

Exclusive Coverage of the
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Frontline Cemiplimab With Chemo Offers Benefits in Advanced NSCLC Regardless of PD-L1 Status

Mary Caffrey

CEMIPLIMAB, APPROVED AS a first-line monotherapy to treat patients with advanced or metastatic non-small cell lung cancer (NSCLC) and high levels of PD-L1, offered benefits to patients regardless of PD-L1 status when given with a platinum-based chemotherapy doublet in the same setting, according to new findings.

Interim results from the EMPOWER-Lung 3 study¹ were presented September 19 during the European Society for Medical Oncology (ESMO) 2021 Congress, by trial investigator Miranda Gogishvili, MD, oncologist at the High Technology Medical Center University Clinic in Tbilisi, Georgia (see interview, page 15).

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On Heels of FDA Approval, Mobocertinib Data Take the Stage at ESMO

Mary Caffrey

ON THE EVE OF the European Society for Medical Oncology (ESMO) 2021 Congress, the FDA approved mobocertinib, a first-in-class oral tyrosine kinase inhibitor (TKI), for patients with non-small cell lung cancer (NSCLC) who have *EGFR* exon 20 insertion mutations and prior treatment with platinum-based chemotherapy. The novel therapy will be sold as Exkivity by Takeda.¹

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- Dr Miranda Gogishvili: "We Continue to Expect Great Things" From Cemiplimab, [page 15](#)
- In HER2+ MBC, Trastuzumab Deruxtecan Slashes Risk of Disease Progression or Death by 72% vs T-DM1, [page 17](#)
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LIBTAYO works with the immune system to help treat the following types of cancer¹:

- 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 palsy, 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., and sanofi-aventis U.S. LLC.

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LIBTAYO® (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 paresthesia, 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 ≥ 6 months and 25% were exposed for ≥ 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 %
General and Administration Site		
Fatigue ^a	34	3
Skin and Subcutaneous Tissue		
Rash ^b	31	1
Pruritus ^c	18	0
Gastrointestinal		
Diarrhea ^d	25	0.5
Nausea	21	0
Constipation	13	0.5
Vomiting	10	0.5
Musculoskeletal and Connective Tissue		
Musculoskeletal pain ^e	24	3
Arthralgia	11	1
Respiratory		
Cough ^f	14	0

(continued)

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 %
Hematology		
Anemia	11	4
Endocrine		
Hypothyroidism	10	0
Metabolism and Nutrition		
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 (%) ^a
Chemistry	
Increased aspartate aminotransferase	2
Increased INR	2
Hematology	
Lymphopenia	9
Anemia	5
Electrolytes	
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 %
General disorders and administration site conditions		
Fatigue ^a	49	3.8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain ^b	33	1.5
Gastrointestinal disorders		
Diarrhea	25	0
Nausea	12	0.8
Constipation	11	0.8
Skin and subcutaneous tissue disorders		
Rash ^c	22	0.8
Pruritus	20	0
Infections and infestations		
Upper respiratory tract infection ^d	15	0
Urinary tract infection	12	2.3
Metabolism and nutrition disorders		
Decreased appetite	14	1.5
Blood and lymphatic system disorders		
Anemia	13	0.8
Nervous system disorders		
Headache	12	1.5
Respiratory, thoracic and mediastinal disorders		
Dyspnea ^e	11	0
Vascular disorders		
Hypertension ^f	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 (%) ^a
Electrolytes	
Hyponatremia	3.1
Hypokalemia	1.5
Coagulation	
Activated partial thromboplastin time prolonged	2.3
Hematology	
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		Chemotherapy N=342	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain ^a	26	0.6	27	1.5
Skin and subcutaneous tissue disorders				
Rash ^b	15	1.4	6	0
Blood and lymphatic system disorders				
Anemia	15	3.4	50	16
General disorders and administration site conditions				
Fatigue ^c	14	1.1	26	2
Metabolism and nutrition disorders				
Decreased appetite	12	0.6	18	0.3
Infections and infestations				
Pneumonia ^d	11	5	12	5
Respiratory, thoracic and mediastinal disorders				
Cough ^e	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 ^a %	
Chemistry		
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
Hematology		
Lymphopenia	7	9
Anemia	2.7	16
Electrolytes		
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 mSCC or laSCC 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.

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Frontline Cemiplimab With Chemo Offers Benefits in Advanced NSCLC Regardless of PD-L1 Status

(CONTINUED FROM COVER)

“Cemiplimab in combination with platinum-doublet chemotherapy is a new first-line treatment option for patients [with] advanced NSCLC without targetable mutations irrespective of histology and PD-L1 levels,” she concluded.

Gogishvili noted a previously announced finding that patients taking cemiplimab saw a 29% relative reduction in the risk of death (overall survival [OS]) compared with those taking chemotherapy alone. She also highlighted a 46% relative reduction in the risk of disease progression (progression-free survival [PFS]) compared with those taking chemotherapy.

The 12-month probability of survival was 66% for those taking the cemiplimab combination vs 56% for those taking chemotherapy.

