

Exclusive Coverage of the  
European Society for Medical Oncology Congress 2022

OCTOBER 2022

SEPTEMBER 9-13, 2022 | PARIS, FRANCE

## Patients With Locally Advanced NSCLC Ineligible for Chemoradiotherapy Have Longer OS With Cemiplimab Plus Chemo

Mary Caffrey

**RECENTLY PUBLISHED RESULTS FROM** the phase 3 EMPOWER-Lung 3 trial (NCT03409614) support using cemiplimab with chemotherapy in newly diagnosed patients with locally advanced non-small cell lung cancer (NSCLC). Now, data from a subset of patients in that trial, presented in a poster session during the European Society for Medical Oncology (ESMO) Congress 2022, highlight the combination's ability to address an unmet need.

CONTINUED ON PAGE 11

## MD Anderson's Neil Gross, MD, FACS, on the Importance of Neoadjuvant Immunotherapy Against CSCC

Interview by Maggie L. Shaw

**AMONG A COHORT OF** 79 patients with advanced stage (stage II-IV) cutaneous squamous cell carcinoma (CSCC) who received neoadjuvant intravenous 350-mg cemiplimab-rwlc (Libtayo) every 3 weeks for up to 4 doses before surgery, pathologic complete response was seen in 50.6% of patients and major pathologic response was seen in 12.7% of patients, following the trial at The University of Texas MD Anderson Cancer Center (MD Anderson) in Houston.

CONTINUED ON PAGE 12

### ALSO IN THIS ISSUE:

- Neoadjuvant Cemiplimab Offers 63.3% Response Rate in Stage II to IV Resectable CSCC in Confirmatory Phase 2 Trial, [page 15](#)
- Ribociclib Gives Patients With Aggressive Breast Cancer an Additional Year of Survival, Pooled Data Show, [page 16](#)
- Georgetown's Aiwu Ruth He, MD, PhD, Discusses Improved Long-term Benefit of Durvalumab Combo in BTC, [page 17](#)
- COSMIC-313 Data Show Immunotherapy Triplet Bests Doublet in Advanced, Metastatic RCC, [page 19](#)
- Abramson's Naomi B. Haas, MD, Talks Immunotherapy Implications Following ECOG-ACRIN's PROSPER RCC Data Release, [page 20](#)

Opinions expressed by authors, contributors, and advertisers are their own and not necessarily those of Managed Care & Healthcare Communications, LLC, the editorial staff, or any member of the editorial advisory board. Managed Care & Healthcare Communications, LLC, is not responsible for accuracy of dosages given in articles printed herein. The appearance of advertisements in this publication is not a warranty, endorsement, or approval of the products or services advertised or of their effectiveness, quality, or safety. Managed Care & Healthcare Communications, LLC, disclaims responsibility for any injury to persons or property resulting from any ideas or products referred to in the articles or advertisements.



## LIBTAYO works with the immune system to help treat the following types of cancer<sup>1</sup>:

- The first-line treatment of patients with **non–small cell lung cancer (NSCLC)** whose tumors have high PD-L1 expression (tumor proportion score [TPS]  $\geq 50\%$ ) as determined by an FDA-approved test, with no EGFR, ALK, or ROS1 aberrations, and is locally advanced where patients are not candidates for surgical resection or definitive chemoradiation OR metastatic
- The treatment of patients with **locally advanced basal cell carcinoma (laBCC)** previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate
- The treatment of patients with **metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC)** who are not candidates for curative surgery or curative radiation

 Visit [LIBTAYOhcp.com](https://www.libtayohcp.com) for more information.

## Important Safety Information

### Warnings and Precautions

#### Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue at any time after starting treatment. While immune-mediated adverse reactions usually occur during treatment, they can also occur after discontinuation. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. Early identification and management are essential to ensuring safe use of PD-1/PD-L1–blocking antibodies. The definition of immune-mediated adverse reactions included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Monitor 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.

# Important Safety Information (cont'd)

## Warnings and Precautions (cont'd)

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

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

Withhold or permanently discontinue LIBTAYO depending on severity. In general, if LIBTAYO 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 corticosteroids.

**Immune-mediated pneumonitis:** LIBTAYO can cause immune-mediated pneumonitis. In patients treated with other PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 4 (0.5%), Grade 3 (0.5%), and Grade 2 (2.1%). Pneumonitis led to permanent discontinuation in 1.4% of patients and withholding of LIBTAYO in 2.1% of patients. Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 58% of the 26 patients. Of the 17 patients in whom LIBTAYO was withheld, 9 reinitiated after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis. Withhold LIBTAYO for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

**Immune-mediated colitis:** LIBTAYO can cause immune-mediated colitis. The primary component of immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1–blocking antibodies. In cases of corticosteroid-refractory immune-mediated colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.1%). Colitis led to permanent discontinuation in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients. Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients. Of the 12 patients in whom LIBTAYO was withheld, 4 reinitiated LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence. Withhold LIBTAYO for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

**Immune-mediated hepatitis:** LIBTAYO can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 2% (16/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1.4%), and Grade 2 (0.2%). Hepatitis led to permanent discontinuation of LIBTAYO in 1.2% of patients and withholding of LIBTAYO in 0.5% of patients. Systemic corticosteroids were required in all patients with hepatitis. Additional immunosuppression with mycophenolate was required in 19% (3/16) of these patients. Hepatitis resolved in 50% of the 16 patients. Of the 5 patients in whom LIBTAYO was withheld, 3 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence.

For hepatitis with no tumor involvement of the liver: Withhold LIBTAYO if AST or ALT increases to more than 3 and up to 8 times the upper limit of normal (ULN) or if total bilirubin increases to more than 1.5 and up to 3 times the ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 8 times the ULN or total bilirubin increases to more than 3 times the ULN.

For hepatitis with tumor involvement of the liver: Withhold LIBTAYO if baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN. Also, withhold LIBTAYO if baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN. Permanently discontinue LIBTAYO if AST or ALT increases to more than 10 times ULN or if total bilirubin increases to more than 3 times ULN. If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue LIBTAYO based on recommendations for hepatitis with no liver involvement.

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

**Immune-mediated endocrinopathies:** For Grade 3 or 4 endocrinopathies, withhold until clinically stable or permanently discontinue depending on severity.

- **Adrenal insufficiency:** LIBTAYO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold LIBTAYO depending on severity. Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%). Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff

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

# Important Safety Information (cont'd)

## Warnings and Precautions (cont'd)

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

#### Immune-mediated endocrinopathies: (cont'd)

- **Hypophysitis:** LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue depending on severity. Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) of patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff
- **Thyroid disorders:** LIBTAYO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity
- **Thyroiditis:** Thyroiditis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued LIBTAYO due to thyroiditis. Thyroiditis led to withholding of LIBTAYO in 1 patient. Systemic corticosteroids were not required in any patient with thyroiditis. Thyroiditis had not resolved in any patient at the time of data cutoff. Blood thyroid stimulating hormone increased and blood thyroid stimulating hormone decreased have also been reported
- **Hyperthyroidism:** Hyperthyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.9%). No patient discontinued treatment and LIBTAYO was withheld in 0.5% of patients due to hyperthyroidism. Systemic corticosteroids were required in 3.8% (1/26) of patients. Hyperthyroidism resolved in 50% of 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hyperthyroidism, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hyperthyroidism
- **Hypothyroidism:** Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%). Hypothyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients. Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. Majority of the patients with hypothyroidism required long-term thyroid hormone replacement. Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reinitiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy
- **Type 1 diabetes mellitus, which can present with diabetic ketoacidosis:** Monitor for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold LIBTAYO depending on severity. Type 1 diabetes mellitus occurred in 0.1% (1/810) of patients, including Grade 4 (0.1%). No patient discontinued treatment due to type 1 diabetes mellitus. Type 1 diabetes mellitus led to withholding of LIBTAYO in 0.1% of patients

**Immune-mediated nephritis with renal dysfunction:** LIBTAYO can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%), and Grade 2 (0.4%). Nephritis led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients. Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld, 2 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence. Withhold LIBTAYO for Grade 2 or 3 increased blood creatinine, and permanently discontinue for Grade 4 increased blood creatinine. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

**Immune-mediated dermatologic adverse reactions:** LIBTAYO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) has occurred with PD-1/PD-L1–blocking antibodies. Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%). Immune-mediated dermatologic adverse reactions led to permanent discontinuation in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients. Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reactions, 7 reinitiated LIBTAYO after symptom improvement; of these, 43% (3/7) had recurrence of the dermatologic adverse reaction. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold LIBTAYO for suspected SJS, TEN, or DRESS. Permanently discontinue LIBTAYO for confirmed SJS, TEN, or DRESS. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.

**Other immune-mediated adverse reactions:** The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% in 810 patients who received LIBTAYO 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, and vasculitis. Permanently discontinue for Grades 2, 3, or 4 myocarditis
- **Nervous system:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, and autoimmune neuropathy. Withhold for Grade 2 neurological toxicities and permanently discontinue for Grades 3 or 4 neurological toxicities. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids

# Important Safety Information (cont'd)

## Warnings and Precautions (cont'd)

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

#### Other immune-mediated adverse reactions: (cont'd)

- **Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include 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, stomatitis
- **Musculoskeletal and connective tissue:** Myositis/polymyositis, rhabdomyolysis, and associated sequelae including renal failure, arthritis, polymyalgia rheumatica
- **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

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients receiving LIBTAYO as a single agent. Monitor patients for signs and symptoms of infusion-related reactions. The most common symptoms of infusion-related reaction were nausea, pyrexia, rash and dyspnea. Interrupt or slow the rate of infusion for Grade 1 or 2, and permanently discontinue for Grade 3 or 4.

### Complications of allogeneic HSCT

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

### Embryo-fetal toxicity

LIBTAYO can cause fetal harm when administered to a pregnant woman due to an increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

## Adverse Reactions

- In the pooled safety analysis of 810 patients, the most common adverse reactions ( $\geq 15\%$ ) with LIBTAYO were musculoskeletal pain, fatigue, rash, and diarrhea
- In the pooled safety analysis of 810 patients, the most common Grade 3-4 laboratory abnormalities ( $\geq 2\%$ ) with LIBTAYO were lymphopenia, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia

## Use in Specific Populations

- **Lactation:** Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO
- **Females and males of reproductive potential:** Verify pregnancy status in females of reproductive potential prior to initiating LIBTAYO

Please see Brief Summary of Prescribing Information on the following pages.

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; PD-L1, programmed death ligand-1; ROS1, c-ros oncogene 1 receptor tyrosine kinase.

**Reference: 1.** LIBTAYO (cemiplimab-rwlc) injection full U.S. prescribing information. Regeneron Pharmaceuticals, Inc.

**REGENERON**

©2022 Regeneron Pharmaceuticals, Inc. All rights reserved.  
LIB.22.07.0032 08/2022



## LIBTAYO<sup>®</sup> (cemiplimab-rwlc) injection, for intravenous use

### Brief Summary of Prescribing Information

#### 1 INDICATIONS AND USAGE

##### 1.1 Cutaneous Squamous Cell Carcinoma

LIBTAYO is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation.

##### 1.2 Basal Cell Carcinoma

LIBTAYO is indicated for the treatment of patients with locally advanced basal cell carcinoma (laBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.

##### 1.3 Non-Small Cell Lung Cancer

LIBTAYO is indicated for the first-line treatment of patients with non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS)  $\geq$  50%] as determined by an FDA-approved test [see *Dosage and Administration (2.1) in the full prescribing information*], with no EGFR, ALK or ROS1 aberrations, and is:

- locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or
- metastatic.

