TRADEMARK ASSIGNMENT COVER SHEET

Electronic Version v1.1
Stylesheet Version v1.2

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SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT OF THE ENTIRE INTEREST AND THE GOODWILL

CONVEYING PARTY DATA

Name	Formerly	Execution Date	Entity Type
SANOFI BIOTECHNOLOGY		11/30/2018	Corporation: FRANCE

RECEIVING PARTY DATA

Name:	REGENERON PHARMACEUTICALS, INC.
Street Address:	777 Old Saw Mill River Road
City:	Tarrytown
State/Country:	NEW YORK
Postal Code:	10591
Entity Type:	Corporation: NEW YORK

PROPERTY NUMBERS Total: 1

Property Type	Number	Word Mark
Registration Number:	5432812	LIBTAYO

CORRESPONDENCE DATA

Fax Number: 2033276401

Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent using a fax number, if provided; if that is unsuccessful, it will be sent via US Mail.

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Email: trademark@ogrp.com
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CH $40.00 5432812

ATTORNEY DOCKET NUMBER:	554.1557UST1
NAME OF SUBMITTER:	Terrence J. McAllister
SIGNATURE:	/Terrence J. McAllister/
DATE SIGNED:	12/07/2018

Total Attachments: 10
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TRADEMARK ASSIGNMENT AGREEMENT

This Trademark Assignment Agreement (the "Agreement") is effective as of the 30th of November 2018 (the "Effective date"), by and between SANOFI BIOTECHNOLOGY with its principal place of business located at 54, rue La Boétie, 75008 Paris, France (the "Assignor") and REGENERON PHARMACEUTICALS, INC. (the "Assignee") with its principal place of business located at 777 Old Saw Mill River Road, Tarrytown, NY 10591, USA.

The Assignor and the Assignee are individually referred to as a "Party" and collectively as the "Parties."

Unless otherwise indicated explicitly herein, all the provisions set forth in the Immuno-Oncology License and Collaboration Agreement (the "Collaboration Agreement," as defined below) shall be applicable to this Agreement. All capitalized terms used in the present Agreement and the Collaboration Agreement shall have the meaning ascribed in the Collaboration Agreement.

WITNESSETH

WHEREAS on July 1, 2015 the Assignor and the Assignee entered into an Immuno-Oncology License and Collaboration Agreement (the "Collaboration Agreement"); and

WHEREAS the Product Trademark LIBTAYO has been chosen for the cemiplimab-rwlc, PD-1 Licensed Product for the treatment of advanced cutaneous squamous cell carcinoma (CSCC) ("LIBTAYO Product"), and

WHEREAS Assignor is the owner of the trademark LIBTAYO in the United States of America ("USA") and the USA Trademark Registration No. 5432812 for LIBTAYO, registered on March 27, 2018 (the "Trademark"); and

WHEREAS on September 28, 2018, the US Food and Drug Administration approved the LIBTAYO Product for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation and Assignor and Assignee have sold the LIBTAYO Product in the USA for such treatment; and

WHEREAS Assignor and Assignee co-market the LIBTAYO Product in the USA and the packaging, vials and package insert for such LIBTAYO Product in the USA include the LIBTAYO Product Trademark, respective examples of which are attached to this Agreement; and

WHEREAS pursuant to the Collaboration Agreement, Assignee is the Lead Commercialization Party for all PD-1 Licensed Products in the USA and is therefore entitled pursuant to the Collaboration Agreement to own and retain all right, title and interest in and to the Product Trademark for the cemiplimab-rwlc, PD-1 Licensed Product in the USA; and

WHEREAS in accordance with the terms of the Collaboration Agreement, the Assignor now wishes to assign the Trademark to the Assignee and the Assignee wishes to accept such assignment;

NOW THEREFORE, it is hereby agreed as follows:

Section 1/ Assignment

NOW THEREFORE, for good and valuable consideration, receipt and sufficiency of which is hereby acknowledged, the Assignor hereby expressly assigns, as of the Effective Date, to the Assignee, Assignor's entire right, title and interest in and to the Trademark, including the goodwill of the business connected with the use of and symbolized by the Trademark, and the right to claim priority, in accordance with the terms and conditions set forth herein.

Section 2/ Representations and warranties

2.1 Assignor hereby represents and warrants that it is the sole and beneficial owner of the Trademark.

2.2 Assignor makes no warranty with respect to the Trademark other than the one relating to their material existence.

Section 3 /Enforcement of the Trademark

3.1 The Assignment shall also include all the Assignor's rights to sue for past infringements which are not barred pursuant to any applicable statute of limitation at the Effective Date.

3.2 Only the Assignee will be entitled to act against any counterfeiter or infringer of the assigned Trademark including concerning any counterfeiting or infringing acts that have occurred before the Effective Date.

