

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LIBTAYO® (cemiplimab-rwlc) injection, for intravenous use
Initial U.S. Approval: 2018

RECENT MAJOR CHANGES

Indications and Usage (1.2, 1.3)	02/2021
Dosage and Administration (2.1)	02/2021
Dosage and Administration (2.3)	11/2020
Warnings and Precautions (5.1, 5.3)	11/2020
Warnings and Precautions (5.2)	02/2021

INDICATIONS AND USAGE

LIBTAYO is a programmed death receptor-1 (PD-1) blocking antibody indicated:

Cutaneous Squamous Cell Carcinoma (CSCC)

- 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. (1.1)

Basal Cell Carcinoma (BCC)

- for the treatment of patients with locally advanced BCC (laBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate. (1.2)
- for the treatment of patients with metastatic BCC (mBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.¹ (1.2)

¹The mBCC indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for mBCC may be contingent upon verification and description of clinical benefit.

Non-Small Cell Lung Cancer (NSCLC)

- for the first-line treatment of patients with 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. (1.3, 2.1)

DOSAGE AND ADMINISTRATION

The recommended dosage of LIBTAYO is 350 mg as an intravenous infusion over 30 minutes every 3 weeks. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 350 mg/7 mL (50 mg/mL) solution in a single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Immune-Mediated Adverse Reactions (5.1)
 - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, immune-mediated nephritis and renal dysfunction, and solid organ transplant rejection.
 - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
 - Withhold or permanently discontinue LIBTAYO based on the severity of reaction. (2.3)
- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue based on severity of reaction. (2.3, 5.2)
- Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT): Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)

ADVERSE REACTIONS

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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-877-542-8296 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

1	INDICATIONS AND USAGE	8.2	Lactation
1.1	Cutaneous Squamous Cell Carcinoma	8.3	Females and Males of Reproductive Potential
1.2	Basal Cell Carcinoma	8.4	Pediatric Use
1.3	Non-Small Cell Lung Cancer	8.5	Geriatric Use
2	DOSAGE AND ADMINISTRATION	11	DESCRIPTION
2.1	Patient Selection for NSCLC	12	CLINICAL PHARMACOLOGY
2.2	Recommended Dosage	12.1	Mechanism of Action
2.3	Dosage Modifications for Adverse Reactions	12.3	Pharmacokinetics
2.4	Preparation and Administration	13	NONCLINICAL TOXICOLOGY
3	DOSAGE FORMS AND STRENGTHS	13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility
4	CONTRAINDICATIONS	13.2	Animal Toxicology and/or Pharmacology
5	WARNINGS AND PRECAUTIONS	14	CLINICAL STUDIES
5.1	Severe and Fatal Immune-Mediated Adverse Reactions	14.1	Cutaneous Squamous Cell Carcinoma (CSCC)
5.2	Infusion-Related Reactions	14.2	Basal Cell Carcinoma (BCC)
5.3	Complications of Allogeneic HSCT	14.3	Non-Small Cell Lung Cancer (NSCLC)
5.4	Embryo-Fetal Toxicity	16	HOW SUPPLIED/STORAGE AND HANDLING
6	ADVERSE REACTIONS	17	PATIENT COUNSELING INFORMATION
6.1	Clinical Trials Experience		
6.2	Immunogenicity		
8	USE IN SPECIFIC POPULATIONS		
8.1	Pregnancy		

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

FULL 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.
- with metastatic BCC (mBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate. The mBCC indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for the mBCC indication may be contingent upon verification and description of clinical benefit.

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)*], with no EGFR, ALK or ROS1 aberrations, and is:

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for NSCLC

Select patients with locally advanced or metastatic NSCLC for treatment with LIBTAYO based on PD-L1 expression on tumor cells [*see Clinical Studies (14.3)*].

Information on FDA-approved tests for the detection of PD-L1 expression is available at: <http://www.fda.gov/CompanionDiagnostics>.

2.2 Recommended Dosage

The recommended dosage of LIBTAYO is 350 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

2.3 Dosage Modifications for Adverse Reactions

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 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.