#### 4 CONTRAINDICATIONS

None.

#### 5 WARNINGS AND PRECAUTIONS

##### 5.1 Severe and Fatal Immune-Mediated Adverse Reactions

LIBTAYO is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or 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 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. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor 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 LIBTAYO depending on severity [see *Dosage and Administration (2.3) in the full prescribing information*]. In general, if LIBTAYO 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 corticosteroids.

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

LIBTAYO can cause immune-mediated pneumonitis. The definition of immune-mediated pneumonitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. In patients treated with other PD-1/PD-L1 blocking antibodies the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 4 (0.5%), Grade 3 (0.5%), and Grade 2 (2.1%) adverse reactions. Pneumonitis led to permanent discontinuation of LIBTAYO in 1.4% of patients and withholding of LIBTAYO in 2.1% of the patients.

Systemic corticosteroids were required in all patients with pneumonitis. Pneumonitis resolved in 58% of the 26 patients. Of the 17 patients in whom LIBTAYO was withheld for pneumonitis, 9 reinitiated LIBTAYO after symptom improvement; of these, 3/9 (33%) had recurrence of pneumonitis.

#### Immune-Mediated Colitis

LIBTAYO can cause immune-mediated colitis. The definition of immune-mediated colitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. The primary component of the immune-mediated colitis was diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1 blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 2.2% (18/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (1.1%) adverse reactions. Colitis led to permanent discontinuation of LIBTAYO in 0.4% of patients and withholding of LIBTAYO in 1.5% of patients.

Systemic corticosteroids were required in all patients with colitis. Colitis resolved in 39% of the 18 patients. Of the 12 patients in whom LIBTAYO was withheld for colitis, 4 reinitiated LIBTAYO after symptom improvement; of these, 3/4 (75%) had recurrence of colitis.

#### Immune-Mediated Hepatitis

LIBTAYO can cause immune-mediated hepatitis. The definition of immune-mediated hepatitis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology.

Immune-mediated hepatitis occurred in 2% (16/810) of patients receiving LIBTAYO, including fatal (0.1%), Grade 4 (0.1%), Grade 3 (1.4%), and Grade 2 (0.2%) adverse reactions. Hepatitis led to permanent discontinuation of LIBTAYO in 1.2% of patients and withholding of LIBTAYO in 0.5% of patients.

Systemic corticosteroids were required in all patients with hepatitis. Nineteen percent (19%) of these patients (3/16) required additional immunosuppression with mycophenolate. Hepatitis resolved in 50% of the 16 patients. Of the 5 patients in whom LIBTAYO was withheld for hepatitis, 3 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hepatitis.

#### Immune-Mediated Endocrinopathies

##### *Adrenal Insufficiency*

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

Adrenal insufficiency occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.4%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. LIBTAYO was not withheld in any patient due to adrenal insufficiency. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these 67% (2/3) remained on systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.

##### *Hypophysitis*

LIBTAYO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue LIBTAYO depending on severity [see *Dosage and Administration (2.3) in the full prescribing information*].

Hypophysitis occurred in 0.4% (3/810) of patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.1%) adverse reactions. Hypophysitis led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient and withholding of LIBTAYO in 1 (0.1%) patient. Systemic corticosteroids were required in 67% (2/3) patients with hypophysitis. Hypophysitis had not resolved in any patient at the time of data cutoff.

#### *Thyroid Disorders*

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

**Thyroiditis:** Thyroiditis occurred in 0.6% (5/810) of patients receiving LIBTAYO, including Grade 2 (0.2%) adverse reactions. No patient discontinued LIBTAYO due to thyroiditis. Thyroiditis led to withholding of LIBTAYO in 1 patient. Systemic corticosteroids were not required in any patient with thyroiditis. Thyroiditis had not resolved in any patient at the time of data cutoff. Blood thyroid stimulating hormone increased and blood thyroid stimulating hormone decreased have also been reported.

**Hyperthyroidism:** Hyperthyroidism occurred in 3.2% (26/810) of patients receiving LIBTAYO, including Grade 2 (0.9%) adverse reactions. No patient discontinued treatment due to hyperthyroidism. Hyperthyroidism led to withholding of LIBTAYO in 0.5% of patients.

Systemic corticosteroids were required in 3.8% (1/26) of patients with hyperthyroidism. Hyperthyroidism resolved in 50% of the 26 patients. Of the 4 patients in whom LIBTAYO was withheld for hyperthyroidism, 2 patients reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of hyperthyroidism.

**Hypothyroidism:** Hypothyroidism occurred in 7% (60/810) of patients receiving LIBTAYO, including Grade 2 (6%) adverse reactions. Hypothyroidism led to permanent discontinuation of LIBTAYO in 1 (0.1%) patient. Hypothyroidism led to withholding of LIBTAYO in 1.1% of patients. Systemic corticosteroids were not required in any patient with hypothyroidism. Hypothyroidism resolved in 8.3% of the 60 patients. The majority of patients with hypothyroidism required long-term thyroid hormone replacement. Of the 9 patients in whom LIBTAYO was withheld for hypothyroidism, 1 reinitiated LIBTAYO after symptom improvement; 1 required ongoing hormone replacement therapy.

*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 LIBTAYO depending on severity [see *Dosage and Administration (2.3) in the full prescribing information*].

Type 1 diabetes mellitus occurred in 0.1% (1/810) of patients, including Grade 4 (0.1%) adverse reactions. No patient discontinued treatment due to Type 1 diabetes mellitus. Type 1 diabetes mellitus led to withholding of LIBTAYO in 0.1% of patients.

#### Immune-Mediated Nephritis with Renal Dysfunction

LIBTAYO can cause immune-mediated nephritis. The definition of immune-mediated nephritis included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology.

Immune-mediated nephritis occurred in 0.6% (5/810) patients receiving LIBTAYO, including fatal (0.1%), Grade 3 (0.1%) and Grade 2 (0.4%) adverse reactions. Nephritis led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 0.4% of patients.

Systemic corticosteroids were required in all patients with nephritis. Nephritis resolved in 80% of the 5 patients. Of the 3 patients in whom LIBTAYO was withheld for nephritis, 2 reinitiated LIBTAYO after symptom improvement; of these, none had recurrence of nephritis.

#### Immune-Mediated Dermatologic Adverse Reactions

LIBTAYO can cause immune-mediated rash or dermatitis. The definition of immune-mediated dermatologic adverse reaction included the required use of systemic corticosteroids or other immunosuppressants and the absence of a clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms), 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 LIBTAYO depending on severity [see *Dosage and Administration (2.3) in the full prescribing information*].

Immune-mediated dermatologic adverse reactions occurred in 1.6% (13/810) of patients receiving LIBTAYO, including Grade 3 (0.9%) and Grade 2 (0.6%) adverse reactions. Dermatologic adverse reactions led to permanent discontinuation of LIBTAYO in 0.1% of patients and withholding of LIBTAYO in 1.4% of patients.

Systemic corticosteroids were required in all patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 69% of the 13 patients. Of the 11 patients in whom LIBTAYO was withheld for dermatologic adverse reaction, 7 reinitiated LIBTAYO after symptom improvement; of these 43% (3/7) had recurrence of the dermatologic adverse reaction.

#### Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% in 810 patients who received LIBTAYO 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-Barre syndrome, nerve paresis, autoimmune neuropathy

**Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include 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, stomatitis

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

**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**

Severe infusion-related reactions (Grade 3) occurred in 0.1% of patients receiving LIBTAYO as a single agent. Monitor patients for signs and symptoms of infusion-related reactions. The most common symptoms of infusion-related reaction were nausea, pyrexia, rash and dyspnea.

Interrupt or slow the rate of infusion or permanently discontinue LIBTAYO based on severity of reaction [see *Dosage and Administration (2.3) in the full prescribing information*].

#### **5.3 Complications of Allogeneic HSCT**

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 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit 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, LIBTAYO can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose [see *Use in Specific Populations (8.1, 8.3)*].

#### **6 ADVERSE REACTIONS**

The following serious adverse reactions are described elsewhere in the labeling.

- Severe and Fatal Immune-Mediated Adverse Reactions [see *Warnings and Precautions (5.1)*]

- Infusion-Related Reactions [see Warnings and Precautions (5.2)]
- Complications of Allogeneic HSCT [see Warnings and Precautions (5.3)]

### 6.1 Clinical Trials Experience

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

The data described in Warnings and Precautions reflect exposure to LIBTAYO as a single agent in 810 patients in three open-label, single-arm, multicohort studies (Study 1423, Study 1540 and Study 1620), and one open-label randomized multi-center study (Study 1624). These studies included 219 patients with advanced CSCC (Studies 1540 and 1423), 132 patients with advanced BCC (Study 1620), 355 patients with NSCLC (Study 1624), and 104 patients with other advanced solid tumors (Study 1423). LIBTAYO was administered intravenously at doses of 3 mg/kg every 2 weeks (n=235), 350 mg every 3 weeks (n=543), or other doses (n=32: 1 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, 200 mg every 2 weeks). Among the 810 patients, 57% were exposed for  $\geq 6$  months and 25% were exposed for  $\geq 12$  months. In this pooled safety population, the most common adverse reactions ( $\geq 15\%$ ) were musculoskeletal pain, fatigue, rash, and diarrhea. The most common Grade 3-4 laboratory abnormalities ( $\geq 2\%$ ) were lymphopenia, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, anemia, and hyperkalemia.

#### Cutaneous Squamous Cell Carcinoma (CSCC)

The safety of LIBTAYO was evaluated in 219 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540 [see Clinical Studies (14.1) in the full prescribing information]. Of these 219 patients, 131 had mCSCC (nodal or distant) and 88 had laCSCC. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=162) or 350 mg every 3 weeks (n=56) as an intravenous infusion until disease progression, unacceptable toxicity, or completion of planned treatment. The median duration of exposure was 38 weeks (2 weeks to 110 weeks).

The safety population characteristics were: median age of 72 years (38 to 96 years), 83% male, 96% White, and European Cooperative Oncology Group (ECOG) performance score (PS) of 0 (44%) and 1 (56%).

Serious adverse reactions occurred in 35% of patients. Serious adverse reactions that occurred in at least 2% of patients were pneumonitis, cellulitis, sepsis, and pneumonia.

Permanent discontinuation due to an adverse reaction occurred in 8% of patients. Adverse reactions resulting in permanent discontinuation were pneumonitis, cough, pneumonia, encephalitis, aseptic meningitis, hepatitis, arthralgia, muscular weakness, neck pain, soft tissue necrosis, complex regional pain syndrome, lethargy, psoriasis, rash maculopapular, proctitis, and confusional state.

The most common ( $\geq 20\%$ ) adverse reactions were fatigue, rash, diarrhea, musculoskeletal pain, and nausea. The most common Grade 3 or 4 adverse reactions ( $\geq 2\%$ ) were cellulitis, anemia, hypertension, pneumonia, musculoskeletal pain, fatigue, pneumonitis, sepsis, skin infection, and hypercalcemia. The most common ( $\geq 4\%$ ) Grade 3 or 4 laboratory abnormalities worsening from baseline were lymphopenia, anemia, hyponatremia, and hypophosphatemia.

Table 2 summarizes the adverse reactions that occurred in  $\geq 10\%$  of patients and Table 3 summarizes Grade 3 or 4 laboratory abnormalities worsening from baseline in  $\geq 1\%$  of patients receiving LIBTAYO.