Section 4/Financial provisions

The Financial provisions applicable to this Agreement are those set forth in the Collaboration Agreement.

Section 5/Management of the Trademark

The prosecution and maintenance rules of the Trademark applicable to this Agreement are those set forth in the Collaboration Agreement.

Section 6/License

Assignee hereby grants to Assignor a co-exclusive license to the Trademark under the terms set forth in the Collaboration Agreement.

Section 7/Applicable Law and conflict Resolution

The Governing law, Jurisdiction and Conflict Resolution applicable to this Agreement are those set forth in the Collaboration Agreement.

Section 8/Miscellaneous

8.1 This Trademark Assignment Agreement shall be binding upon and inure to the benefit of the Parties and their respective successors and permitted assigns. Nothing in this Agreement shall create or be deemed to create any third party beneficiary rights in any individual, corporation, partnership, association, trust or other legal entity or organization not Party to this Agreement. No assignment of this Agreement or of any rights or obligations hereunder may be made by either Party without the prior written consent of the other Party and any attempted assignment without such required consent shall be null and void.

8.2 This Trademark Assignment Agreement may only be amended, supplemented or modified and any provision hereof may only be waived, pursuant to a written instrument making specific reference to this Agreement and executed by duly authorized representatives of the Parties.

8.3 This Trademark Assignment Agreement may be executed in any number of counterparts, each of which shall be deemed to be an original, and all of which together shall constitute one and the same instrument.

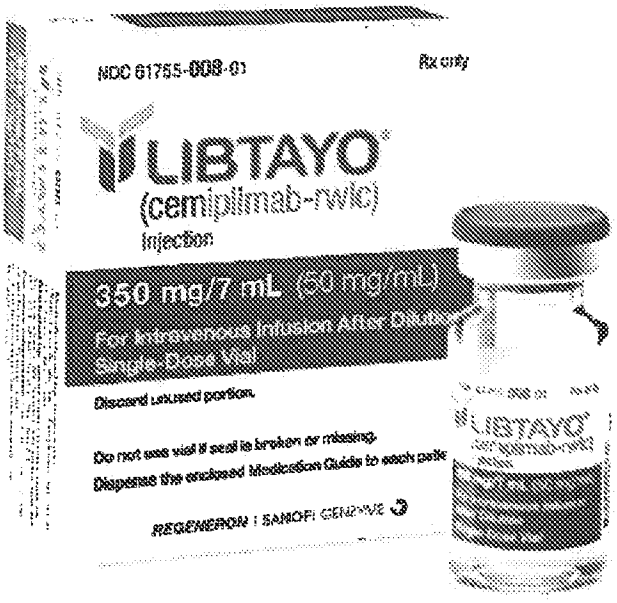
IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their duly authorized representatives.

At:

Date:

Sanofi Biotechnology	**Regeneron Pharmaceuticals, Inc.**
Signature:	Signature:
Printed Name: Emmanuelle RAGON	Printed Name: Gonzalo Mesino
Title: Proxy Holder	Title: VP and Chief IP Counsel

EM


NDC 61755-008-01
Rx only
LIBTAYO
(cemiplimab-rwlc)
Injection
350 mg/7 mL (50 mg/mL)
For Intravenous Infusion After Dilution
Single-Dose Vial
Discard unused portion.
Do not use vial if seal is broken or missing.
Dispense the enclosed Medication Guide to each patie
REGENERON | SANOFI GENZYME
LIBTAYO

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 a type of skin cancer 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. 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 symptoms of the following problems or these symptoms get worse:

Lung problems (pneumonitis). Signs and symptoms of pneumonitis may include:
- new or worsening cough
- shortness of breath
- chest pain

Intestinal problems (colitis) that can lead to tears or holes in your intestine. Signs and symptoms of colitis may include:
- 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 (hepatitis). Signs and symptoms of hepatitis may include:
- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- drowsiness
- dark urine (tea colored)
- bleeding or bruising more easily than normal
- feeling less hungry than usual

Hormone gland problems (especially the adrenal glands, pituitary, thyroid, and pancreas). Signs and symptoms that your hormone glands are not working properly may include:
- headache that will not go away or unusual headaches
- rapid heart beat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- dizziness or fainting
- feeling more hungry or thirsty than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- very low blood pressure
- urinating more often than usual
- nausea or vomiting
- stomach-area (abdomen) pain
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems, including nephritis and kidney failure. Signs of these problems may include:
- decrease in your amount of urine
- blood in your urine
- swelling in your ankles
- loss of appetite

Skin problems. Signs of these problems may include:
- rash
- itching
- skin blistering
- painful sores or ulcers in mouth or nose, throat, or genital area