Dosage modifications for LIBTAYO for adverse reactions that require management different from these general guidelines are summarized in [Table 1](#).

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity ^a	Dosage Modifications
Immune-Mediated Adverse Reactions [<i>see Warnings and Precautions (5.1)</i>]		
Pneumonitis	Grade 2	Withhold ^b
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold ^b
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times the ULN	Withhold ^b
	AST or ALT increases to more than 8 times the ULN or Total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver ^c	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold ^b
	AST or ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue

Adverse Reaction	Severity^a	Dosage Modifications
Endocrinopathies	Grades 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold ^b
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold ^b
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3 or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold ^b
	Grades 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions [<i>see Warnings and Precautions (5.2)</i>]	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

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

- a. Based on National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
- b. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg per day (or equivalent) within 12 weeks of initiating steroids.
- c. If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue LIBTAYO based on recommendations for hepatitis with no liver involvement

2.4 Preparation and Administration

- Visually inspect for particulate matter and discoloration prior to administration. LIBTAYO is a clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles. Discard the vial if the solution is cloudy, discolored or contains extraneous particulate matter other than trace amounts of translucent to white particles.

Preparation

- Do not shake.

- Withdraw 7 mL from a vial and dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 1 mg/mL to 20 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard any unused medicinal product or waste material.

Storage of Infusion Solution

- Store at room temperature up to 25°C (77°F) for no more than 8 hours from the time of preparation to the end of the infusion or at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of preparation to the end of infusion.
- Allow the diluted solution to come to room temperature prior to administration.
- Do not freeze.

Administration

- Administer by intravenous infusion over 30 minutes through an intravenous line containing a sterile, in-line or add-on 0.2-micron to 5-micron filter.

3 DOSAGE FORMS AND STRENGTHS

Injection: 350 mg/7 mL (50 mg/mL), clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles in a single-dose vial.

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 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)*].

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)*].

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)*].

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)*].

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)*].

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

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

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% in 810 patients who received LIBTAYO or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis

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

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

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

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

Endocrine: Hypoparathyroidism

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

5.2 Infusion-Related Reactions

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

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

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)*]. 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
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

- a. Composite term includes fatigue and asthenia
- b. 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
- c. Composite term includes pruritus and pruritus allergic
- d. Composite term includes diarrhea and colitis
- e. Composite term includes back pain, pain in extremity, myalgia, musculoskeletal pain, and neck pain
- f. 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

- a. 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)*]. 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 $\geq 10\%$ of patients and Table 5 summarizes Grade 3 or 4 laboratory abnormalities worsening from baseline in $\geq 1\%$ of patients receiving LIBTAYO.

Table 4: Adverse Reactions in $\geq 10\%$ 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 $\geq 1\%$ 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

a. 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 \(14.3\)](#)]. 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 $\geq 10\%$ of patients and [Table 7](#) summarizes Grade 3 or 4 laboratory abnormalities in patients receiving LIBTAYO.

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

Adverse Reactions	LIBTAYO		Chemotherapy	
	N=355		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

- a. 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
- b. 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
- c. Fatigue is a composite term that includes fatigue, asthenia, and malaise
- d. 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
- e. Cough is a composite term that includes cough and productive cough

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

Laboratory Abnormality	LIBTAYO	Chemotherapy
	N=355	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)*]. There are no available data on the use of LIBTAYO in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death (see *Data*). Human IgG4 immunoglobulins (IgG4) are known to cross the placenta; therefore, LIBTAYO has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of cemiplimab-rwlc in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Females

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

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

11 DESCRIPTION

Cemiplimab-rwlc is a human programmed death receptor-1 (PD-1) blocking antibody. Cemiplimab-rwlc is a recombinant human IgG4 monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2. Cemiplimab-rwlc is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture. Cemiplimab-rwlc has an approximate molecular weight of 146 kDa.

LIBTAYO (cemiplimab-rwlc) injection for intravenous use is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution with a pH of 6. The solution may contain trace amounts of translucent to white particles.