**Table 2: Adverse Reactions in  $\geq 10\%$  of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540**

Adverse Reactions	LIBTAYO N=219	
	All Grades %	Grades 3-4 %
<b>General and Administration Site</b>		
Fatigue <sup>a</sup>	34	3
<b>Skin and Subcutaneous Tissue</b>		
Rash <sup>b</sup>	31	1
Pruritus <sup>c</sup>	18	0
<b>Gastrointestinal</b>		
Diarrhea <sup>d</sup>	25	0.5
Nausea	21	0
Constipation	13	0.5
Vomiting	10	0.5

(continued)

**Table 2: Adverse Reactions in  $\geq 10\%$  of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540 (continued)**

Adverse Reactions	LIBTAYO N=219	
	All Grades %	Grades 3-4 %
<b>Musculoskeletal and Connective Tissue</b>		
Musculoskeletal pain <sup>e</sup>	24	3
Arthralgia	11	1
<b>Respiratory</b>		
Cough <sup>f</sup>	14	0
<b>Hematology</b>		
Anemia	11	4
<b>Endocrine</b>		
Hypothyroidism	10	0
<b>Metabolism and Nutrition</b>		
Decreased appetite	10	0

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03

- Composite term includes fatigue and asthenia
- Composite term includes rash, rash maculopapular, erythema, dermatitis, dermatitis bullous, rash generalized, pemphigoid, rash erythematous, rash macular, rash pruritic, drug eruption, psoriasis, and skin reaction
- Composite term includes pruritus and pruritus allergic
- Composite term includes diarrhea and colitis
- Composite term includes back pain, pain in extremity, myalgia, musculoskeletal pain, and neck pain
- Composite term includes cough and upper airway cough syndrome

**Table 3: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in  $\geq 1\%$  of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540**

Laboratory Abnormality	Grade 3-4 (%) <sup>a</sup>
<b>Chemistry</b>	
Increased aspartate aminotransferase	2
Increased INR	2
<b>Hematology</b>	
Lymphopenia	9
Anemia	5
<b>Electrolytes</b>	
Hyponatremia	5
Hypophosphatemia	4
Hypercalcemia	2

Toxicity graded per NCI CTCAE v. 4.03

- Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter

#### Basal Cell Carcinoma (BCC)

The safety of LIBTAYO was evaluated in 132 patients with advanced BCC (mBCC N=48, laBCC N=84) in an open-label, single-arm trial (Study 1620) [see Clinical Studies (14.2) in the full prescribing information]. Patients received LIBTAYO 350 mg every 3 weeks as an intravenous infusion for up to 93 weeks or until disease progression or unacceptable toxicity. The median duration of exposure was 42 weeks (range: 2.1 weeks to 94 weeks).

The safety population characteristics were: median age of 68 years (38 to 90 years), 67% male, 74% White, and ECOG performance score (PS) of 0 (62%) and 1 (38%).

Serious adverse reactions occurred in 32% of patients. Serious adverse reactions that occurred in  $> 1.5\%$  (at least 2 patients) were urinary tract infection, colitis, acute kidney injury, adrenal insufficiency, anemia, infected neoplasm, and somnolence. Fatal adverse reactions occurred in 1.5% of patients who received LIBTAYO, including acute kidney injury and cachexia.

Permanent discontinuation of LIBTAYO due to an adverse reaction occurred in 13% of patients. Adverse reactions resulting in permanent discontinuation of LIBTAYO in  $> 1.5\%$  (at least 2 patients) were colitis and general physical health deterioration.

Dosage delays of LIBTAYO due to an adverse reaction occurred in 34% of patients. Adverse reactions which required dosage delay in  $> 2\%$  of patients (at least 3 patients) included blood creatinine increased, diarrhea, colitis, fatigue, headache, pneumonitis, and urinary tract infection.

The most common adverse reactions reported in at least 15% of patients were fatigue, musculoskeletal pain, diarrhea, rash, pruritus, and upper respiratory tract infection.

The most common Grade 3 or 4 adverse reactions (> 2%) were hypertension, colitis, fatigue, urinary tract infection, pneumonia, increased blood pressure, hypokalemia and visual impairment. The most common (> 3%) laboratory abnormality worsening from baseline to Grade 3 or 4 was hyponatremia.

Table 4 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 5 summarizes Grade 3 or 4 laboratory abnormalities worsening from baseline in ≥ 1% of patients receiving LIBTAYO.

**Table 4: Adverse Reactions in ≥ 10% of Patients with Advanced BCC Receiving LIBTAYO in Study 1620**

Adverse Reactions	LIBTAYO N=132	
	All Grades %	Grades 3-4 %
<b>General disorders and administration site conditions</b>		
Fatigue <sup>a</sup>	49	3.8
<b>Musculoskeletal and connective tissue disorders</b>		
Musculoskeletal pain <sup>b</sup>	33	1.5
<b>Gastrointestinal disorders</b>		
Diarrhea	25	0
Nausea	12	0.8
Constipation	11	0.8
<b>Skin and subcutaneous tissue disorders</b>		
Rash <sup>c</sup>	22	0.8
Pruritus	20	0
<b>Infections and infestations</b>		
Upper respiratory tract infection <sup>d</sup>	15	0
Urinary tract infection	12	2.3
<b>Metabolism and nutrition disorders</b>		
Decreased appetite	14	1.5
<b>Blood and lymphatic system disorders</b>		
Anemia	13	0.8
<b>Nervous system disorders</b>		
Headache	12	1.5
<b>Respiratory, thoracic and mediastinal disorders</b>		
Dyspnea <sup>e</sup>	11	0
<b>Vascular disorders</b>		
Hypertension <sup>f</sup>	11	4.5

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v. 4.03

- Composite term includes fatigue, asthenia, and malaise
- Composite term includes arthralgia, back pain, myalgia, pain in extremity, musculoskeletal pain, neck pain, musculoskeletal stiffness, musculoskeletal chest pain, musculoskeletal discomfort, and spinal pain
- Composite term includes rash maculo-papular, rash, dermatitis, dermatitis acneiform, erythema, rash pruritic, dermatitis bullous, dyshidrotic eczema, pemphigoid, rash erythematous, and urticaria
- Composite term includes upper respiratory tract infection, nasopharyngitis, rhinitis, sinusitis, pharyngitis, respiratory tract infection, and viral upper respiratory tract infection
- Composite term includes dyspnea and dyspnea exertional
- Composite term includes hypertension and hypertensive crisis

**Table 5: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥ 1% of Patients with Advanced BCC Receiving LIBTAYO in Study 1620**

Laboratory Abnormality	Grade 3-4 (%) <sup>a</sup>
<b>Electrolytes</b>	
Hyponatremia	3.1
Hypokalemia	1.5
<b>Coagulation</b>	
Activated partial thromboplastin time prolonged	2.3
<b>Hematology</b>	
Lymphocyte count decreased	2.3

Toxicity graded per NCI CTCAE v. 4.03

- Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter

### Non-Small Cell Lung Cancer (NSCLC)

The safety of LIBTAYO was evaluated in 355 patients with locally advanced or metastatic NSCLC in Study 1624 [see *Clinical Studies (14.3) in the full prescribing information*]. Patients received LIBTAYO 350 mg every 3 weeks (n=355) or investigator's choice of chemotherapy (n=342), consisting of paclitaxel plus cisplatin or carboplatin; gemcitabine plus cisplatin or carboplatin; or pemetrexed plus cisplatin or carboplatin followed by optional pemetrexed maintenance. The median duration of exposure was 27.3 weeks (9 days to 115 weeks) in the LIBTAYO group and 17.7 weeks (18 days to 86.7 weeks) in the chemotherapy group. In the LIBTAYO group, 54% of patients were exposed to LIBTAYO for ≥ 6 months and 22% were exposed for ≥ 12 months.

The safety population characteristics were: median age of 63 years (31 to 79 years), 44% of patients 65 or older, 88% male, 86% White, 82% had metastatic disease and 18% had locally advanced disease and ECOG performance score (PS) of 0 (27%) and 1 (73%).

LIBTAYO was permanently discontinued due to adverse reactions in 6% of patients; adverse reactions resulting in permanent discontinuation in at least 2 patients were pneumonitis, pneumonia, ischemic stroke and increased aspartate aminotransferase. Serious adverse reactions occurred in 28% of patients. The most frequent serious adverse reactions in at least 2% of patients were pneumonia and pneumonitis.

Table 6 summarizes the adverse reactions that occurred in ≥ 10% of patients and Table 7 summarizes Grade 3 or 4 laboratory abnormalities in patients receiving LIBTAYO.

**Table 6: Adverse Reactions in ≥ 10% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624**

Adverse Reactions	LIBTAYO N=355			
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
<b>Musculoskeletal and connective tissue disorders</b>				
Musculoskeletal pain <sup>a</sup>	26	0.6	27	1.5
<b>Skin and subcutaneous tissue disorders</b>				
Rash <sup>b</sup>	15	1.4	6	0
<b>Blood and lymphatic system disorders</b>				
Anemia	15	3.4	50	16
<b>General disorders and administration site conditions</b>				
Fatigue <sup>c</sup>	14	1.1	26	2
<b>Metabolism and nutrition disorders</b>				
Decreased appetite	12	0.6	18	0.3
<b>Infections and infestations</b>				
Pneumonia <sup>d</sup>	11	5	12	5
<b>Respiratory, thoracic and mediastinal disorders</b>				
Cough <sup>e</sup>	11	0	8	0.3

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v. 4.03

- Musculoskeletal pain is a composite term that includes back pain, arthralgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, bone pain, myalgia, neck pain, spinal pain, and musculoskeletal stiffness
- Rash is a composite term that includes rash, dermatitis, urticaria, rash maculo-papular, erythema, rash erythematous, rash pruritic, psoriasis, autoimmune dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, drug eruption, dyshidrotic eczema, lichen planus, and skin reaction
- Fatigue is a composite term that includes fatigue, asthenia, and malaise
- Pneumonia is a composite term that includes atypical pneumonia, embolic pneumonia, lower respiratory tract infection, lung abscess, paraneoplastic pneumonia, pneumonia, pneumonia bacterial, and pneumonia klebsiella
- Cough is a composite term that includes cough and productive cough

**Table 7: Grade 3 or 4 Laboratory Abnormalities Worsening from Baseline in ≥1% of Patients with Locally Advanced or Metastatic NSCLC Receiving LIBTAYO in Study 1624**

Laboratory Abnormality	LIBTAYO N=355	Chemotherapy N=342
	Grades 3-4 <sup>a</sup> %	
<b>Chemistry</b>		
Increased aspartate aminotransferase	3.9	1.2
Increased alanine aminotransferase	2.7	0.3
Increased alkaline phosphatase	2.4	0.3
Increased blood bilirubin	2.1	0.3
Hypoalbuminemia	1.8	1.3
Increased creatinine	1.2	1.6
<b>Hematology</b>		
Lymphopenia	7	9
Anemia	2.7	16
<b>Electrolytes</b>		
Hyponatremia	6	7
Hyperkalemia	4.2	1.9
Hypocalcemia	3.9	3.4
Hypophosphatemia	2.4	4.1
Hypermagnesemia	2.1	1.6
Hypokalemia	1.5	2.2
Hypercalcemia	1.2	2.2

Toxicity graded per NCI CTCAE v. 4.03

a. Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.