In announcing topline results in August, officials from Regeneron and Sanofi, which market the immunotherapy as Libtayo, said that independent monitors had called for ending EMPOWER-Lung 3 early due to results seen during a protocol-specific interim analysis.²

Based on earlier findings in the EMPOWER-Lung 1 trial,³ cemiplimab received FDA approval in February 2021 as a first-line therapy in advanced NSCLC for patients with ≥50% PD-L1 expression.⁴ The EMPOWER-Lung 3 study studied patients with squamous and nonsquamous advanced NSCLC, irrespective of PD-L1 expression. These patients screened negative for *ALK*, *EGFR*, and *ROS1* mutations; had not been treated for metastatic or locally advanced disease; and were not eligible for chemoradiation.⁵

The 466 patients in the trial were randomized 2:1 to receive the cemiplimab combination or a placebo plus chemotherapy doublet. At the time of enrollment, 30% had tumors with less than 1% PD-L1 expression, 38% had tumors with 1% to 49% PD-L1 expression, and 33% of patients had tumors with 50% or greater PD-L1 expression. Details of the findings showed:

- The patients' median age was 63.0 years, 57.1% had nonsquamous NSCLC, and 85.2% had stage IV disease.
- Median OS was 21.9 months with cemiplimab plus chemotherapy compared with 13.0 months for chemotherapy and placebo (HR, 0.71; 95% CI, 0.53-0.93; $P = .014$).
- Median PFS was 8.2 months with cemiplimab plus chemotherapy vs 5.0 months for chemotherapy and placebo (HR, 0.56; 95% CI, 0.44-0.70; $P < .0001$).
- The objective response rate was higher and the duration of response was longer with cemiplimab/chemotherapy vs placebo/chemotherapy (43.3% vs 22.7% and 15.6 months vs 7.3 months, respectively).
- Adverse events of grade 3 or higher were more frequent in the cemiplimab vs the placebo arm: 43.6% vs 31.4%.

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- The HRs for OS and PFS in patients with 50% or greater PD-L1 expression were 0.61 and 0.47, respectively, both favoring cemiplimab. The HRs for OS and PFS in patients with 1% to 49% PD-L1 expression were 0.52 and 0.47, respectively, both favoring cemiplimab. The HRs in patients with less than 1% PD-L1 expression were 1.01 for OS, not favoring either arm, and 0.76 for PFS, favoring cemiplimab.
- Analyses of results of most subgroups favored cemiplimab, with the exception of never-smokers and women; however, both groups had low overall enrollment in the trial. Of the 466 patients, 75 were women and 67 were never-smokers.

Lung cancer is the leading cause of cancer death in both the United States and worldwide. Last year, an estimated 225,000 new cases were diagnosed in the United States, most at later stages when it is difficult to treat successfully. In response, the US Preventive Services Task Force recently adopted new screening guidelines to diagnose more people with lung cancer at earlier stages.⁶

According to a statement from Sanofi and Regeneron, approximately 70% of all patients with newly diagnosed NSCLC have less than 50% PD-L1 expression, making it the most common treatment setting. The latest results will likely affect most patients diagnosed with this disease.⁷

“This phase 3 trial was stopped early because Libtayo significantly improved OS compared with chemotherapy, a milestone also achieved by our phase 3 trial for Libtayo monotherapy as a first-line treatment for advanced NSCLC with high PD-L1 expression,” Israel Lowy, MD, PhD, senior vice president for Translational and Clinical Sciences, Oncology at Regeneron, said in the statement.

“Both trials were designed to reflect everyday clinical practice by allowing for the enrollment of patients with difficult-to-treat disease characteristics,” he said.

“This is the second Libtayo trial to demonstrate significant improvement in its primary and key secondary end points for these patient populations, compared with chemotherapy.” ♦

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On Heels of FDA Approval, Mobocertinib Data Take the Stage at ESMO

(CONTINUED FROM COVER)

Approval was based on results from an ongoing phase 1/2 trial (NCT02716116) presented during the American Society of Clinical Oncology 2021 virtual meeting.² Following the September 15 approval, investigators at ESMO presented abstracts involving mobocertinib using both clinical trial and real-world data (RWD).³

USE OF REAL-WORLD DATA. A team led by Sai-Hong I. Ou, MD, PhD, from the Chao Family Comprehensive Cancer Center, University of California, Irvine, School of Medicine, presented a poster that indirectly compared clinical outcomes between 2 patient groups: those treated with mobocertinib 160 mg in a clinical trial and those who

received standard of care, based on deidentified RWD from the Flatiron Health database.³

As precision medicine gains ground in cancer care, the use of RWD has received notice as a way to address ethical and practical solutions to the challenge of studying new therapies in increasingly small populations. An estimated 4% to 12% of patients with NSCLC have *EGFR* exon 20 insertion mutations, making this a rare condition—but one that has faced an unmet need. Using RWD as a comparator arm can reduce the time and cost of a trial.⁴

“Despite differences between controlled trial data and real-world data, in the absence of direct head-to-head trial data, real-world [data] can be used as a comparator for single-arm clinical trials,” the investigators stated.

A total of 164 patients with NSCLC and *EGFR* exon 20 insertion mutations and prior treatment with platinum-based chemotherapy were included in the analysis—114 in the mobocertinib group and 50 in the RWD group. In the mobocertinib group, the median age was 60 years, and 65.8% of patients were women; in the RWD group, the median age was 64 years, and 68% of patients were women. A far higher percentage of the RWD group had a smoking history: 42% vs 28.9% for the mobocertinib group.