Each vial contains 350 mg of cemiplimab-rwlc. Each mL contains cemiplimab-rwlc 50 mg, L-histidine (0.74 mg), L-histidine monohydrochloride monohydrate (1.1 mg), sucrose (50 mg), L-proline (15 mg), Polysorbate 80 (2 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binding of the PD-1 ligands PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors.

Cemiplimab-rwlc is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

12.3 Pharmacokinetics

Cemiplimab-rwlc pharmacokinetic data were collected in 1062 patients with various solid tumors in a population pharmacokinetic analysis. The pharmacokinetics of cemiplimab-rwlc were linear and dose proportional in the dose range of 1 mg/kg to 10 mg/kg LIBTAYO administered intravenously every 2 weeks.

At 350 mg every 3 weeks, the mean cemiplimab-rwlc concentrations (coefficient of variation, CV%) at steady-state ranged between a minimum concentration of 61 mg/L (45%) and a maximum concentration of 171 mg/L (28%). Steady-state exposure is achieved after 4 months of treatment.

In patients with CSCC, cemiplimab-rwlc steady-state exposure at 350 mg every 3 weeks was comparable to the exposure at 3 mg/kg every 2 weeks.

Distribution

The volume of distribution of cemiplimab-rwlc at steady state is 5.3 L (26%).

Elimination

Cemiplimab-rwlc clearance (CV%) after the first dose is 0.29 L/day (33%) and decreases over time by 29%, resulting in a steady-state clearance (CL_{ss}) (CV%) of 0.20 L/day (40%). The elimination half-life (CV%) at steady state is 20.3 days (29%).

Specific Populations

The following factors have no clinically important effect on the exposure of cemiplimab-rwlc: age (27 to 96 years), sex, body weight (31 to 172 kg), cancer type, albumin level (20 to 93 g/L), renal function (creatinine clearance determined by Cockcroft-Gault 21 mL/min or greater) and hepatic function (total bilirubin greater than 1.0 times up to 3.0 times the ULN). Race [White (N=931), Black (N=47), Asian (N=21)] appears to have no clinically important effect on the exposure of cemiplimab-rwlc. LIBTAYO has not been studied in patients with severe hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of cemiplimab-rwlc for carcinogenicity or genotoxicity.

In a 3-month repeat-dose toxicology study in sexually mature cynomolgus monkeys, there were no cemiplimab-rwlc-related effects on fertility parameters (menstrual cycle, semen analysis, or testicular measurements) or in male or female reproductive organs at doses up to the highest dose tested, 50 mg/kg/week (approximately 5.5 to 25.5 times the human exposure based on AUC at the clinical dose of 350 mg once every 3 weeks).

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. *M. tuberculosis*-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout

mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Cutaneous Squamous Cell Carcinoma (CSCC)

The efficacy of LIBTAYO in 219 patients with metastatic (nodal or distant) cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who were not candidates for curative surgery or curative radiation was evaluated in two open-label, multi-center, non-randomized, multicohort studies: Study 1423 (NCT02383212) and Study 1540 (NCT02760498). Both studies excluded patients with autoimmune disease that required systemic therapy with immunosuppressant agents within 5 years; history of solid organ transplant; prior treatment with anti-PD-1/PD-L1 blocking antibodies or other immune checkpoint inhibitor therapy; infection with HIV, hepatitis B or hepatitis C; or ECOG PS \geq 2.

Patients received LIBTAYO 3 mg/kg intravenously every 2 weeks for up to 48 weeks in Study 1423 or up to 96 weeks in Study 1540. An additional cohort of patients in Study 1540 received 350 mg every 3 weeks for up to 54 weeks. Treatment continued until progression of disease, unacceptable toxicity, or completion of planned treatment. Tumor response assessments were performed every 8 or 9 weeks. The major efficacy outcome measures were confirmed objective response rate (ORR), defined as complete response (CR) plus partial response (PR) as assessed by independent central review (ICR), and ICR-assessed duration of response (DOR). For patients with mCSCC without externally visible target lesions, ORR was determined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1). For patients with externally visible target lesions (laCSCC and mCSCC), ORR was determined by a composite endpoint that integrated ICR assessments of radiologic data (RECIST 1.1) and digital medical photography (WHO criteria).