## 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 cemiplimab-rwlc in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Anti-drug antibodies (ADA) were tested in 823 patients who received LIBTAYO. The incidence of cemiplimab-rwlc treatment-emergent ADAs was 2.2% using an electrochemiluminescent (ECL) bridging immunoassay; 0.4% were persistent ADA responses. In the patients who developed anti-cemiplimab-rwlc antibodies, there was no evidence of an altered pharmacokinetic profile of cemiplimab-rwlc.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on its mechanism of action, LIBTAYO can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)* in the full prescribing information]. There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see *Data*). Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

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

#### Data

##### Animal Data

Animal reproduction studies have not been conducted with LIBTAYO to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering LIBTAYO during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 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 cemiplimab-rwlc 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 cemiplimab-rwlc in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

### 8.3 Females and Males of Reproductive Potential

#### Pregnancy Testing

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

#### Contraception

LIBTAYO can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

#### Females

Advise females of reproductive potential to use effective contraception during treatment with LIBTAYO and for at least 4 months after the last dose.

### 8.4 Pediatric Use

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

### 8.5 Geriatric Use

Of the 810 patients who received LIBTAYO in clinical studies, 32% were 65 years up to 75 years and 22% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 219 patients with mCSCC or laCSCC who received LIBTAYO in clinical studies, 34% were 65 years up to 75 years and 41% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 132 patients with BCC who received LIBTAYO in Study 1620, 27% were 65 years up to 75 years, and 32% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

## REGENERON

© 2022 Regeneron Pharmaceuticals, Inc. All rights reserved.

LIB.22.08.0003 08/22

## Patients With Locally Advanced NSCLC Ineligible for Chemoradiotherapy Have Longer OS With Cemiplimab Plus Chemo

(CONTINUED FROM COVER)

Subgroup results from EMPOWER-Lung 3 trial show that combining the PD-1 inhibitor cemiplimab with platinum-based doublet chemotherapy produces overall survival (OS) results in patients who are not eligible for chemoradiotherapy that are on par with results seen in the broader study.<sup>1</sup> Cemiplimab is marketed as Libtayo by Regeneron and Sanofi.

Authors of the abstract presented at ESMO noted that chemoradiotherapy treatment, followed by durvalumab, has become the standard of care for eligible patients. But this regimen is not for everyone, and evidence has been lacking for other options. By contrast, the authors wrote, “EMPOWER-Lung 3 used broad inclusion criteria and enrolled patients with [stage III locally advanced NSCLC] who were not candidates for surgical resection or concurrent chemoradiation.”

The EMPOWER-Lung 3 trial was stopped early in August 2021 and results appeared in August 2022 in *Nature Medicine*.<sup>2</sup> In the overall study of 466 patients, patients were randomly assigned 2:1 to be treated with cemiplimab plus chemotherapy or placebo plus chemotherapy. The cemiplimab group reached a median OS of 21.9 months compared with 13 months for the placebo group (HR, 0.71; 95% CI, 0.53-0.93; *P* = .014).

Previously, cemiplimab showed efficacy as monotherapy compared with chemotherapy in the EMPOWER-Lung 1 trial (NCT03088540), which led to FDA’s 2021 approval for patients with advanced NSCLC and high PD-L1 expression (tumor proportion score ≥50%), and with no EGFR, ALK, or ROS1 aberrations.

The new results presented at ESMO 2022 covered 69 patients ineligible for chemoradiotherapy; 45 patients received cemiplimab plus chemotherapy, compared with 24 who received chemotherapy plus placebo. Groups were well balanced between patients with squamous and nonsquamous cancers and by median age, although the cemiplimab group had a wider age range (39-82 years) compared with the placebo group (52-77 years).

At a median follow-up of 16.7 months (range, 9-24 months), patients in the cemiplimab arm had significantly longer progression-free survival (PFS), 12.5 months vs 6.2 months, and numerically longer OS, 21.9 months vs 13.8 months, than those in the placebo arm. Overall response rate (ORR) was 57.8% with a median duration of response of 16 months with cemiplimab plus chemotherapy, vs 33.3% and 4.2 months with placebo plus chemotherapy. Treatment-emergent adverse events of grade 3 or higher were 42.2% in the cemiplimab arm vs 25.0% in the placebo arm.<sup>1</sup>

The authors concluded that for patients with locally advanced NSCLC, first-line cemiplimab plus chemotherapy “provided significant improvement in PFS, numerically longer OS, higher ORR, and longer durable response than control. The safety profile was consistent with that reported in the overall population of this study.”

### EDITORIAL

<b>Vice President, Content</b> Laura Joszt, MA	<b>Assistant Managing Editor</b> Christina Mattina
<b>Associate Editorial Director</b> Mary K. Caffrey	<b>Editor</b> Maggie L. Shaw

### COPY & PRODUCTION

<b>Vice President, Copy</b> Jennifer Potash	<b>Copy Editors</b> Georgina Carson Kirsty Mackay Justin Mancini Ron Panarotti Mercedes Pérez Yasmeen Qahwash
<b>Copy Chief</b> Paul Silverman	<b>Creative Director, Publishing</b> Melissa Feinen
<b>Copy Supervisor</b> Nicole Canfora Lupo	<b>Art Director</b> Julianne Costello
<b>Senior Copy Editors</b> Cheney Baltz Marie-Louise Best Kelly King	

### SALES & MARKETING

<b>Vice President</b> Gil Hernandez	<b>National Account Managers</b> Kevin George Shaye Zyskowski
<b>Associate Director, Business Development</b> Ben Baruch	<b>National Account Associates</b> Carly Mauro Alessandra Santorelli
<b>Senior National Account Manager</b> Robert Foti	

### OPERATIONS & FINANCE

<b>Circulation Director</b> Jon Severn circulation@mjhassoc.com	<b>Vice President, Finance</b> Leah Babbit, CPA
	<b>Controller</b> Katherine Wyckoff

### CORPORATE

<b>President &amp; CEO</b> Mike Hennessy Jr	<b>Senior Vice President, Content</b> Silas Inman
<b>Chief Financial Officer</b> Neil Glasser, CPA/CFE	<b>Senior Vice President, Human Resources &amp; Administration</b> Shari Lundenberg
<b>Chief Operating Officer</b> Michael Ball	<b>Senior Vice President, Mergers &amp; Acquisitions, Strategic Innovation</b> Phil Talamo
<b>Chief Marketing Officer</b> Brett Melillo	<b>Executive Creative Director, Creative Services</b> Jeff Brown
<b>Executive Vice President, Global Medical Affairs &amp; Corporate Development</b> Joe Petroziello	

<b>Founder</b> Mike Hennessy Sr 1960-2021
---



AN **MJ** life sciences<sup>®</sup> BRAND

2 Clarke Drive, Suite 100  
Cranbury, NJ 08512 • (609) 716-7777

Copyright © 2022 by Managed Care & Healthcare Communications, LLC

The American Journal of Managed Care<sup>®</sup> ISSN 1088-0224 (print) & ISSN 1936-2692 (online) is published monthly by Managed Care & Healthcare Communications, LLC, 2 Clarke Drive, Suite 100, Cranbury, NJ 08512. Copyright © 2022 by Managed Care & Healthcare Communications, LLC. All rights reserved. As provided by US copyright law, no part of this publication may be reproduced, displayed, or transmitted in any form or by any means, electronic or mechanical, without the prior written permission of the publisher. For subscription inquiries or change of address, please call 888-826-3066. For permission to photocopy or reuse material from this journal, please contact the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923; Tel: 978-750-8400; Web: www.copyright.com. Reprints of articles are available in minimum quantities of 250 copies. To order custom reprints, please contact Gilbert Hernandez, The American Journal of Managed Care<sup>®</sup>, gherandez@ajmc.com; Tel: 609-716-7777. The American Journal of Managed Care is a registered trademark of Managed Care & Healthcare Communications, LLC. www.ajmc.com • Printed on acid-free paper.

The FDA has previously accepted for review the supplemental biologics license application for cemiplimab with chemotherapy in first-line treatment of advanced NSCLC.<sup>3</sup> ♦

*Jaime Rosenberg contributed to this report.*

#### REFERENCES

1. Kalinka E, Gogishvili M, Makhardadze T, et al. Cemiplimab with platinum-based chemotherapy (chemo) for first-line (1L) locally advanced non-small cell lung cancer (laNSCLC): EMPOWER-Lung 3 subgroup analysis. *Ann Oncol*. 2022;33(suppl 7): S438-S447. doi: 10.1016/annonc/annonc1063
2. Gogishvili M, Melkadze T, Makharadze T, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial. *Nat Med*. Published online August 25, 2022. doi:10.1038/s41591-022-01977-y
3. Virgil H. FDA accepts review of supplemental biologics license application for first-line cemiplimab/chemo in advanced NSCLC. CancerNetwork®. January 26, 2022. Accessed September 27, 2022. <https://bit.ly/3USK1oi>

## MD Anderson's Neil Gross, MD, FACS, on the Importance of Neoadjuvant Immunotherapy Against CSCC

(CONTINUED FROM COVER)

These findings<sup>1</sup> were presented at the recent European Society for Medical Oncology (ESMO) Congress 2022 by lead investigator Neil D. Gross, MD, FACS, head and neck surgeon and director of clinical research in the Department of Head and Neck Surgery at MD Anderson, with simultaneous publication in the *New England Journal of Medicine*.<sup>2</sup>

With cemiplimab-rwlc already investigated in a pilot study at MD Anderson and approved for use in unresectable, or metastatic, CSCC, this new study marks the first investigation of neoadjuvant immunotherapy for advanced stages of the skin cancer in the resectable setting. Disease-free survival is currently being investigated.

Gross spoke with *Evidence-Based Oncology*<sup>™</sup> (EBO) about the findings presented at ESMO. This interview has been edited for length and clarity.

**EBO:** Please tell us about the study you presented at ESMO on cemiplimab. Why is this monoclonal antibody important to making progress against CSCC?

**GROSS:** I'm pleased to discuss our trial on neoadjuvant immunotherapy in resectable stage II to IV CSCC. Immunotherapy is approved for use in unresectable, or metastatic, CSCC. But this is the first trial—other than a pilot trial—we completed to test immunotherapy in the neoadjuvant setting in resectable CSCC. The pilot study was performed here at MD Anderson; it included only 20 patients with resectable but advanced stage disease, where the intent was really not to influence treatment but rather to help us better understand how immunotherapy

works in CSCC. In that study, patients had to undergo the full extent of surgery after neoadjuvant therapy, as they would have at baseline.

We were astounded to see the responses to treatment in that pilot trial. Over half of the patients had a complete pathologic response to treatment. And based on the strength of those results, it prompted a multicenter confirmatory trial that was reported at ESMO<sup>1</sup> and published in the *New England Journal of Medicine*.<sup>2</sup>

That confirmatory trial was completed at over 20 centers in the United States, Australia, and Europe. It enrolled 79 patients with stage II to stage IV resectable cSCC. One important difference with this study from the pilot trial is that it allowed for smaller surgery as patients responded to immunotherapy. Patients in this study were allowed to have less invasive surgery if it was oncologically appropriate. Surgeons were still required to remove all tumor, but if they felt safe, they could preserve functionally important structures. We had several patients in the trial where that was the case. We highlighted 2 patients in the manuscript who were recommended for up-front orbital exenteration as part of their surgery, [as well as] planned adjuvant radiation. In both cases, they had a partial response on imaging but a complete pathologic response at the time of surgery, sparing the eye, and then have gone on to follow-up. So, very dramatic responses were observed.

In the multicenter trial, we confirmed what we saw in the pilot trial. Over half of the patients had a complete pathologic response—no residual viable tumor—when it came time for surgery. Another 10 patients of the 79 had a near complete pathologic response, less than or equal to

10% residual viable tumor cells in the specimens. So [these were] very encouraging early results from this trial.