Regarding second-line or later treatments in the RWD group, 20% had received EGFR TKI therapy, 40% had been treated with immunotherapy alone, and 40% had received chemotherapy with or without immunotherapy or a monoclonal antibody.

Results were as follows³:

- After propensity score weighting, the objective response rate (ORR) for the mobocertinib group was 35.1% (95% CI, 26.4%-44.6%) vs 11.9% in the RWD group, (95% CI, 5.8%-18.0%), for an absolute difference of 23.2 percentage points (odds ratio, 3.75; 95% CI, 2.05-6.89; $P < .01$).
- Weighted mean progression-free survival (PFS) was 7.3 months for the mobocertinib group (95% CI, 5.6-8.8) vs 3.3 months in the RWD group (95% CI, 2.2-7.3) (HR, 0.57; 95% CI, 0.36-0.90; $P = .0138$).
- Weighted mean overall survival (OS) for the mobocertinib group was 24.0 months (95% CI, 14.6-28.8) vs 12.4 months for the RWD group (95% CI, 7.1-16.6) (HR, 0.53; 95% CI, 0.33-0.83; $P = .0089$).

For patients with NSCLC and *EGFR* exon 20 insertion mutations who had had prior chemotherapy, “mobocertinib demonstrated significantly higher ORR [and] prolonged PFS and OS compared with treatment options used in the real-world setting, even after propensity score weighting,” the investigators said.

DOSE-ESCALATION STUDY. The safety profile of mobocertinib remained manageable across multiple doses in a drug tolerability study involving Japanese patients, leading to the determination that the highest dose, 160 mg, would be recommended for further study.

Other doses of the once-daily oral therapy examined in the study were 40 mg and 120 mg, according to a poster presented during ESMO Congress 2021.⁵

“Mobocertinib 160 mg was confirmed to be tolerable in Japanese patients with NSCLC. In this study, no new safety signals for mobocertinib were observed. The pharmacokinetics of mobocertinib and its 2 active metabolites were characterized in Japanese patients with NSCLC, supporting the once-daily dosing regimen,” the authors wrote.

“Despite differences between controlled trial data and real-world data, in the absence of direct head-to-head trial data, real-world [data] can be used as a comparator for single-arm clinical trials.”

According to the investigators, patients were started on the 40-mg daily dose, followed by higher doses according to an adaptive design model, until a maximum tolerated dose was reached or 160 mg was determined to be safe and tolerable. Twenty patients were enrolled, with 4 patients taking 40 mg, 4 taking 120 mg, and 12 taking 160 mg. Patients were evaluated for dose-limiting toxicities (DLTs).

Patients took mobocertinib for a median duration of 3.45 months, with a median dose level of 119.3 mg per day. No patients had a DLT at the 40-mg dose. One patient receiving the 120-mg dose had a measurable DLT of grade 3 diarrhea. Two patients at the 160-mg dose had DLTs: The first had grade 3 interstitial lung disease (ILD), which led to dose discontinuation; the second patient missed more than 25% of doses because of an aspartate aminotransferase level increase, a grade 3 alanine aminotransferase (ALT) level increase, and grade 2 diarrhea.

Grade 3 or higher treatment-emergent adverse events (TEAEs) were seen in patients who started at the 120- and 160-mg doses. TEAEs at the 120-mg level included diarrhea, lymphocyte count decrease, dehydration, depressed level of consciousness, and embolism. At the 160-mg dose, TEAEs included pneumonia, ILD, ALT level increase, neutrophil count decrease, white blood cell count decrease, and decreased appetite. In the 120-mg cohort, 1 patient died because of underlying disease.

“Almost all patients had at least 1 drug-related diarrhea event, and the median time to initial onset of event was 3 to 4 days (post dose), grade [2 or less] and manageable with concomitant loperamide with no need for dose modification,” the authors wrote.

ORRs were 25.0% in the 120-mg cohort and 16.7% in the 160-mg cohort. The investigator-assessed disease control rate was 50%, 75%, and 75% in the 40-mg, 120-mg, and 160-mg cohorts, respectively. ♦

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Phase 3 Data Solidify Cemiplimab's Role in Second-line Treatment of Cervical Cancer

Mary Caffrey

IN 2018, PRESENTERS at the American Society of Clinical Oncology (ASCO) turned heads with word that they were moving straight to a phase 3 trial in cervical cancer with the checkpoint inhibitor cemiplimab, based on responses from 2 of 3 patients in a phase 1 dose-escalation trial.¹

Results from just 3 patients led to the largest trial to date involving patients with an unmet need in cervical cancer: those with recurrent or metastatic disease who had already been treated with platinum-based chemotherapy. The investigators, led by Krishnansu S. Tewari, MD, professor and director of the Division of Gynecologic Oncology at the University of California, Irvine, launched GOG 3016 (NCT03257267), a study by the Gynecologic Oncology Group (GOG), a nonprofit organization funded by the National Cancer Institute.