Study 1540

Among the 193 patients with advanced CSCC enrolled in Study 1540 who received LIBTAYO at either 3 mg/kg every 2 weeks or 350 mg every three weeks, 115 had mCSCC and 78 had laCSCC. The median age was 72 years (38 to 96 years); 83% were male; 97% were White; 45% had ECOG PS 0 and 55% had ECOG PS 1; 34% received at least one prior anti-cancer systemic therapy; 90% received prior cancer-related surgery; and 68% received prior radiotherapy. Among patients with mCSCC, 77% had distant metastases and 23% had only nodal metastases.

For the responding patients presented in [Table 8](#) below, the median time to response was 1.9 months (range: 1.7 to 9.1 months).

Efficacy results in patients who received 3 mg/kg every 2 weeks are presented in [Table 8](#).

Table 8: Efficacy Results for Study 1540 in CSCC: 3 mg/kg every 2 weeks

Efficacy Endpoints^a	Metastatic CSCC LIBTAYO 3 mg/kg every 2 weeks	Locally Advanced CSCC LIBTAYO 3 mg/kg every 2 weeks	Combined CSCC
	N = 59	N = 78	N = 137
Confirmed Objective Response Rate (ORR)			
ORR (95% CI)	49% (36, 63)	44% (32, 55)	46% (37, 55)
Complete response (95% CI) ^b	17% (8, 29)	13% (6, 22)	15% (9, 22)
Partial response (95% CI)	32% (21, 46)	31% (21, 42)	31% (24, 40)
Duration of Response (DOR)			
Median DOR in months (Range)	NR (2.8 – 21.6+)	NR (1.9 – 24.2+)	NR (1.9 – 24.2+)
Patients with observed DOR ≥ 6 months, n (%) ^c	27 (93%)	23 (68%)	50 (79%)
Patients with observed DOR ≥ 12 months, n (%) ^c	22 (76%)	12 (35%)	34 (54%)

CI: confidence interval; NR: Not reached; +: Denotes ongoing at last assessment

- Median duration of follow up: mCSCC: 16.5 months; laCSCC: 9.3 months; combined CSCC: 11.1 months
- Only includes patients with complete healing of prior cutaneous involvement; laCSCC patients in Study 1540 required biopsy to confirm CR
- The numerator includes the number of patients whose observed DOR reached at least the specified times of 6 or 12 months. Patients who did not have the opportunity to reach the specified timepoint were included in the denominator only

Study 1540: 350 mg every 3 weeks

In an additional cohort in Study 1540, 56 patients received cemiplimab-rwlc at a dose of 350 mg intravenously every 3 weeks for up to 54 weeks. With a median duration of follow-up of 8.0 months, the confirmed ORR was 41% (95% CI: 28, 55), and 65% of responders had a DOR ≥ 6 months.

Study 1423

Among 26 CSCC patients in Study 1423, 16 had mCSCC and 10 had laCSCC. The median age was 73 years (52 to 88 years); 81% of patients were male; 92% of patients were White; the ECOG PS was 0 (38%) and 1 (62%); 58% of patients had received at least 1 prior anti-cancer systemic therapy; 92% of patients had received prior cancer-related surgery and 81% had

received prior radiotherapy. One patient in the mCSCC group was dosed at 1 mg/kg. The rest received 3 mg/kg every 2 weeks.

With a median duration of follow-up of 13.3 months, the confirmed ORR was 50% (95% CI: 30, 70); all responses were PRs. The median time to response was 1.9 months (range: 1.7 to 7.3 months) and 85% of responders had a DOR \geq 6 months.