Some patients come in because they have neglected disease. For whatever reason, they're afraid of going to the doctor or they have just let it get out of hand. But most patients will have very aggressive disease that they are being treated for, and this approach can have a huge impact on quality of life and function.

CSCC is so common that it's not even included in national data registries in the United States. That is because most cancers are seen and treated in the local dermatology office or in a primary care setting, most with surgery alone, but a certain percentage will escape that early stage and get to a more advanced setting. Then it becomes a very serious cancer. But for many years, advanced CSCC was under the radar; it wasn't appreciated by the public or even pharmaceutical companies as a potential therapeutic target because it just is not seen in in the numbers nationally.

**EBO:** How does cemiplimab fulfill an unmet need in the immunotherapy space? What is so advantageous about this treatment in the neoadjuvant setting vs the current standard of care?

**GROSS:** Immunotherapy is currently approved for use in unresectable CSCC, and it's taken a page from the history of melanoma treatment, having changed the practice of melanoma over the past decade or two. But until now, immunotherapy had yet to change the practice of resectable CSCC. However, both melanoma and CSCC are uniquely responsive to immunotherapy, [which] has to do with the UV damage created from sun exposure, and that is particularly well suited to immunotherapy. Historically, patients with advanced CSCC would be treated with surgery and radiation as the primary treatment, but that has a lot of potential toxicities. Surgeries can be functionally devastating, and radiation can have long-term [adverse] effects. Immunotherapy is approved for unresectable disease, but this is the first study to bring it earlier into the phase of care and to see [whether] that can impact function and outcomes for patients.

We don't have the long-term survival data for the patients in this trial, [and] we don't have the long-term quality-of-life data either—those data are maturing—but I think we'll see that the oncologic outcomes will be at least as good and durable. We know this from the long-term follow-up from the pilot trial, which is now over 3 years old. I think, importantly, it will demonstrate significant improvement in quality of life for patients, enabling less invasive

surgeries, and for many patients, enabling the avoidance of radiation therapy, which can be very toxic in the head and neck region.

Radiation therapy can be a grind going in for treatment over and over again. These patients, at least [with disease] in the head and neck, go for 6 weeks after surgery. The impact on quality of life is particularly dramatic in the head and neck; it's just such a sensitive area. It's where people eat, where they breathe, where they're seen, or where they see from. It can affect their hearing [and] all their senses. Cancer treatments can be functionally devastating, and that can last a lifetime, not just during treatment.

The huge benefit of this approach is that I believe many patients will be able to avoid radiation treatment after surgery, [which is] where I think it can have a profound impact on quality of life long term. So, a smaller surgery, a more focused surgery, and perhaps avoiding radiation altogether—just a smarter approach to this disease than what we've been using in the past.

**EBO:** Breaking down your pathologic complete response (pCR), 51% had a pCR. For those who may not view this as a good result, can you explain why it is a positive in the setting of advanced disease?

**GROSS:** Comparing this study with the current standard of care, which is surgery and radiation, there's a lot of room for improvement. The effects of surgery and standard radiation can be devastating in the long term. In this study, just over half of the patients had a pCR. So, they could have a more limited surgery, and those patients are probably safe not having radiation as well.... Overall, about two-thirds of patients had a deep pathologic response; most of those were complete pathologic responses—a smaller percentage had a near complete pathologic response. Those patients also do exceedingly well. They seem to behave similarly well to the patients who have a complete response.

Now there are [approximately] a third of patients who just don't respond as well. They may have a partial response. There [are] even some patients where the disease progressed. That's why, in this study, we included imaging assessment after 2 doses. As long as patients were responding and were not having toxicity, they could go on to receive 4 doses. Some patients did stop after 2 doses and go on to have surgery, but most patients were able to complete all 4 doses of treatment. If you scale this up into a larger group, there's a lot of room for potential benefit for [approximately] two-thirds of the patients treated using this approach.

**EBO:** Your ESMO research also noted that there is no systemic therapy for CSCC. Considering the effect this cancer can have on psychosocial functioning and quality of life, what must future treatments for this type of skin cancer address for adverse effects beyond just the physical?

**GROSS:** There's no systemic therapy approved for CSCC in the resectable setting. Immunotherapy is approved for patients with unresectable, or metastatic, disease, and it can improve survival for these patients. There can be durable disease control and even cures in that setting. This study was designed to push it earlier into treatment to see whether we could improve quality of life, whether we could spare patients functionally devastating surgery and potentially avoid radiation.

But it also has the opportunity to improve survival outcomes for patients. That is yet to be determined, and this will need to be compared [with] a standard-of-care approach in a phase 3 setting to be definitive evidence. I'm confident there is room for improvement in how we're currently doing things, and this approach has a very good chance of beating the alternative.

**EBO:** Is there any potential for biomarkers in the space?

**GROSS:** We don't know currently which patients will respond to neoadjuvant treatment and which ones will not. We don't have a biomarker, and in this study, we looked at tumor mutational burden [and] PD-L1 status; we've collected circulating tumor DNA, and that is being analyzed. But as of yet, we don't have predictors of response to treatment. That's going to be critical moving forward. If we can identify biomarkers of response and select our patients better for treatment, then it'll be a win-win for everyone.

One thing that's nice about the neoadjuvant approach is that you can see the responses almost in real time. Patients will tell you it's improving. Patients have even told me they've seen other skin cancers or skin lesions fall off during the neoadjuvant treatment, or their tumor itself, they felt it shrinking or have seen it shrink. We've seen this on imaging, as well, so you can measure the responses and see how it's working. If it's working, great, you can continue. If it's not, you can shift gears, and you can always go to a standard approach of surgery and radiation for advanced cancer.

**EBO:** Can you discuss potential advantages for cemiplimab in an earlier-stage disease setting? Is there room for progress in this area, as well?

**GROSS:** Applying immunotherapy to an earlier-stage setting has the possibility of just improving the responses. So, the smaller the tumor—the earlier stage of tumor—I suspect the better the responses. We know this just comparing the neoadjuvant trial [with] what we've seen in patients with advanced unresectable disease.

It does offer the potential for patients to avoid radiation in some cases. And I think in the future, there will be patients who can avoid surgery altogether, although I would caution that in this trial, and in the pilot trial, we noticed that the imaging responses significantly underestimated the pathologic responses. So, when it came time to do the surgery, looking at the scans, there was still something there. It was only after surgery, when they looked at the specimens under the microscope, that they determined there was no residual cancer or just a small amount of residual viable cancer.

We still need either a biomarker or better imaging to help us understand who will or will not need surgery, or just to help define the extent of surgery and adjuvant treatments.

**EBO:** What's up next in the space? Can you tell us about any trials that are planned or underway and what indications they may be investigating?

**GROSS:** It's a very active time. There are lots of different thoughts about the next steps for this. There are so many unanswered questions. We still don't know the optimal number of neoadjuvant doses of immunotherapy. In the pilot trial, we used 2 doses. In the confirmatory trial, we used up to 4, with the hopes of expanding the number of pathologic responses.

We don't know which patients can safely avoid radiation therapy, and this could be an important question to answer in a cooperative group setting. We don't know which patients can avoid surgery or the extent that surgery can be reduced for patients who respond, which is another very important question.

Ultimately, we need to understand how this stacks up to standard-of-care treatment. This is only done in a phase 3 setting, and I think those studies are being contemplated right now, but I'm not aware of anything that's ready to go.

The patient stories are just so powerful. Just meeting some of the patients who've gone through this treatment, they're so grateful. They are some of the most grateful patients I have. Just understanding that we focus on improving quality of life and survival is so important to patients.

We aim for cure. We expect to cure patients, but we really want to make patients whole on the back end, as well. And this is just another tool in our armamentarium to

help patients get through with the least amount of adverse effects long term. ♦

#### REFERENCES

1. Gross N, Miller DM, Khushalani N, et al. Neoadjuvant cemiplimab in patients (pts) with stage II-IV (M0) cutaneous squamous cell carcinoma (CSCC): primary

analysis of a phase II study. Presented at: European Society for Medical Oncology Congress 2022; September 9-13, 2022; Paris, France. Abstract 789O. Accessed September 27, 2022. <https://bit.ly/3BAFtK6>

2. Gross ND, Miller DM, Khushalani NI, et al. Neoadjuvant cemiplimab for stage II to IV cutaneous squamous-cell carcinoma. *N Engl J Med*. Published online September 12, 2022. doi:10.1056/NEJMoa2209813

## Neoadjuvant Cemiplimab Offers 63.3% Response Rate in Stage II to IV Resectable CSCC in Confirmatory Phase 2 Trial

Mary Caffrey

**THE PD-1 INHIBITOR CEMIPILIMAB**, when used alone before surgery to treat resectable stage II to IV cutaneous squamous cell carcinoma (CSCC), produced a 63% combined pathologic response rate in a phase 2 trial, showing it could help some patients avoid surgery or improve their outcomes after surgery, according to data presented during the European Society for Medical Oncology (ESMO) Congress 2022, held September 9 to 13 in Paris, France. Results were presented in an oral session and published simultaneously in the *New England Journal of Medicine*.<sup>1</sup>

Cemiplimab is already approved to treat patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation. Results presented at ESMO demonstrate the therapy's potential in earlier stages of the disease, company officials said. Cemiplimab is marketed as Libtayo by Regeneron Pharmaceuticals, Inc, and Sanofi, which funded the study.

"Regeneron conducted the first pivotal trial of [cemiplimab] in advanced [CSCC] that was unlikely to be curable by surgery or radiation, and we are now studying the utility of [cemiplimab] in earlier stages of this disease," Israel Lowy, MD, PhD, senior vice president of translational and clinical sciences, oncology at Regeneron, said in a statement.<sup>2</sup>

According to the authors, led by Neil D. Gross, MD, FACS, head and neck surgeon and director of clinical research in the Department of Head and Neck Surgery at The University of Texas MD Anderson Cancer Center in Houston, a pilot study had demonstrated a high rate of pathologic complete response (pCR) or major pathologic

response of no more than 10% of the viable tumor when using cemiplimab in the neoadjuvant setting. Data presented at ESMO represented the primary analysis of a confirmatory, open-label, multicenter, phase 2 single-arm trial (NCT04154943), which used neoadjuvant cemiplimab in patients who had resectable stage II to IV CSCC. (See related interview, **Cover Story**).

In the phase 2 trial, patients received 350 mg of cemiplimab every 3 weeks for up to 4 doses before receiving surgery. The primary end point was a pCR, which was the absence of viable tumor cells in the surgical specimen, upon independent review at a central laboratory, with a null hypothesis that a pCR would be observed in 25% of patients.

Key secondary end points included a pathologic major response, which was presence of viable tumor cells that constitute no more than 10% of the surgical specimen on independent review, a pCR and a pathologic major response on investigator assessment at a local laboratory, an objective response on imaging, and adverse events (AEs).

The trial enrolled 79 patients who received neoadjuvant cemiplimab. On independent review, a pCR was observed in 40 patients (50.6%; 95% CI, 39-62) and a pathologic major response in 10 patients (12.7%; 95% CI, 6-22), for a combined rate of 63.3%. These results were consistent with the pathologic responses determined on investigator assessment.

An objective response on imaging was observed in 54 patients (68%; 95% CI, 57-78). There were 5 complete

responses and 49 partial responses, according to the local imaging review.