Now called EMPOWER-Cervical 1, the trial reported interim results in a May 2021 virtual plenary session of the European Society for Medical Oncology (ESMO), and Tewari followed with a presentation at the ESMO Congress 2021, held September 16 to 21.²

The May results showed that cemiplimab (Libtayo; Regeneron/Sanofi) produced significant benefits:

a 31% reduction in the risk of death (overall survival [OS]) and a 25% reduction in the risk of disease progression (progression-free survival [PFS]). At a September 17 ESMO session, Tewari elaborated on those results and discussed their importance within the context of what women with advanced cervical cancer faced just a few years ago.

Tewari was part of the last big breakthrough in cervical cancer, when in 2013 he was the lead author of a GOG study whose results showed that adding bevacizumab to chemotherapy could improve OS in advanced cervical cancer by 21%.³ But “after that, we had a bit of a drought,” he said.

Commentator Rosalind Glasspool, MBBS, PhD, of the University of Glasgow in Scotland, who appeared before Tewari, agreed. “It was actually Dr. Tewari who led the last practice-changing study back that was published... which demonstrated that the addition of bevacizumab to first-line chemotherapy can improve overall survival. But since then, there's really been no standard treatment in the second line,” she said.

The phase 3 trial compared 304 patients taking cemiplimab with 304 taking investigator's choice of chemotherapy in patients in the second-line setting, regardless

of PD-L1 expression. Patients received either 350 mg of cemiplimab intravenously every 3 weeks or chemotherapy for up to 96 weeks. Results showed the following²:

- Median patient age was 51 years (range 22-87); 477 patients had squamous cell carcinoma (SCC), and 131 had adenocarcinoma (AC).
- Median cemiplimab exposure was 15 weeks.
- Overall, the median OS was 12 months in the cemiplimab group vs 8.5 months in the chemotherapy group (HR, 0.69; 95% CI, 0.56-0.84; $P < .001$).
- In the SCC group, median OS was 11.1 months for cemiplimab vs 8.8 months for chemotherapy (HR, 0.73; 95% CI, 0.58-0.91; $P = .003$). In the AC group, the median OS was 13.3 months for cemiplimab vs 7.0 months for chemotherapy (HR, 0.56; 95% CI, 0.36-0.85; $P < .005$).
- Although patients received benefits regardless of PD-L1 status, Tewari's presentation showed that the benefit compared with chemotherapy was higher among patients with PD-L1 expression of at least 1%.
- Quality-of-life scores for patients taking cemiplimab were maintained or slightly improved from baseline, whereas scores declined for those on chemotherapy.

Tewari said EMPOWER-Cervical 1 stands out for its size and the nature of the patient population, and there were no new safety signals. "We feel this is a drug that can be used in the second-line setting for patients," he said. The arrival of bevacizumab originally met an unmet need, "but it created a new group of patients that also had an unmet need. And [those are] patients who need a second-line therapy."

Glasspool had discussed several emerging issues with the use of immunotherapy in advanced cervical cancer, including the possible use of combination therapy—particularly anti-TIGIT treatment. Tewari added that these are all interesting possibilities but noted that remembering how rapidly the field has moved is important.

"When Regeneron/Sanofi started the [EMPOWER-Cervical 1] trial studying single-agent PD-1 inhibitor cemiplimab vs physician's choice [of] chemotherapy, there was nothing else really being done," he said. "Now the space is so crowded, and I think as we get more and more of the molecular data from these studies and [can] better characterize who are going to be the exceptional responders to various therapies—and who are going to be the poor responders—we're going to be able to figure out where to plug in all these different agents. Because I think there's space for all of them." ♦

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Dr Miranda Gogishvili: "We Continue to Expect Great Things" From Cemiplimab

CEMPLIMAB (LIBTAYO; REGENERON/SANOFI) plus platinum doublet chemotherapy is being investigated in the EMPOWER-Lung 3 trial for first-line use among patients with stage III/IV non-small cell lung cancer (NSCLC) of squamous or nonsquamous histology that is either locally advanced or metastatic and runs the spectrum of programmed death ligand 1 (PD-L1) expression levels. This trial was notably stopped early upon meeting its

overall survival primary end point.¹ Secondary end points were progression-free survival (PFS) and objective response rate (ORR).

An interim data analysis of study data was presented at the European Society for Medical Oncology (ESMO) 2021 Congress by Miranda Gogishvili, MD, showing treatment with a cemiplimab/chemotherapy combination bested the mortality risk seen with placebo/chemotherapy. The

combination increased overall survival by 29%. Superior results with the combination were also seen for PFS, ORR, number of complete and partial responses, and duration of response.

Cemiplimab is already approved in the United States and the European Union for first-line monotherapy treatment of patients with locally advanced or metastatic NSCLC with PD-L1 levels 50% or greater.

In an interview with *Evidence-Based Oncology*[™] (EBO), Gogishvili, an oncologist at High Technology Medical Center University Clinic, in Tbilisi, Georgia, and lead investigator on EMPOWER-Lung 3, discussed data from previous trials on the benefits of cemiplimab, monotherapy vs combination treatment, and plans for regulatory approval.

This interview has been edited slightly for clarity and conciseness.

EBO: Can you discuss the history of cemiplimab in the non-small cell lung cancer setting?

GOGISHVILI: Libtayo is a fully human monoclonal antibody targeting the immune checkpoint receptor PD-1. It's already approved in the United States and the European Union for first-line monotherapy treatment of patients with locally advanced or metastatic NSCLC with a PD-L1 expression of 50% or greater and no targetable mutations.