14.2 Basal Cell Carcinoma (BCC)

The efficacy of LIBTAYO in 112 patients with advanced basal cell carcinoma (BCC) [unresectable locally advanced (laBCC) or metastatic (nodal or distant) (mBCC)] who had progressed on hedgehog pathway inhibitor (HHI) therapy, had not had an objective response after 9 months on HHI therapy, or were intolerant of prior HHI therapy was evaluated in Study 1620 (NCT03132636), an open-label, multi-center, non-randomized study. The study excluded patients with autoimmune disease that required systemic therapy with immunosuppressant agents within 5 years; history of solid organ transplant; prior treatment with anti-PD-1/PD-L1 therapy or other immune checkpoint inhibitor therapy; infection with HIV, hepatitis B or hepatitis C; or ECOG performance score (PS) \geq 2.

Patients received LIBTAYO 350 mg every 3 weeks for up to 93 weeks until disease progression, unacceptable toxicity, or completion of planned treatment. Tumor assessments were performed every 9 weeks for the first 45 weeks of treatment and every 12 weeks thereafter. The major efficacy outcome measures were confirmed objective response rate (ORR) and duration of response (DOR) as assessed by independent central review (ICR). For patients with mBCC without externally visible target lesions, ORR was determined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1). For patients with externally visible target lesions (laBCC and mBCC), ORR was determined by a composite endpoint that integrated ICR assessments of radiologic data (RECIST 1.1) and digital medical photography (WHO criteria).

A total of 112 patients with advanced BCC were included in the efficacy analysis of Study 1620. Of these, 25% had mBCC and 75% had laBCC. In patients with laBCC, the median age was 70 years (42 to 89 years); 67% were male; 68% were White; 61% had ECOG PS 0 and 39% had ECOG PS 1; 83% had received at least 1 prior cancer-related surgery; and 50% had received prior radiotherapy. In patients with mBCC, the median age was 65.5 years (38 to 90 years); 82% were male; 79% were White; 57% had ECOG PS 0 and 43% had ECOG PS 1; 82% had received at least 1 prior cancer-related surgery; and 61% had received prior radiotherapy. Among patients with mBCC, 32% had distant metastases only, 14% had nodal disease only, and 54% had both distant and nodal disease.

Efficacy results are presented in [Table 9](#). For the responding patients, the median time to response was 3.2 months (range 2.1 to 10.5 months) for the mBCC group and 4.2 months (range 2.1 to 13.4 months) for the laBCC group.

Table 9: Efficacy Results for Study 1620 in BCC

Efficacy Endpoints^a	Metastatic BCC	Locally Advanced BCC
	N = 28	N = 84
Confirmed Objective Response Rate (ORR)		
ORR, n (%) (95% CI)	6 (21%) (8, 41)	24 (29%) (19, 40)
Complete response, n (%)	0	5 (6%)
Partial response, n (%)	6 (21%)	19 (23%)
Duration of Response (DOR)		
Median DOR in months (Range)	NR (9.0 - 23.0+)	NR (2.1 - 21.4+)
Patients with observed DOR ≥ 6 months, n (%)	6 (100%)	19 (79.2%)

CI: confidence interval; NR: Not reached; +: Denotes ongoing at last assessment

a. Median duration of follow up: mBCC 9.5 months; laBCC 15.1 months

14.3 Non-Small Cell Lung Cancer (NSCLC)

The efficacy of LIBTAYO was evaluated in Study 1624 (NCT03088540), a randomized, multi-center, open-label, active-controlled trial in 710 patients with locally advanced NSCLC who were not candidates for surgical resection or definitive chemoradiation, or with metastatic NSCLC.

Only patients whose tumors had high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit and who had not received prior systemic treatment for metastatic NSCLC were eligible.

Patients with EGFR, ALK or ROS1 genomic tumor aberrations; a medical condition that required systemic immunosuppression; autoimmune disease that required systemic therapy within 2 years of treatment; or who had never smoked were ineligible. Patients with a history of brain metastases were eligible if they had been adequately treated and had neurologically returned to baseline for at least 2 weeks prior to randomization.