AEs of any grade that occurred during the study period, whether attributed to study treatment, were seen in 69 patients (87%). AEs of grade 3 or higher were seen in 14 patients (18%). “Neoadjuvant therapy with cemiplimab was associated with a [pCR] in a high percentage of patients with resectable [CSCC],” the authors concluded. ♦

#### REFERENCES

1. Gross ND, Miller DM, Khushanlani NI, et al. Neoadjuvant cemiplimab for stage II to IV cutaneous squamous-cell carcinoma. *N Engl J Med*. Published online September 12, 2022. doi:10.1056/NEJMoa2209813
2. Positive neoadjuvant Libtayo (cemiplimab) monotherapy data in resectable cutaneous squamous cell carcinoma presented at ESMO and published in NEJM. News release. Regeneron. September 12, 2022. Accessed September 29, 2022. <https://bit.ly/3RvjHNU>

## Ribociclib Gives Patients With Aggressive Breast Cancer an Additional Year of Survival, Pooled Data Show

Mary Caffrey

**AN EXPLORATORY ANALYSIS OF** data from the MONALEESA phase 3 trials investigating ribociclib (Kisqali) showed that the CDK4/6 inhibitor with endocrine therapy offers patients with breast cancer an additional year of survival benefit, including those with aggressive hormone receptor-positive/HER2– advanced breast cancer.

Data from the MONALEESA-2 (NCT01958021), MONALEESA-3 (NCT02422615), and MONALEESA-7 (NCT02278120) trials were presented during the European Congress for Medical Oncology (ESMO) Congress 2022, held in September in Paris, France.<sup>1</sup> The trials compared treatment with ribociclib with endocrine therapy to endocrine therapy alone.

The analysis showed the following results for ribociclib with endocrine therapy in several subgroups of patients with hard-to-treat disease, compared with endocrine therapy alone:

- Patients with visceral metastases and multiple metastatic sites achieved a median overall survival (OS) of 62.7 months, compared with 52.1 months for endocrine therapy alone (HR, 0.79; 95% CI, 0.65-0.97).
- Patients with liver metastases on ribociclib and endocrine therapy in first-line treatment had a median OS of 44.2 months, compared with 38.1 months for endocrine therapy alone (HR, 0.77; 95% CI, 0.55-1.07).
- Patients with visceral metastases in 3 or more organs who received the ribociclib-endocrine therapy

combination in first line achieved a median OS of 57.7 months, compared with 49.3 months for those receiving endocrine therapy alone (HR, 0.81; 95% CI, 0.63-1.03).

The analysis evaluated 1889 patients across the MONALEESA trials, including 1124 (59.5%) with visceral metastases. Of the patients studied, 1229 received first-line therapy, including 709 (57.7%) with visceral metastases. The authors reported no new safety signals in these patients with a high disease burden and aggressive disease, and no difference in liver enzymes in patients with liver metastases.

“Patients who have visceral metastases typically have a worse prognosis and often demonstrate resistance to treatment, so as a clinician it is encouraging to see significant survival benefit with ribociclib in the first-line setting in patients with more aggressive disease,” Denise A. Yardley, MD, a senior investigator in the breast cancer research program at Sarah Cannon Research Institute in Nashville, Tennessee, said in a statement.<sup>2</sup> “Ribociclib is the only CDK4/6 inhibitor to show a consistent overall survival benefit in combination with endocrine therapy while also maintaining quality of life across the phase 3 program.”<sup>2</sup>

Jeff Legos, executive vice president and global head of oncology and hematology of Novartis, said in the statement, “The goal for advanced breast cancer treatment is to help people live longer, and we are proud that Kisqali continues to deliver a significant survival benefit while also maintaining quality of life, even for those with

harder-to-treat disease. We are committed to demonstrating what makes Kisqali a unique CDK4/6 inhibitor, thus providing patients and oncologists confidence in this therapeutic option.”

Novartis also reported the trial design for HARMONIA (NCT05207709) during ESMO.<sup>3</sup> The trial will be a head-to-head phase 3 trial of ribociclib vs rival CDK4/6 inhibitor palbociclib (Ibrance) for patients with advanced hormone receptor–positive/HER2–, HER2-enriched subtype, which Novartis officials said will explore what makes [ribociclib] unique at a molecular level.” The investigators anticipate the trial will enroll 456 patients and will have a primary outcome of progression-free survival; OS is among the secondary outcomes. The head-to-head trial follows disappointing OS results for palbociclib in the PALOMA-2 trial (NCT01740427), presented during the 2022 American Society of Clinical Oncology Annual Meeting in Chicago, Illinois.<sup>4</sup> ♦

#### REFERENCES

1. Yardley DA, Yap YS, Azim HA, et al. Pooled exploratory analysis of survival in patients with HR+/HER- advanced breast cancer and visceral metastases treated with ribociclib + endocrine therapy in MONALEESA trials. *Ann Oncol*. 2022;33(suppl 7):S85-S87. doi:10.1016/annonc/annonc1039
2. Novartis' Kisqali adds one more year of survival benefit in broadest set of patients, including those with aggressive HR+/HER2- advanced breast cancer. News release. Novartis. September 9, 2022. Accessed September 29, 2022. <https://bit.ly/3E3qZVY>
3. Pascual T, Stover DG, Thuerigen A, et al. HARMONIA SOLTI-2101 / AFT-58: a head-to-head phase 3 study comparing ribociclib and palbociclib in patients with hormone receptor-positive/HER2-negative/HER2-enriched (HR+/HER2-/HER2-E) advanced breast cancer (ABC). *Ann Oncol*. 2022;33(suppl 7):S662 doi:10.1016/annonc/annonc1040
4. Finn RS, Rugo HS, Dieras VC, et al. Overall survival (OS) with first-line palbociclib plus letrozole (PAL + LET) versus placebo plus letrozole (PBO + LET) in women with estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (ER+/HER2– ABC): analyses from PALOMA-2. *J Clin Oncol*. 2022;40(suppl 17):LBA1003. doi:10.1200/JCO.2022.40.17

## Georgetown's Aiwu Ruth He, MD, PhD, Discusses Improved Long-term Benefit of Durvalumab Combo in BTC

Interview by Mary Caffrey

**AMONG THE UPDATED RESULTS** presented at the European Society for Medical Oncology (ESMO) Congress 2022 were those for TOPAZ-1, the phase 3 trial that demonstrated the effectiveness of durvalumab with the chemotherapy combination of gemcitabine and cisplatin in first-line treatment of adults with locally advanced or metastatic biliary tract cancer.

Days before the opening of ESMO 2022, the FDA approved durvalumab, marketed as Imfinzi, when used with the chemotherapy combination in this setting—the first such approval for an immunotherapy. Approval was based on interim results presented in January, which showed the regimen reduced the risk of death by 20% compared with chemotherapy alone (HR, 0.80; 95% CI, 0.66-0.97;  $P = .021$ ).<sup>1</sup> New results showed that at 2 years, after an additional 6.5 months of follow-up, the durvalumab/chemotherapy regimen produced a 24% reduction in the risk of death compared with chemotherapy alone (HR, 0.76; 95% CI, 0.64-0.91).<sup>2</sup>

To learn more about these results, *Evidence-Based Oncology*<sup>™</sup> (EBO) spoke with Aiwu Ruth He, MD, PhD,

medical oncologist, associate professor of medicine, and leader of the Gastrointestinal Cancer Program, Georgetown Lombardi Comprehensive Cancer Center, MedStar Georgetown University Hospital, Washington, DC. She was a lead investigator in the TOPAZ-1 trial.

This interview has been edited lightly for length and clarity.

**EBO:** Can you discuss the improved survival advantage with these updated data in TOPAZ-1, compared with data presented in January?

**HE:** So, we had first-line palliative systemic chemotherapy with cisplatin and gemcitabine for advanced unresectable biliary cancer for over 10 years. The initial data on cisplatin/gemcitabine was supported by the ABC-02 study, which was presented in 2010.<sup>3</sup> For the first time in over 10 years, TOPAZ-1 is a positive, global randomized phase 3 study that met the primary end point of overall survival. And when the data were initially presented, the HR was

0.80; the updated data at ESMO showed an HR of 0.76. So, when the data mature and you can see the HR actually improves, this further supports the long-term benefit of immunotherapy in these patients—this time in combination with chemotherapy, and, in theory, [with other patients with cancer].

**EBO:** Biliary tract cancers (BTCs), as a group, have been notoriously hard to treat. Can you discuss why the use of immunotherapy in the first line is such an important breakthrough, given that the survival results seem to hold up across all the different types of BTCs?

**HE:** Immunotherapy has changed the landscape of cancer treatment for many types of cancer. In BTC, if you look at the tissue data, 70% of BTCs are rich in immune cells; 10% to 20% of BTCs express PD-L1. Of course, currently we're not sure whether those serve as good biomarkers, and if you look at the early data, unfortunately most people with BTC who receive immune checkpoint inhibitor monotherapy do not achieve response, although it was a small subset of patients [that] showed long-lasting response or disease stabilization.

So then, in this disease we suspect there was activity, but how can we use immunotherapy? There are quite a few preclinical data testing the combination of immunotherapy with chemotherapy. In the lab, people used different chemotherapy agents and have shown chemotherapy can kill cancer cells, increase the tumor neoantigen release, sometimes activate the effector T cells directly, or deplete the suppressor cells. So, there's rationale [for] combining immunotherapy with chemotherapy, [which] provided the rationale to do a study of immunotherapy plus chemotherapy in cholangiocarcinoma. When investigators initially did a single-arm phase 2 study, that showed a very promising response rate, which led to the design of the TOPAZ-1 study—a global, randomized study. Patients were randomized to [gemcitabine and cisplatin] plus placebo or [gemcitabine and cisplatin] plus durvalumab, which is an anti-PD-L1 antibody. All the patients received up to 8 cycles, which is 6 months of [chemotherapy], in combination with the durvalumab or placebo; then we stop the chemotherapy and patients continue the durvalumab or placebo until disease progression or toxicities. So that's the study design and rationale to support this study.

**EBO:** Three days before the start of the ESMO Congress came the news that the FDA had approved this durvalumab combination in first-line treatment for BTCs. Do you anticipate rapid adoption as the new standard of care?

**HE:** I would think so. I think education is the key, to make sure all practicing oncologists are aware of this information. Patients who have no contraindications for immunotherapy should be provided with the combination. In addition to the FDA approval, the combination has [been made] the preferred first-line therapy for BTC, with level 1 evidence, in the [National Comprehensive Cancer Network] guidelines.<sup>4</sup> So, hopefully that is helpful, because many practicing oncologists would also look at the NCCN guidelines.

**EBO:** Although TOPAZ-1 has shown significant benefit using this immunotherapy and chemotherapy combination, the overall survival was 23.6% at the 2-year year mark. So, what are the ongoing studies about BTCs for patients who relapse? Do we know what agents or what combinations we would look at in the second line after this combination? Among the targeted therapies that are already approved, which ones would be used after this combination?

**HE:** It's a very exciting time because there's a lot of progress being made. There are other immune combinations being evaluated in combination with chemotherapy; there's a lot of triplets and 4-drug combinations being evaluated as frontline therapy. We should learn more [about] what combinations will produce even more benefit, in addition to this one; in the next few years, we should have the readouts from other studies testing immunotherapy in combination with chemotherapy for advanced BTC.

The other area of excitement is precision oncology. As you know, close to 50% of BTCs have potentially targetable mutations. Currently, we have some FDA indications in patients who are being treated in a second-line setting; for patients have progressed on frontline treatment and carry certain mutations, such as *FGFR2* fusions or *IDH1* mutations, we have compounds that showed very promising results and the FDA has approved these in a second-line setting. These drugs are being evaluated in the frontline setting.