Problems in other organs. Signs of these problems may include:
- headache
- tiredness or weakness
- sleepiness
- changes in heartbeat, such as beating fast, or seeming to skip a beat, or pounding sensation
- seeing or hearing things that are not there (hallucinations)
- severe muscle weakness
- low red blood cells (anemia)
- bruises on the skin or bleeding
- changes in eyesight
- confusion, fever, muscle weakness, balance problems, nausea, vomiting, stiff neck, memory problems, or seizures (encephalitis)
- swollen lymph nodes, rash or tender lumps on skin, cough, shortness of breath, vision changes, or eye pain (sarcoidosis)

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

Infusion (IV) reactions that can sometimes be severe and life-threatening. Signs of these problems may include:
- chills or shaking
- itching or rash
- flushing
- shortness of breath or wheezing
- dizziness
- fever
- feel like passing out
- back or neck pain
- facial swelling

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 delay or completely stop treatment with LIBTAYO if you have severe side effects.

Efficacy results are presented in Table 4.

Table 4: Efficacy Results for Study 1423 and Study 1540

Efficacy Endpoints*	Metastatic CSCC N = 75	Locally Advanced CSCC N = 33	Combined CSCC N = 108
Confirmed Objective Response Rate			
Objective response rate (95% CI)	46.7% (35.1%, 58.6%)	48.5% (30.8%, 66.5%)	47.2% (37.5%, 57.1%)
Complete response (CR) rate†	5.3%	0%	3.7%
Partial response (PR) rate	41.3%	48.5%	43.5%
Duration of Response			
Range in months	2.8 – 15.2+	1 – 12.9+	1 – 15.2+
Patients with DOR ≥ 6 months, n %	21 (60%)	10 (63%)	31 (61%)

CI: confidence interval; +: Denotes ongoing at last assessment

* Median duration of follow up: metastatic CSCC: 8.1 months; locally advanced CSCC: 10.2 months; combined CSCC: 8.9 months

† Only includes patients with complete healing of prior cutaneous involvement; locally advanced CSCC patients in Study 1540 required biopsy to confirm complete response.

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)]*.

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 (5.3) 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.
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)

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 398 of 534 patients who received LIBTAYO and the incidence of cemiplimab-rwlc treatment-emergent ADAs was 1.3% using an electrochemiluminescent (ECL) bridging immunoassay; 0.3% 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 163 patients with metastatic and locally advanced CSCC who received LIBTAYO in clinical studies, 72% were 65 years or older and 37% were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

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, 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 (PK) data were collected in 505 patients with various solid tumors, including 135 patients with CSCC. The PK of cemiplimab-rwlc was linear and dose proportional in the dose range of 1 mg/kg to 10 mg/kg administered intravenously every two weeks and 350 mg intravenously administered every three weeks.

After a dose of 350 mg LIBTAYO administered intravenously every 3 weeks, median steady-state concentrations (CV%) of cemiplimab-rwlc ranged between a maximum concentration ($C_{max,ss}$) of 186 mcg/mL (28%) and a minimum concentration ($C_{min,ss}$) of 59 mcg/mL (42%). Steady-state exposure is achieved after approximately 4 months of treatment.

Distribution

The volume of distribution of cemiplimab-rwlc at steady state is 5.3 L (25%).

Elimination

Cemiplimab-rwlc clearance (CV%) after the first dose is 0.32 L/day (39%) and decreases over time by 34%, resulting in a steady-state clearance (CL_{ss}) (CV%) of 0.21 L/day (39%). The elimination half-life (CV%) at steady state is 19 days (36%).

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 166 kg), race (White, Black, Asian and other), cancer type, albumin level (22 to 48 g/L), renal function (creatinine clearance determined by Cockcroft-Gault 25 to 429 mL/min) and hepatic function (total bilirubin 0.35 to 45 µmol/L). LIBTAYO has not been studied in patients with moderate or 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

The efficacy of LIBTAYO in patients with metastatic (nodal or distant) cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC 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 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 performance score (PS) ≥ 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. Treatment continued until progression of disease, unacceptable toxicity, or completion of planned treatment. Tumor response assessments were performed every 8 weeks. The major efficacy outcome measures were confirmed objective response rate (ORR), as assessed by independent central review (ICR) and ICR-assessed duration of response. For patients with metastatic CSCC 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 (locally advanced and metastatic CSCC), ORR was determined by a composite endpoint that integrated ICR assessments of radiologic data (RECIST 1.1) and digital medical photography (WHO criteria). The efficacy analysis was conducted when all patients had the opportunity for at least 6 months of follow-up.

A total of 28 patients with CSCC were enrolled in Study 1423 and 82 patients were enrolled in Study 1540. Of these 108 patients, 75 had metastatic CSCC and 33 had locally advanced CSCC. The median age was 71 years (38 to 96 years); 89% were male; 97% were White; 43% had ECOG PS 0 and 57% had ECOG PS 1; 50% received at least one prior anti-cancer systemic therapy; 96% received prior cancer-related surgery; and 79% received prior radiotherapy. Among patients with metastatic CSCC, 69% had distant metastases and 31% had only nodal metastases.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of < 1% in 534 patients who received LIBTAYO *[see Adverse Reactions (6.1)]* 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.