Randomization was stratified by histology (non-squamous vs squamous) and geographic region (Europe vs Asia vs Rest of world). Patients were randomized (1:1) to receive LIBTAYO 350 mg intravenously (IV) every 3 weeks for up to 108 weeks or a platinum-doublet chemotherapy regimen for 4 to 6 cycles followed by optional pemetrexed maintenance for patients with non-squamous histology who received a pemetrexed containing regimen.

Treatment with LIBTAYO continued until RECIST 1.1-defined progressive disease, unacceptable toxicity, or up to 108 weeks. Patients who experienced IRC-assessed RECIST 1.1-defined progressive disease on LIBTAYO therapy were permitted to continue treatment with LIBTAYO (up to an additional 108 weeks) with the addition of 4 cycles of histology-specific chemotherapy until further progression was observed. Of the 203 patients randomized to receive chemotherapy who had IRC-assessed RECIST 1.1- defined disease progression, 150 (74%)

patients crossed over to treatment with LIBTAYO. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS). An additional efficacy outcome measure was overall response rate (ORR).

The study population characteristics were: median age of 63 years (range: 31 to 84 years), 45% age 65 or older; 85% male; 86% White, 11% Asian; and 0.6% Black. Nine percent were Hispanic or Latino. Twenty-seven percent had ECOG PS 0 and 73% had ECOG PS 1; 84% had metastatic disease and 16% had stage IIIB or IIIC disease and were not candidates for surgical resection or definitive chemoradiation per investigator assessment; 56% had non-squamous and 44% had squamous histology; and 12% had history of treated brain metastases at baseline.

The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to LIBTAYO as compared with chemotherapy.

Efficacy results are presented in [Table 10](#) and [Figure 1](#).

Table 10: Efficacy Results from Study 1624 in Non-Small Cell Lung Cancer

Endpoints	LIBTAYO N=356	Chemotherapy N=354
Overall Survival		
Number of deaths (%)	108 (30)	141 (40)
Median in months (95% CI) ^a	22.1 (17.7, NE)	14.3 (11.7, 19.2)
Hazard ratio (95% CI) ^b	0.68 (0.53, 0.87)	
p-value	0.0022	
Progression-free Survival per BICR		
Number of events (%)	201 (57)	262 (74)
Median in months (95% CI) ^a	6.2 (4.5, 8.3)	5.6 (4.5, 6.1)
Hazard ratio (95% CI) ^b	0.59 (0.49, 0.72)	
p-value	<0.0001	
Overall Response Rate per BICR (%)^c		
ORR (95% CI)	37 (32, 42)	21 (17, 25)
Complete response (CR) rate	3	1
Partial response (PR) rate	33	20
Duration of Response per BICR		
Median in months (range)	21.0 (1.9+, 23.3+)	6.0 (1.3+, 16.5+)