These approvals were based on results from the phase 3 EMPOWER-Lung 1 trial, in which Libtayo monotherapy demonstrated superior overall survival compared with chemotherapy. Complementing this trial is the phase 3 EMPOWER-Lung 3 trial I presented at ESMO Congress 2021. This trial evaluated Libtayo in combination with physician's choice of platinum doublet chemotherapy vs chemotherapy alone.

As in EMPOWER-Lung 1, enrollment of patients included those with locally advanced or metastatic NSCLC and both squamous and nonsquamous histologies. However, unlike EMPOWER-Lung 1, this trial enrolled patients across all PD-L1 expression levels. The trial demonstrated that the Libtayo combination led to a significant improvement in overall survival compared with chemotherapy, with a median overall survival of 22 months. Significant improvements were also seen in progression-free survival, objective response rate, and duration of response compared with chemotherapy.

EBO: Results presented last year at ESMO from EMPOWER-Lung 4 showed cemiplimab plus ipilimumab produced a superior overall response rate vs cemiplimab monotherapy alone, but in the second-line setting.² Do the latest findings from the first-line setting add novel insight to our

knowledge of cemiplimab, especially that results were seen across the PD-L1 expression spectrum vs just among patients with PD-L1 below 50%?³

GOGISHVILI: The EMPOWER-Lung clinical program has provided a robust set of data for Libtayo in locally advanced and metastatic NSCLC with squamous and nonsquamous histology, as well as with diverse disease characteristics commonly considered difficult to treat. EMPOWER-Lung 1 demonstrated that Libtayo monotherapy could extend patient survival in advanced NSCLC with high PD-L1 expression.

Now, EMPOWER-Lung 3 has demonstrated that Libtayo can also extend patient survival in advanced NSCLC with low PD-L1 expression when combined with chemotherapy.

EBO: Cemiplimab has shown benefit as both a monotherapy and combination therapy for NSCLC, but in the advanced-staged NSCLC setting. Is there also potential benefit for patients with early-stage disease, and what criteria would they need to have to benefit most?

GOGISHVILI: I cannot speculate on this, as there have not been any studies of cemiplimab in early-stage NSCLC.

EBO: Can you discuss why cemiplimab monotherapy has shown success in cases of high PD-L1 expression but combination treatment was more successful across the PD-L1 spectrum?

GOGISHVILI: Several trials have shown that tumor response to PD-1 inhibitor treatment is directly correlated to PD-L1 expression. In other words, the response to PD-1 inhibitor monotherapy treatment tends to decrease as PD-L1 expression decreases. Combining PD-1 inhibitor treatment with chemotherapy has helped to improve the response in patients with low PD-L1 expression, and this has become the standard of care in these patients.

EBO: Duration of response was more than doubled (15.6 vs 7.3 months), number of partial responses was more than tripled (127 vs 35), overall response rate was nearly doubled (43.3% vs 22.7%), and progression-free survival was 64% higher (8.2 vs 5.0 months) in the cemiplimab-plus-chemotherapy arm compared with the placebo-plus-chemotherapy arm. These results were deemed so significant that the trial was stopped early.¹ What next steps are planned in EMPOWER-Lung 3?

GOGISHVILI: These data form the basis of regulatory submissions in the United States, the European Union,

and other countries. We're also planning to conduct additional analysis of the EMPOWER-Lung 3 data, which will hopefully offer new insights to help clinicians in their everyday practice.

EBO: Can you summarize the findings you presented at ESMO and what you hope are the important next steps?

GOGISHVILI: EMPOWER-Lung 3 demonstrated that Libtayo in combination with chemotherapy could significantly extend patient survival compared with chemotherapy alone and achieved these results in a patient population with varied baseline characteristics. Indeed, the trial was designed to reflect everyday clinical practice by allowing for the enrollment of patients with difficult-to-treat disease characteristics.

Furthermore, the trial found that Libtayo in combination helps delay deterioration in patients' reported quality of life and pain symptoms compared with chemotherapy alone. Through more analysis on EMPOWER-Lung 3,

I look forward to seeing what additional insights will be presented that might help oncologists in managing the varied situations they come across in daily clinical practice. ♦

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In HER2+ MBC, Trastuzumab Deruxtecan Slashes Risk of Disease Progression or Death by 72% vs T-DM1

Mary Caffrey

TRASTUZUMAB DERUXTECAN, the HER2-directed antibody-drug conjugate (ADC) sold as Enhertu (AstraZeneca/Daiichi Sanyko), tripled progression-free survival (PFS) over trastuzumab emtansine (T-DM1) in HER2-positive (HER2+) metastatic breast cancer (MBC), according to interim results of a phase 3 trial that showed a 72% reduction in the risk of disease progression or death.¹

The prespecified analysis of DESTINY-Breast03 opened a Presidential Symposium on September 18, during the European Society for Medical Oncology (ESMO) 2021 Congress, with the study's lead author predicting a new standard of care and a commentator calling the results "startling."

