also promising.

The study results suggested that the combination of a PD-1 inhibitor and a tyrosine kinase inhibitor could prolong overall survival and potentially improve recurrence-free survival in patients with HCC who are undergoing resection.[14] The data will need to be confirmed in a larger, prospective, randomized clinical trial. However, the promising results raise the possibility that the use of a systemic therapy earlier in the disease may improve outcomes.

Novel Treatments

Several abstracts evaluated new treatments for HCC. Dr David Hsieh presented results of a phase 2 clinical trial of the phosphatidylserine-targeting antibody bavituximab combined with pembrolizumab among patients with HCC.[15] Phosphatidylserine is an immunosuppressive molecule that becomes externalized in cells that line tumor blood vessels and in tumor cells. Phosphatidylserine is active in the tumor microenvironment. Currently, bavituximab is used to modulate the tumor microenvironment by driving innate and adaptive immunity. The addition of bavituximab to pembrolizumab could potentially increase the clinical activity of the latter agent.

The trial enrolled only 25 patients,

and was a pilot study.[15] Bavituximab combined with pembrolizumab did not lead to any complete responses. Partial responses were reported in 31% of patients, and 25% of patients had stable disease. These efficacy results are better than would be expected with pembrolizumab alone in this patient population.[11] Treatment was well tolerated and had a good safety profile. The results of this study hint that by combining this phosphatidylserine-targeting antibody with pembrolizumab, it may be possible to improve the efficacy of PD-1/programmed death ligand 1 therapies.

The phase 2 LEOPARD study, presented by Dr Masafumi Ikeda from Japan, evaluated lenvatinib plus hepatic arterial infusional chemotherapy (HAIC) with cisplatin.[16] In the United States, lenvatinib is used in advanced HCC, but HAIC is not a standard treatment. In Japan and some other countries, HAIC is a frequent treatment for HCC. Physicians strongly recommend this treatment to many patients.

This pilot study enrolled 36 patients. The patients' median age was 68 years. Most patients were male, and they had a good performance status. Approximately one-quarter of patients had hepatitis B, and one-quarter of patients had hepatitis C. Nearly half of patients had portal vein invasion, and approximately a quarter of patients had extrahepatic metastases.

The combination of lenvatinib plus HAIC with cisplatin led to an overall response rate of nearly 65% by modified RECIST assessment and of 45% by RECIST 1.1.[9,16,17] The disease control rate was approximately 75%. The median progression-free survival was 6.3 months, and the median overall survival was 17.2 months. These outcomes are better than those reported in the REFLECT study of lenvatinib monotherapy.[18] Larger, multiphase, randomized, prospective clinical trials are needed to further evaluate the combination of lenvatinib plus HAIC with cisplatin.

Disclosures

Dr Frenette is a member of the advisory boards of Eisai, Exelixis, Genentech, and AstraZeneca. She is a consultant for Bayer, Eisai, Merck, and Genentech. She has received research support from Bayer, Merck, and Exelixis. She was a member of the speakers bureaus (all discontinued June 1, 2021) of Bristol Myers Squibb, Gilead, AbbVie, Eisai, Salix, Exelixis, Genentech, and Intercept. She does not own any stocks or have any other financial interests to report.

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