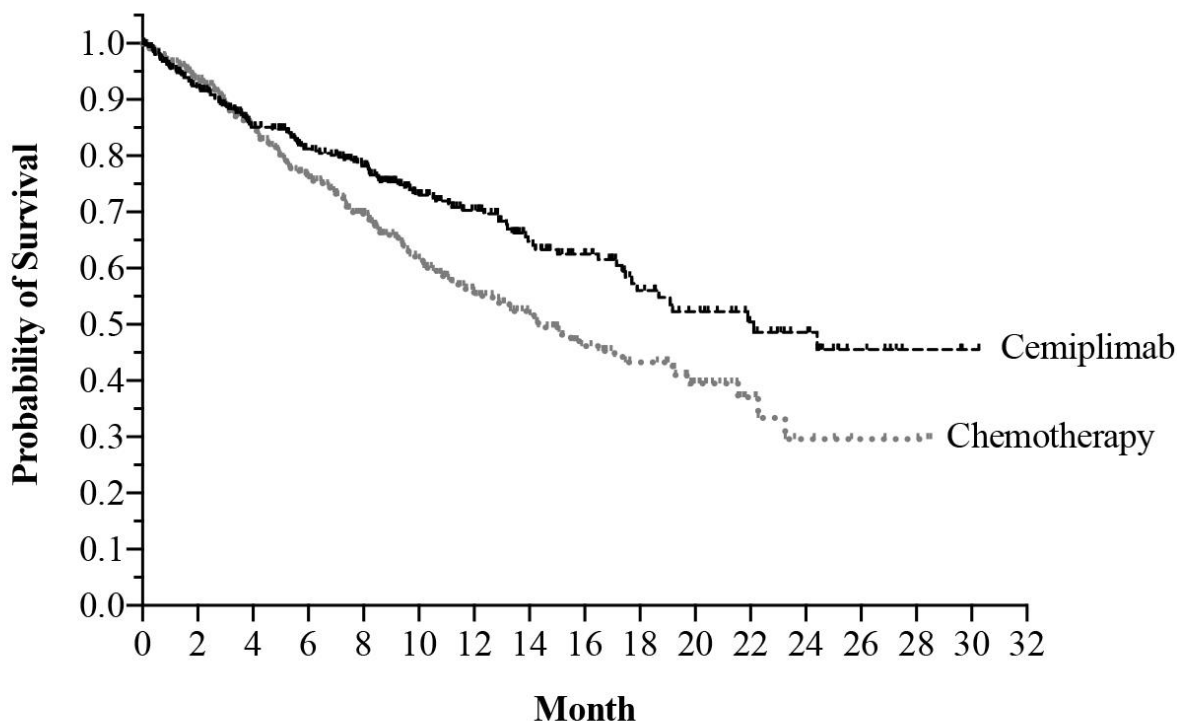
BICR: blinded independent central review, CI: confidence interval; NE: Not evaluable; +: Ongoing response

^a Based on Kaplan-Meier method

^b Based on stratified proportional hazards model

^c Clopper-Pearson exact confidence interval

Figure 1: Kaplan-Meier Curve for OS from Study 1624



Number of Subjects at Risk

Cemiplimab	356	304	254	223	198	147	120	87	71	48	37	27	18	8	3	1	0
Chemotherapy	354	303	254	205	172	126	93	73	52	41	27	12	7	4	3	0	0

16 HOW SUPPLIED/STORAGE AND HANDLING

LIBTAYO (cemiplimab-rwlc) injection is a clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles. It is supplied in a carton containing 1 single-dose vial of:

- 350 mg/7 mL (50 mg/mL) (NDC 61755-008-01)

Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Protect from light. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

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

Immune-Mediated Adverse Reactions

Advise patients that LIBTAYO can cause immune-mediated adverse reactions including the following [see [Warnings and Precautions \(5.1\)](#)]:

- **Pneumonitis:** Advise patients to contact their healthcare provider immediately for signs or symptoms of pneumonitis, including new or worsening symptoms of cough, chest pain, or shortness of breath.

- Colitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of colitis, including diarrhea, blood or mucus in stools, or severe abdominal pain.
- Hepatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatitis.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, or type 1 diabetes mellitus.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.
- Dermatologic Adverse Reactions: Advise patients to contact their healthcare provider immediately if they develop a new rash.

Infusion-Related Reactions

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

Complications of Allogeneic HSCT or Solid Organ Transplant Rejection

Advise patients to contact their healthcare provider immediately if they develop signs or symptoms of post-allogeneic HSCT complications or of solid organ transplant rejection [see *Warnings and Precautions (5.1, 5.3)*].

Embryo-Fetal Toxicity

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

Advise females of reproductive potential to use effective contraception during treatment and for at least 4 months after the last dose of LIBTAYO [see *Use in Specific Populations (8.3)*].

Lactation

Advise female patients not to breastfeed while taking LIBTAYO and for at least 4 months after the last dose [see *Use in Specific Populations (8.2)*].

REGENERON

Manufactured by:

Regeneron Pharmaceuticals, Inc.
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Tarrytown, NY 10591-6707
U.S. License No. 1760

Marketed by:

Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591) and
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MEDICATION GUIDE

LIBTAYO® (Lib-TIE-oh)
(cemiplimab-rwlc)
injection

What is the most important information I should know about LIBTAYO?