"Patients with previously treated HER2+ metastatic breast cancer will typically experience disease progression in less than a year with available HER2-directed treatments," said Javier Cortés, MD, PhD, who presented the results. Cortés, head of the International Breast Cancer Center in Barcelona, Spain, pointed to the "high and consistent benefit" seen in both the efficacy end points and key subgroups.²

"DESTINY-Breast03 is remarkable and supports the potential of [trastuzumab deruxtecan] to become the new standard of care for those who have previously been treated for HER2+ metastatic breast cancer," Cortés said.

Taking note of the PFS curves, with an HR of 0.28, commentator Shanu Modi, MD, of Memorial Sloan Kettering Cancer Center, said, "I don't believe I've seen a hazard ratio like this in HER2+ breast cancer before."

Despite progress in prevention and treatment over the past 2 decades, breast cancer remains the most common cancer in women after skin cancer, and the second-leading cause of cancer death in women worldwide. More than 2 million patients with breast cancer received their diagnosis in 2020, and 685,000 patients died.³

About 1 in 5 patients with breast cancer has HER2+ disease,⁴ which means the disease is triggered by the HER2 protein, a tyrosine kinase receptor that can cause aggressive tumor growth in breast, gastric, lung, and colorectal cancers. Patients with HER2+ MBC will often see their disease progress even after treatment with

trastuzumab and chemotherapy drugs called taxanes, such as paclitaxel.

Trastuzumab deruxtecan (T-DXd) was approved in December 2019 for patients with unresectable or metastatic HER2+ breast cancer who have undergone 2 or more prior anti-HER2–based regimens for MBC. The approval was based on results of an open-label, phase 2 study, DESTINY-Breast01,⁵ for which Modi was the lead author. The drug has also received approval in gastric cancer, and positive results for lung cancer were presented during ESMO 2021 and published in the *New England Journal of Medicine*.⁶

The other ADC, T-DM1, is indicated for the adjuvant treatment of patients with HER2+ breast cancer who have residual invasive disease after being treated with trastuzumab and taxane or who have disease recurrence within 6 months. Thus, DESTINY-Breast03 was designed to compare the 2 ADC therapies head-to-head.

The trial randomized 524 patients in North America, Asia, Europe, South America, and Oceania 1:1 to receive either T-DM1 or T-DXd. The primary end point is PFS as determined by blinded independent central review. Secondary end points include overall survival (OS), objective response rate (ORR), duration of response, and safety.

Results show the following:

- Patients' median age was 54 years (range, 20-83).
- With a data cutoff of May 21, 2021, for the interim analysis, the HR for PFS was 0.2840 ($P = 7.8 \times 10^{-22}$). Median PFS was not reached for T-DXd vs 6.8 months for T-DM1.
- The estimated 12-month OS event rates were 94.1% (95% CI, 90.3%-96.4%) for T-DXd and 85.9% (95% CI, 80.9%-89.7%) for T-DM1 (HR, 0.5546; 95% CI, 0.3587-0.8576). Data are not considered mature, and $P = .007172$ did not cross a prespecified boundary for significance.
- Confirmed ORRs were 79.1% (95% CI, 74.3%-84.4%) for T-DXd vs 34.2% (95% CI, 28.5%-40.3%); $P < .0001$.
- Treatment-emergent adverse events were similar in both arms. There were no drug-related deaths. Adjudicated drug-related interstitial lung disease occurred in 10.5% of patients with T-DXd (most [9.7%] grade 1/2) vs 1.9% with T-DM1 (all grade 1/2).

Modi had presented updated phase 2 results from DESTINY-Breast01 during the Miami Breast Cancer Conference in March 2020 and highlighted the “landmark” 18-month OS of 74%,⁷ but she still seemed surprised by the size of the benefit relative to T-DM1. One question now, she said, is whether T-DM1 will work for patients after T-DXd.

“I do believe that the DESTINY-03 data support T-DXd as a new second-line option for HER2+ metastatic breast cancer,” Modi said. “In particular, there is a clear benefit for the population of patients who have brain metastases. Most importantly, T-DXd delivered in this early-line setting was associated with less lung toxicity, resetting the risk benefit analysis in its favor.”

“Today’s results are groundbreaking,” said Susan Galbraith, executive vice president, Oncology R&D, AstraZeneca. “Enhertu tripled progression-free survival as assessed by investigators, and provided a disease control rate exceeding 95% compared with 77% for T-DM1.”

Taken together with the safety results, “these unprecedented data represent a potential paradigm shift in the treatment of HER2+ metastatic breast cancer,” she said. ♦

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Adjusted Cross-Trial Comparison Finds Larotrectinib Advantages

USE OF MAIC PRESENTED FOR THERAPY THAT TARGETS *NTRK* FUSION+ CANCERS; BENEFIT SEEN REGARDLESS OF PRIOR LINES OF THERAPY.

Mary Caffrey

AN ANALYSIS THAT USES a method of comparing data across clinical trials found benefits in overall survival (OS), duration of response (DOR), and complete response (CR) for larotrectinib (Vitrakvi; Bayer) over entrectinib (Rozlytrek; Genentech), another of the first-generation tropomyosin receptor kinase (TRK) inhibitors approved by FDA.¹⁻³

Authors of the analysis, which was presented in a poster during the virtual European Society for Medical Oncology 2021 Congress, also found a numerical edge for larotrectinib in progression-free survival (PFS) and overall response rate (ORR) but said the results were not statistically significant.³ Safety results were similar and low for both therapies, according to the findings, which were sponsored by Bayer.