In the future, we will have data on the frontline setting. It depends on the benefit in the frontline setting—we will have multiple options, and then we will have to face the decision on what to use in the frontline setting. Currently, we have [gemcitabine and cisplatin] plus durvalumab; in the next few years, we should also see data coming out in the first line for targeted therapy. There are other targeted therapies that have shown promising results that have FDA approval in other diseases that are now being tested

in cholangiocarcinoma, such as targeting *HER2* or *BRAF* mutations, and these [studies] have shown promising results. We will see more data coming out [in a] larger study in patients with those genetic alterations.

If you look at the whole profile, I would say about 30% of BTCs do not have any known targetable mutations. Then we have about 40% with targetable mutations and the rest have targets that we believe are driving mutations, but we're still trying to figure out how to target those mutations. So, I think [we will have] more and more options in the frontline setting—the question will be how to select treatment for patients, and how to sequence in the treatment for patients. In the next couple of years, we should see a lot more progress made in this disease.

**EBO:** Is there anything else that you would like to add?

**HE:** In the area of toxicities, durvalumab plus [chemotherapy] in the TOPAZ-1 study was quite well tolerated. The addition of durvalumab seems to have not really [created] additional toxicity....If you look at the immediate adverse effects, [these are] consistent with the mechanism

of action. And you see a little more intermediate toxicities, but [these are] usually either at a lower grade, so we need to watch out for those toxicities, but if you look at the grade 3 for more severe treatment-related toxicities, it really has not changed much by addition of the durvalumab, so it is a very well-tolerated treatment. ♦

#### REFERENCES

1. Oh DY, He AR, Qin S, et al. A phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin (GemCis) in patients (pts) with advanced biliary tract cancer (BTC): TOPAZ-1. *NEJM Evid.* 2022;1(8): doi: 10.1056/EVIDoa2200015
2. Oh DY, He AR, Qin S, et al. Updated overall survival (OS) from the phase III TOPAZ-1 study of durvalumab (D) or placebo (PBO) plus gemcitabine and cisplatin (+GC) in patients with advanced biliary tract cancer. *Ann Oncol.* 2022;33(suppl 33):S19-S26. doi: 10.1016/annonc/annonc1036
3. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med.* 2010;362(14):1273-1281. doi:10.1056/NEJMoa0908721
4. NCCN. Clinical Practice Guidelines in Oncology. Hepatobiliary cancers, version 2.2022. July 15, 2022. Accessed September 25, 2022. [https://www.nccn.org/professionals/physician\\_gls/pdf/hepatobiliary.pdf](https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf)

## COSMIC-313 Data Show Immunotherapy Triplet Bests Doublet in Advanced, Metastatic RCC

Maggie L. Shaw

**CAN ADDING THE KINASE** inhibitor cabozantinib to combination immunotherapy—specifically, the monoclonal antibodies nivolumab plus ipilimumab, also known as checkpoint inhibitors—improve patient outcomes in metastatic kidney cancer? In a study that sought to answer the question, the primary end point of progression-free survival (PFS) was met, according to lead investigator Toni K. Choueiri, MD, who is director, Lank Center for Genitourinary Oncology, and medical director, International Strategic Initiatives, Dana-Farber Cancer Institute.<sup>1</sup>

The COSMIC-313 trial randomly assigned 855 patients between June 2019 and March 2021 to the triplet regimen (n = 428; nivolumab and ipilimumab plus cabozantinib) or a doublet regimen (n = 427; nivolumab and ipilimumab plus placebo), which were the investigative and control

arms, respectively.<sup>2</sup> All patients enrolled in the global double-blind randomized phase 3 study were treatment naive and had clear cell advanced renal cell carcinoma (aRCC) that was intermediate risk (75%) or poor risk (25%), according to International Metastatic RCC Database Consortium (IMDC) criteria.

Choueiri, who is also the Jerome and Nancy Kohlberg Professor of Medicine at Harvard Medical School, presented the results of this subgroup analysis at the European Society for Medical Oncology Congress 2022.<sup>3</sup>

The risk of disease progression—measured in the first 550 randomly assigned patients (intent-to-treat patients, or PITT)—was reduced by 27% overall (HR, 0.73; 95% CI, 0.57-0.94; *P* = .013) in the investigative vs control arms (median PFS, not reached vs 11.3 months; 95% CI, 14.0 months to not estimable). The activity of the nivolumab/

ipilimumab combination, considered a first-line standard-of-care treatment for aRCC, may be enhanced by cabozantinib.

Patients were stratified by geographical region and IMDC risk. The investigative regimen was 40-mg cabozantinib administered 4 times a day on specified days plus intravenous (IV) nivolumab 3 mg/kg and IV ipilimumab 1 mg/kg, both given every 3 weeks for 4 cycles. Those in the control group received the same immunotherapy regimen with placebo instead of cabozantinib. The 4 treatment cycles in both arms were followed by 480 mg IV nivolumab administered every 4 weeks for up to 2 years.

Among the PITT population, the overall response rate was 19.4% lower in the control vs the investigative group: 36% (95% CI, 30.1%-41.8%) vs 43% (95% CI, 37.2%-49.2%). Neither group achieved a median duration of response.

Seventy-three percent of patients in the investigative group experienced grade 3/4 treatment-related adverse events (TRAEs) vs 41% in the control group, and 1% of patients in each group had grade 5 TRAEs. Further, TRAEs led to study discontinuation in 12% and 5% of the study and control groups, respectively.

The safety profile of the triplet regimen “was consistent with the known profiles of the treatment components,” the trial investigators noted.

The COSMIC-313 trial is ongoing, with a scheduled completion date of March 2025.<sup>2</sup>

“Overall, in terms of potential impact on patient care, [we can say that] this is the first study where a triplet beats a doublet in kidney cancer,” Choueiri said. “I think the most important next step is to find subsets of patients who will benefit—it’s not for everyone—from 3 drugs rather than 2 and wait a bit to understand the impact on overall survival.”<sup>1</sup> ♦

#### REFERENCES

1. #ESMO22: abstract LBA8. Phase 3 study of cabozantinib (C) in combination with nivolumab (N) and ipilimumab (I) in previously untreated advanced renal cell carcinoma (aRCC) of IMDC intermediate or poor risk (COSMIC-313). Toni Choueiri, MD, Dana-Farber Cancer Institute. YouTube page. Accessed September 26, 2022. <https://www.youtube.com/watch?v=SvsiByF77Vk>
2. Study of cabozantinib in combination with nivolumab and ipilimumab in patients with previously untreated advanced or metastatic renal cell carcinoma (COSMIC-313). ClinicalTrials.gov. Updated March 10, 2022. Accessed September 26, 2022. <https://clinicaltrials.gov/ct2/show/NCT03937219>
3. Choueiri TK, Powles TB, Albiges L, et al. Phase III study of cabozantinib (C) in combination with nivolumab (N) and ipilimumab (I) in previously untreated advanced renal cell carcinoma (aRCC) of IMDC intermediate or poor risk (COSMIC-313). *Ann Oncol*. 2022;33(suppl 7):S808-S869. doi:10.1016/annonc/annonc1089

## Abramson’s Naomi B. Haas, MD, Talks Immunotherapy Implications Following ECOG-ACRIN’s PROSPER RCC Data Release

Interview by Maggie L. Shaw

**THE PHASE 3 PROSPER RCC** (EA8143) trial investigated incorporating a perioperative regimen of the immunotherapy nivolumab in patients with high-risk renal cell carcinoma (RCC) of at least clinical stage T2 or TanyN+ and a high risk of disease recurrence who subsequently underwent nephrectomy. The outcomes of these 404 patients were compared with those of 415 patients who had surgery alone, and the primary outcome was recurrence-free survival (RFS).<sup>1</sup>

Although results of the trial (NCT03055013) show nivolumab did not have an impact on RFS, and the trial

was stopped early, there remains much to learn from these data, said Naomi B. Haas, MD, cochair, Genitourinary Cancer Committee; chair, Renal Cell Carcinoma Subcommittee for the ECOG-ACRIN Cancer Research Group; director, Prostate and Kidney Cancer Program at the Penn Medicine Abramson Cancer Center; and professor of medicine, Perelman School of Medicine at the University of Pennsylvania in Philadelphia.

For example, biopsied tumor samples from the surgeries are available and have potential to provide disease biomarker information and/or evidence of an immune

response in tumors. Haas expressed hope that this might enable better patient selection for clinical trials.

This interview has been edited for length and clarity.

**EVIDENCE-BASED ONCOLOGY™ (EBO):** Please tell us about PROSPER RCC and its primary goals. Why is there a need for neoadjuvant immunotherapy in the RCC setting?

**HAAS:** The design of PROSPER RCC was thought up several years ago. One of the immunologists involved in the design of the study was Charles Drake, MD, PhD, who was at Johns Hopkins at the time.<sup>2</sup> He had been working in mouse models with immunotherapy, and there were some good data... [showing] that giving immunotherapy before taking a primary tumor out of these mouse models showed the immune response was better than if you took the primary tumor out first and then gave immunotherapy.

We thought that since immunotherapy was widely used already in metastatic kidney cancer that there could be an advantage of administering the immunotherapy before the primary tumor was taken out, because in this setting, you're treating patients with very high-risk kidney cancer who, once the kidney tumor is out, won't have any measurable disease that you can see on scan. It made sense to leave the kidney tumor in long enough for the immunotherapy to have more T cells to prime and hopefully make it more effective.

Since this time... trials have been conducted in lung cancer, in melanoma, [and] in breast cancer that show giving neoadjuvant therapy ahead of time in those tumors does give a very good, sometimes pathologic, response—meaning you can see at the time of surgery that the cancer has shrunk or improved. And we thought this approach might work better than simply giving adjuvant therapy when the primary [tumor] had already been removed.

**EBO:** What predisposes patients with RCC to a higher risk of disease returning, and how might biomarkers be used in that setting?

**HAAS:** Kidney cancer is not as far along in the use of biomarkers to predict who is going to be at higher risk. For example, now in lymphoma and leukemia, in lung cancer, and in some other cancers you have very effective molecular testing that can be performed from blood samples that can identify targetable mutations and, in some cases, determine whether a therapy might work and sometimes predict whether [patients] have disease left over [by blood samples].

In kidney cancer, those approaches are not as far along in development. The main things we use to assess risk are the stage of the cancer and sometimes prognostic nomograms, which are statistical modeling tools. These tools incorporate staging, nuclear grade of the cancer, presence of necrosis in certain nomograms, as well as patient activity level, better known as performance status. We know, just from historical data as well as data from our previous adjuvant trials, that cancers that have a higher tumor stage—tumors bigger than 7 cm—and [high] nuclear grade, or lymph node involvement, or necrosis... those things can predict more aggressive cancers.

One of the problems we still have is that we probably are undertreating some [individuals] and we're probably overtreating others and our current tools are not always great at predicting this. There are [patients] whose cancers might never recur, even if they have these big, bad risk factors, and there are others who have a little tumor and you say, "Wow, why did that come back?" There are biomarkers under development that hopefully will inform decision-making and future trials. A lot of these are being looked at in PROSPER with the tissue samples.

For example, transcriptomics identified in a paper in *Cancer Cell* in 2020 by Robert J. Motzer, MD, and colleagues,<sup>1</sup> show 7 clusters of kidney cancer and which cancers you might be able to predict will respond better to [vascular endothelial growth factor]...receptor tyrosine kinase inhibitors [TKIs] and which might respond better to immunotherapy. I think that if we could learn how to do these with a rapid turnaround, and if we can show, looking back, that it does correlate with who relapsed and who didn't, that would be a very useful marker.