LIBTAYO is a medicine that may treat certain types of cancers by working with your immune system. LIBTAYO can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You can have more than one of these problems at the same time. These problems may happen anytime during treatment or even after your treatment has ended.

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

Lung problems.

- cough
- shortness of breath
- chest pain

Intestinal problems.

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

Liver problems.

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

Hormone gland problems.

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

Kidney problems.

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

Skin problems.

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

Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with LIBTAYO. Call or see your healthcare provider right away for any new or worsening signs or symptoms which may include:

- chest pain, irregular heartbeat, shortness of breath or swelling of ankles
- confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs

- double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- persistent or severe muscle pain or weakness, muscle cramps
- low red blood cells, bruising

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

- | | |
|-----------------------------------|-------------------------|
| • nausea | • dizziness |
| • chills or shaking | • feel like passing out |
| • itching or rash | • fever |
| • flushing | • back or neck pain |
| • shortness of breath or wheezing | • facial swelling |

Rejection of a transplanted organ. Your healthcare provider should tell you what signs and symptoms you should report and monitor you, depending on the type of organ transplant that you have had.

Complications, including graft-versus-host disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with LIBTAYO. Your healthcare provider will monitor you for these complications.

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

What is LIBTAYO?

LIBTAYO is a prescription medicine used to treat people with:

- a type of skin cancer called cutaneous squamous cell carcinoma (CSCC). LIBTAYO may be used to treat CSCC that has spread or cannot be cured by surgery or radiation.
- a type of skin cancer called basal cell carcinoma (BCC). LIBTAYO may be used when your BCC:
 - cannot be removed by surgery (locally advanced BCC) and you have received treatment with a hedgehog pathway inhibitor (HHI), or if you cannot receive treatment with a HHI.
 - has spread (metastatic BCC) and you have received treatment with a HHI, or if you cannot receive treatment with a HHI.
- a type of lung cancer called non-small cell lung cancer (NSCLC).
 - LIBTAYO may be used as your first treatment when your lung cancer:
 - has not spread outside your chest (locally advanced lung cancer) and you cannot have surgery or chemotherapy with radiation, **or**
 - your lung cancer has spread to other areas of your body (metastatic lung cancer), **and**
 - your tumor tests positive for high “PD-L1” **and**
 - your tumor does not have an abnormal “EGFR,” ALK “or “ROS1” gene

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

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

- have immune system problems such as Crohn’s disease, ulcerative colitis, or lupus
- have received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. LIBTAYO can harm your unborn baby.

Females who are able to become pregnant:

- Your healthcare provider will give you a pregnancy test before you start treatment with LIBTAYO.
- You should use an effective method of birth control during your treatment and for at least 4 months after the last dose of LIBTAYO. Talk to your healthcare provider about birth control methods that you can use during this time.
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with LIBTAYO.

- are breastfeeding or plan to breastfeed. It is not known if LIBTAYO passes into your breast milk. Do not breastfeed during treatment and for at least 4 months after the last dose of LIBTAYO.

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

How will I receive LIBTAYO?

- Your healthcare provider will give you LIBTAYO into your vein through an intravenous (IV) line over 30 minutes.
- LIBTAYO is usually given every 3 weeks.
- Your healthcare provider will decide how many treatments you will need.
- Your healthcare provider will do blood tests to check you for side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of LIBTAYO?

LIBTAYO can cause serious side effects, including:

- **See “What is the most important information I should know about LIBTAYO?”**

The most common side effects of LIBTAYO include muscle or bone pain, tiredness, rash, and diarrhea.

These are not all the possible side effects of LIBTAYO.

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

General information about the safe and effective use of LIBTAYO.

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

What are the ingredients of LIBTAYO?

Active ingredient: cemiplimab-rwlc

Inactive ingredients: L-histidine, L-histidine monohydrochloride monohydrate, sucrose, L-proline, Polysorbate 80, and Water for Injection, USP.

Manufactured by: Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591-6707 U.S. License No. 1760

Marketed by: Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591) and sanofi-aventis U.S. LLC (Bridgewater, NJ 08807)

For more information, call 1-877-542-8296

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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