Neurotrophic tyrosine receptor kinases (NTRKs) are a group of genes that encode TRK, which regulates the nervous system. When gene fusion causes overexpression of *NTRK* genes, this can trigger tumor development.

Authors of the study said they hoped to offer guidance to stakeholders seeking information on the 2 therapies. “The recent approval of larotrectinib and entrectinib... improved the treatment landscape for patients with *NTRK* fusion-positive cancers, but there is limited information regarding their comparative efficacy and safety,” they wrote in the abstract.

A challenge for payers as the cost of cancer care increases is that the stakes for picking the right therapy are high—but head-to-head clinical trials between competing therapies are rare. Despite limitations, the authors said, use of matching-adjusted indirect comparison, or MAIC, “can balance observed population characteristics to increase comparability between trials and provide comparative evidence in the absence of head-to-head trials.”

The analysis used patient data from 3 trials with larotrectinib through July 2020, along with published aggregate data for entrectinib from 3 trials published through October 2018. Patients were matched by common baseline characteristics, tumor types and disease status, *NTRK* gene, and number of prior therapies. The analysis included 117 patients from larotrectinib’s efficacy population and 147 from its safety population, as well as 74 from entrectinib trials. Median follow-up was 16.9 months for larotrectinib and 14.2 months for entrectinib.

After matching, results showed the following for larotrectinib vs entrectinib, respectively:

- Larotrectinib was associated with longer OS, not reached (NR) vs 23.9 months, for an HR of 0.43 (95% CI, 0.23-0.83; $P < .05$).
- Larotrectinib had numerically longer PFS but missed statistical significance, 19.3 months vs 11.2 months; HR, 0.66 (95% CI, 0.42-1.03; $P = .07$).
- Larotrectinib had better DOR, 32.5 months vs 12.9 months; HR, 0.49 (95% CI, 0.25-0.98; $P < .05$).
- ORR was similar between the therapies, 67.3% vs 63.5%, for a risk difference (RD) of 3.8 (95% CI, -11.7 to 19.3; $P = .63$).
- The CR rate was more favorable for larotrectinib, 20.3% vs 6.8%; RD, 13.5 (95% CI, 2.9-24.1; $P < .05$).

A challenge for payers as the cost of cancer care increases is that the stakes for picking the right therapy are high—but head-to-head clinical trials between competing therapies are rare.

Investigators cited several limitations. MAICs cannot adjust for differences in unobserved baseline characteristics in all trials and those unreported for entrectinib; outcomes and baseline data were not reported by tumor type for entrectinib, which did not allow for subtype analysis. Without a common comparator arm, only an unanchored analysis can occur, the authors said.

Outcomes by Prior Therapy Lines

Here, investigators pooled data from 3 clinical trials for patients with non–central nervous system (CNS) TRK-fusion cancer who received larotrectinib. Patients were stratified by the number of prior lines of therapy or by baseline ECOG performance status, or the equivalent performance status in pediatric patients. The post hoc analysis captured objective response rate (ORR), DOR, PFS, and OS. Data cut-off was July 20, 2020. Results for 218 patients showed the following⁴:

- For all patients, ORR was 75%; median DOR, 49.3 months; median PFS, 35.4 months; and 36-month OS rate, 77%.
- The number of prior lines of therapy (for 216 patients) was 0 lines, 58 patients; 1 line, 59 patients; 2 lines, 42 patients; 3 or more lines, 37 patients. Two patients were excluded from analysis by prior lines of therapy due to data entry ambiguity.
- Grade 3 to 4 adverse events for patients with prior lines of therapy were 0 lines, 19%; 1 line, 24%; 2 lines, 14%; and 3 or more lines, 14%.
- ORR by prior lines 0 lines was 81%; 1 line, 73%; 2 lines, 69%; and 3 or more lines, 75%.
- Median DOR (months) by prior lines was 0 lines, NR; 1 line, NR; 2 lines, 54.7; and 3 or more lines, 33.9.
- Median PFS (months) by prior lines was 0 lines, NR; 1 line, 27.5; 2 lines, 29.4; and 3 or more lines, 28.3.

- Median OS was not reached for any category of prior lines.

Outcomes showed substantial benefit in ORR across ECOG 0 to 2, dropping to 33% for only 3 patients who enrolled at ECOG 3. ORR was 85% for ECOG 0, 66% for ECOG 1, and 61% for ECOG 2. The authors said the findings support the use of larotrectinib in appropriate patients regardless of the priority therapy or ECOG status. “Although the response rates were highest in patients who were treatment naïve or with an ECOG PS of 0, larotrectinib benefited patients across varying degrees of pretreatment and baseline ECOG PS,” they wrote. ♦

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MIL60 Bevacizumab Biosimilar Candidate Demonstrates Equivalence in NSCLC

Tony Hagen

INVESTIGATORS IN CHINA have reported positive equivalence findings from a phase 3 trial of a bevacizumab biosimilar candidate (MIL60) and platinum-based chemotherapy as first-line treatment in Chinese patients with recurrent or advanced non–small cell lung cancer (NSCLC).