Liquid biopsies are another type of tool; for example, circulating tumor DNA has been shown to be helpful in lung cancer and urothelial cancer. But kidney cancer doesn't shed as much, so this kind of approach must be worked on more before we know the right volume that could be looked at and [whether that could] be an approach. There are other types of assays as well, such as methylated DNA. Those are the things of high interest.

Another approach is what we call artificial intelligence, looking at either radiomics or pathomics. By looking at either a simple slice of a tumor—because kidney cancer can be very heterogeneous—or how it looks on the scan, we might be able to predict, by teaching a computer how to analyze hundreds of thousands of specimens and how to predict using those models, who's at higher risk for recurrence. So, we have a lot of work to do.

Another thing that predisposes to higher risk of recurrence is what we call performance status. So, if a patient is

very healthy vs a patient who has a lot of symptoms, that's also been correlated with risk of relapse.

**EBO:** Your trial was stopped early when the interim analysis showed no difference in recurrence-free survival. How will the data you gathered inform future research on immunotherapy use among patients with high-risk RCC?

**HAAS:** This is a very complicated trial. Every time a trial is conducted, one learns other ways that things could be approached in the future. There are a lot of moving parts with this trial that we're still analyzing. One of the things we know is that when patients were registered on this trial, some, even after they were registered, didn't go forward with the therapy, whether it was the surgery arm or the surgery with the nivolumab treatment arm. There were also patients along the way in either arm who might have had surgery and then didn't go forward in the trial or might have had surgery and gotten the neoadjuvant nivolumab and maybe didn't get adjuvant nivolumab.

We're still looking at those data. That's a very complicated process that requires pulling a lot of the case reports and really mining down deep into the data.

**“One of the areas of great interest is whether in the non-White population there are more patients who perhaps have impeded access to care but also might be from a lower socioeconomic bracket and living closer to chemicals in the ground and less optimal industrial areas.”**

There are many things we still must analyze and understand. One of the valuable parts of this clinical trial is that we have both the biopsy and the tumor samples from surgery, and we are going to be able to go back and look at whether there's a particular signal in a particular patient population. The other thing I hope we'll be able to see is whether there's evidence of an immune response in the tumor and that will also better select patients for clinical trials. I don't think by any stretch that we should discount

either other adjuvant approaches or other neoadjuvant approaches in kidney cancer.

**EBO:** Can you talk about why RCC appears in men at a rate twice that of women, as well as why there are higher disease rates in North America and Europe? Could lifestyle or environmental factors influence disease development, or is it that disease detection has improved?

**HAAS:** Yes to both. Starting with disease detection, there certainly is disease migration. We're better with imaging. Kidney cancer typically happens deep in the abdomen, and so [individuals] don't often develop symptoms until a cancer is very advanced. But a lot of kidney tumors are found incidentally because we're so good at doing scans for all sorts of things. A lot of patients [receive a diagnosis of just] an incidental renal mass.

The male vs female [question] is very interesting. I used to think it was only men at higher risk because tobacco is a risk factor for development of kidney cancer and men historically smoked more than women. But now more women are smoking. There also might be some hormonal reasons that aren't clear yet as far as why it's more common in men than in women.

This could also relate to environmental factors. Historically, men would be more out in the workplace than women would be. But again, we're still seeing this difference even as more women are in the workplace. Certainly, environmental influences...one of the areas of great interest is whether in the non-White population there are more patients who perhaps have impeded access to care but also might be from a lower socioeconomic bracket and living closer to chemicals in the ground and less optimal industrial areas. Again, a very complicated question as far as why there's a difference.

**EBO:** What is the current standard of care for patients with high-risk RCC and how does immunotherapy improve upon that treatment?

**HAAS:** Up until about a year ago, the only standard-of-care approaches for high-risk kidney cancer [involved] surveillance, and that was with imaging by either CT or MRI. Initially for higher-risk disease, this would be every 3 to 4 months for the first year and then every 6 months for year 2 and year 3, and then yearly in years 4 and 5.

There were 5 VEGF TKI trials in kidney cancer preceding immunotherapy and only 1 of those showed a disease-free survival [DFS] benefit. That was the S-TRAC trial of sunitinib vs placebo in a very high-risk clear cell population.<sup>2</sup> It

was interesting because that was the only one that did that, but it didn't show an improvement in overall survival [OS]. But based on its improvement in DFS, which was basically 1 year, the drug was approved by the FDA. But it was not approved by the European Medicines Agency [EMA]. But the uptick in the use of sunitinib adjuvantly has been fairly low.

The standard of care has generally been surveillance. However, over a year ago, KEYNOTE-564<sup>3</sup> [NCT03142334] of adjuvant pembrolizumab vs placebo did show an improvement in DFS, and based on that improvement in DFS, the drug was approved by the FDA and the EMA.

The various trials presented at ESMO were very heterogeneous. PROSPER RCC had a primary end point of RFS, which included both non-clear cell and clear cell, so it was a mixed population. CheckMate 914<sup>4</sup> [NCT03138512] was a shorter duration of immunotherapy and used a CTLA-4 inhibitor in combination with a PD-1 inhibitor only in patients with clear cell predominant histology. IMmotion010<sup>5</sup> [NCT03024996] used a PD-L1 inhibitor for a year in clear cell-predominant RCC. Although they didn't meet their primary end points, they had different durations of therapy, different drugs, and some differences in patient eligibility.

And then you also have placebo control trials, you have COVID-19 in the mix, and did patients look at different trials? A certain type of patient might say, "Oh, I'm going to try to go on the CheckMate 914 trial, because it's using ipilimumab/nivolumab and I want to be more aggressive." Another patient might say, "I'm afraid of that approach and I'm not going to do that. I'm going to go on a different trial." There may have been some even patient self-selection for these kinds of trials. I think we have a lot of work to do.

One thing about immunotherapy is that it's generally well tolerated...much better tolerated than VEGF TKIs in the adjuvant setting. However, the adverse effects of VEGF TKIs generally are reversible if you stop the agents, and if you get a severe adverse effect from an immune checkpoint inhibitor, some of those can be permanent—like diabetes, myocarditis, liver failure, meningitis, or hypophysitis. So you're dealing with a lower frequency, but potentially some very serious adverse effects.

I think the [burden] on us is still to understand who doesn't need immunotherapy adjuvantly and who does.

Should you get 1 drug or 2 drugs? Some of the trials, like KEYNOTE-564,<sup>3</sup> enrolled patients who had metastatic disease that was completely resected. The standard of care for treating metastatic disease is generally 2 drugs, so if you're treating those patients with just adjuvant pembrolizumab, are you undertreating those patients? There's a lot to understand.

**EBO:** Nivolumab is already approved for use in kidney cancer. How does this PD-1 inhibitor work compared with other immunotherapies for kidney cancer?

**HAAS:** In the metastatic setting, there are trials using nivolumab, nivolumab with ipilimumab, and nivolumab with cabozantinib that all show survival benefits—not just progression-free survival [PFS], but OS benefits. Likewise, there are combinations of pembrolizumab with lenvatinib or pembrolizumab with axitinib that also show improvements in PFS and OS. I think nivolumab and pembrolizumab are both very active drugs, and I don't think we can make any conclusions at this point about the different drugs used in the high-risk setting. ♦

#### REFERENCES

1. Motzer RJ, Banchereau R, Hamidi H, et al. Molecular subsets in renal cancer determine outcome to checkpoint and angiogenesis blockade. *Cancer Cell*. 2020;38(6):803-817.e4. doi:10.1016/j.ccell.2020.10.011
2. A clinical trial comparing efficacy and safety of sunitinib versus placebo for the treatment of patients at high risk of recurrent renal cell cancer (S-TRAC). ClinicalTrials.gov. Updated September 21, 2018. Accessed September 21, 2022. <https://clinicaltrials.gov/ct2/show/NCT02628067>
3. Choueiri TK, Tomczak P, Park SH, et al; KEYNOTE-564 Investigators. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. *N Engl J Med*. 2021;385(8):683-694. doi:10.1056/NEJMoa2106391
4. A study comparing nivolumab, nivolumab in combination with ipilimumab and placebo in participants with localized kidney cancer who underwent surgery to remove part of a kidney (CheckMate 914). ClinicalTrials.gov. Updated July 20, 2022. Accessed September 21, 2022. <https://clinicaltrials.gov/ct2/show/NCT03138512>
5. A study of atezolizumab as adjuvant therapy in participants with renal cell carcinoma (RCC) at high risk of developing metastasis following nephrectomy (IMmotion010). ClinicalTrials.gov. Updated September 14, 2022. Accessed September 21, 2022. <https://clinicaltrials.gov/ct2/show/NCT03024996>

# JOIN US AT AN IVBM EVENT NEAR YOU!

## WHY ATTEND?



Hear about other people's experiences implementing a value-based care model in oncology and population health



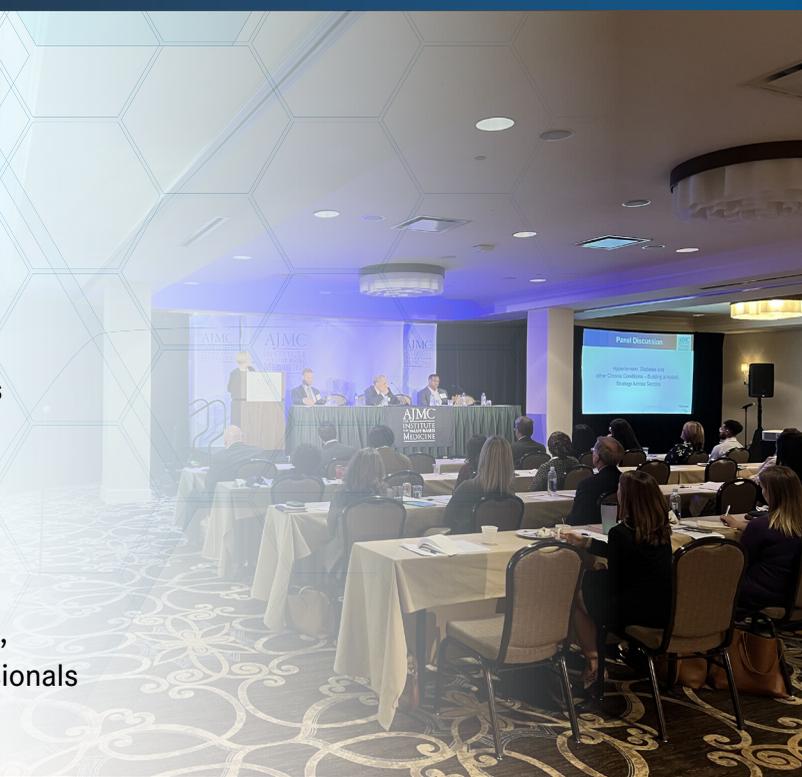
Learn about "best practices" for implementing quality payment programs



Network in-person with health care industry leaders



It's free! Attendance to IVBM events is complimentary for health care providers, administrators, and allied health professionals



## SCHEDULE OF EVENTS

**November 3**

Edison, NJ

Partnered with



**November 16**

Portland, OR

Partnered with



**November 17**

Nashville, TN

Partnered with



**November 29**

Kansas City, MO

Partnered with



**December 1**

Phoenix, AZ

Partnered with



To learn more and view the list of scheduled events, scan this QR code or visit [ajmc.com/ivbmevents](http://ajmc.com/ivbmevents)



*Attendance to IVBM events is complimentary for health care providers, administrators, and allied health professionals. For anyone else who is interested in attending, please contact us at [IVBMevents@ajmc.com](mailto:IVBMevents@ajmc.com).*