The findings, presented in poster form at the European Society for Medical Oncology (ESMO) 2021 Congress, indicated that MIL60 is highly similar to the originator bevacizumab (Avastin; Genentech) in terms of pharmacokinetics (PK), immunogenicity, and safety. MIL60 is

a biosimilar candidate under development by Beijing Mabworks Biotech.

Trial Design

Patients with stage IV or recurrent NSCLC and no previous history of systemic antitumor therapy were randomized 1:1 to 6 cycles of 15 mg/kg intravenous MIL60 plus carboplatin/paclitaxel (full analysis set [FAS], n = 253) or similar dosing of reference bevacizumab plus carboplatin/paclitaxel (FAS, n = 255).

Patients then received MIL60 maintenance therapy (7.5 mg/kg). This afforded further evaluation opportunity through longer exposure.

No patient in either cohort achieved complete response, so the partial response rates were the same as the objective response rates: 48.6% and 43.1% in the biosimilar and reference groups, respectively.

The primary end point was the 12-week objective response rate (ORR) assessed by independent review committee (IRC), and secondary end points included 18-week ORR, duration of response (DOR), disease control rate, progression-free survival (PFS), overall survival (OS), and safety.

The IRC-assessed FAS ORRs for the biosimilar and reference cohorts were 48.6% (95% CI, 42.6%-57.8%) and

43.1% (95% CI, 37.4%-52.1%), respectively. Investigators noted that the ORR finding of 48.6% for the Chinese patient population in the biosimilar cohort was significantly higher than that of Western patients previously studied (38.0%).

Investigators observed no significant differences in median DOR, PFS, or OS. Median OS was 19.3 months and was comparable with previous study findings.

No patients in either cohort achieved complete response, so the partial response rates were the same as the ORRs: 48.6% and 43.1% in the biosimilar and reference groups, respectively. Stable disease was achieved by 44.3% and 45.5%, respectively.

Investigators reported no significant difference between the study arms in the incidence of treatment-emergent adverse events (TEAEs). In the biosimilar and reference cohorts, grade 3 or higher TEAEs occurred in 70.3% and 72.6% of the patients, respectively; the occurrence rates of serious adverse events were 28.1% and 28.6%, and treatment-related TEAEs occurred in 78.9% and 81.1%.

PK parameters also were similar for patients with advanced or recurrent NSCLC. ♦

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Samsung Bioepis Releases Positive 5-Year Follow-up Results for Trastuzumab Biosimilar

Skylar Jeremias

FIVE-YEAR FOLLOW-UP DATA show comparable safety and long-term efficacy profiles between Ontruzant (SB3), a trastuzumab biosimilar developed by Samsung Bioepis, and the reference product, according to a statement from the company.¹

Results from the long-term safety and efficacy analysis were presented at the European Society for Medical Oncology (ESMO) 2021 Congress.²

Trastuzumab medicines are indicated for use in patients with early or metastatic HER2-positive breast cancer, metastatic gastric cancer, and gastroesophageal junction adenocarcinoma. Currently, 5 trastuzumab biosimilars are

approved by the FDA in the United States and 6, including SB3, are approved in the European Union, according to *The Center for Biosimilars*® Biosimilar Approvals.³

“The 5-year follow-up results presented at this year’s ESMO [represent] the longest monitoring data of patients treated with a trastuzumab biosimilar for HER2-positive early or locally advanced breast cancer,” said Donghoon Shin, vice president and team leader of the Medical and Lifecycle Safety Team at Samsung Bioepis, in the company’s statement.

The investigators enrolled 875 patients in a phase 3 trial and administered 8 cycles of the trastuzumab biosimilar or the reference product, Herceptin (Genentech),

in combination with chemotherapy. After completing the regimen and undergoing surgery, the patients received another 10 cycles of the biosimilar or reference product to complete 1 year of treatment.

After the phase 3 trial was completed, 367 patients were enrolled in the follow-up study, during which 186 were in the biosimilar trastuzumab group and 181 were in the reference product group. The median follow-up time was 68 months following randomization.

During the follow-up period, asymptomatic significant left ventricular ejection fraction (LVEF) decrease occurred in 1 patient in the biosimilar group and in 2 patients in the reference product group. All 3 patients recovered with an LVEF of 50% or greater. No cases of symptomatic congestive heart failure or cardiac death were reported in either group.

Recurrence, progression, or death was reported in 32 patients (17.2%) in the biosimilar group and 38 patients (21.0%) in the reference product group (HR, 0.78; 95% CI, 0.48-1.25; $P = .30$). The 5-year event-free survival rates were comparable: 82.8% and 79.7% in the biosimilar and reference product groups, respectively. The 5-year overall survival rate was also similar between the biosimilar and reference product groups (93.1% vs 86.7%; HR, 0.62; 95% CI, 0.32-1.22; $P = .17$).²

“These valuable data signify our continuous dedication in producing high-quality treatments with proven efficacy

and safety....We look forward to sharing our data with the oncology community on the usage of biosimilars based on these long-term follow-up data,” said Shin.

The 150-mg single dose for Ontruzant was approved by the FDA in January 2019 and launched in the US market in April 2020. Ontruzant received marketing authorization from the European Medicines Agency in November 2017. In March 2020, the FDA approved a 420-mg multidose vial of Ontruzant. This dose was also approved in the European Union in March 2019.⁴ ♦

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