Neurological: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome / myasthenia gravis, Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy

Cardiovascular: Myocarditis, pericarditis, vasculitides

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 corticosteroids to reduce the risk of permanent vision loss.

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

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

Hematological and Immunological: 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 0.2% of patients receiving LIBTAYO *[see Adverse Reactions (6.1)]*. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue LIBTAYO based on severity of reaction *[see Dosage and Administration (2.2)]*.

5.3 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)]*

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 in 534 patients in two open-label, single-arm, multicohort studies (Study 1423 and Study 1540), including 98 patients with metastatic (nodal or distant) CSCC, 65 patients with locally advanced CSCC, and 371 patients with other advanced solid tumors. LIBTAYO as a single agent or in combination with chemotherapy or radiation was administered intravenously at doses of 1 mg/kg every 2 weeks (n=27), 3 mg/kg every 2 weeks (n=446), 3 mg/kg every 3 weeks (n=12), 10 mg/kg every 2 weeks (n=6), 200 mg every 2 weeks (n=20) or 350 mg every 3 weeks (n=23). Among the 534 patients, 38% were exposed for ≥ 6 months and 16% were exposed for ≥ 12 months.

The data described below reflect exposure to LIBTAYO in 163 patients with advanced CSCC (metastatic or locally advanced disease) in Study 1423 and Study 1540 *[see Clinical Studies (14)]*. Patients received LIBTAYO 1 mg/kg every 2 weeks (n=1), 3 mg/kg every 2 weeks (n=139) or 350 mg every 3 weeks (n=23) as an intravenous infusion until disease progression, unacceptable toxicity, or completion of planned treatment. The median duration of exposure was 28 weeks (8 days to 1.4 years).

The safety population characteristics were: median age of 71 years (38 to 96 years), 85% male, 96% white, and ECOG performance score (PS) of 0 (44%) or 1 (56%).

The most common adverse reactions reported in at least 20% of patients were fatigue, rash and diarrhea. The most common Grade 3-4 adverse reactions (≥ 2%) were cellulitis, sepsis, hypertension, pneumonia, musculoskeletal pain, skin infection, urinary tract infection and fatigue. LIBTAYO was permanently discontinued due to adverse reactions in 5% of patients; adverse reactions resulting in permanent discontinuation were pneumonitis, autoimmune myocarditis, hepatitis, aseptic meningitis, complex regional pain syndrome, cough, and muscular weakness. Serious adverse reactions occurred in 28% of patients. Serious adverse reactions that occurred in at least 2% of patients were cellulitis, sepsis, pneumonia, pneumonitis and urinary tract infection.

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

Table 2: Adverse Reactions in ≥ 10% of Patients with Advanced CSCC Receiving LIBTAYO in Study 1423 and Study 1540

Adverse Reactions	LIBTAYO N=163	
	All Grades %	Grade 3-4 %
Skin and Subcutaneous Tissue		
Rash[a]	25	1.2
Pruritus[b]	15	0
Gastrointestinal		
Diarrhea[c]	22	0.6
Nausea	19	0
Constipation	12	0.6
General and Administration Site		
Fatigue[d]	29	2
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[e]	17	3
Metabolism and Nutrition		
Decreased appetite	10	0

[a] Rash is a composite term that includes rash maculopapular, rash, dermatitis, rash generalized, dermatitis bullous, drug eruption, erythema, rash erythematous, rash macular, rash pruritic, and skin reaction.

[b] Pruritus is a composite term that includes pruritus and pruritus allergic.

[c] Diarrhea is a composite term that includes diarrhea and colitis.

[d] Fatigue is a composite term that includes fatigue and asthenia.

[e] Musculoskeletal pain is a composite term that includes: musculoskeletal pain, back pain, myalgia, neck pain, pain in extremity.

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

Laboratory Abnormality	Grade 3-4 (%)[a]
Chemistry	
Increased aspartate aminotransferase	3
Increased INR	2
Hypoalbuminemia	1
Hematology	
Lymphopenia	7
Anemia	2
Electrolytes	
Hypophosphatemia	4
Hyponatremia	3
Hypercalcemia	1

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 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.

2.2 Dosage Modifications for Adverse Reactions

Withhold or discontinue LIBTAYO to manage adverse reactions as described in Table 1. No dose reduction of LIBTAYO is recommended.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	LIBTAYO Dosage Modifications
Severe and Fatal Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold†
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold†
	Grade 4	Permanently discontinue
Hepatitis	If AST or ALT increases to more than 3 and up to 10 times the upper limit of normal (ULN) or if total bilirubin increases up to 3 times the ULN	Withhold†
	If AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Endocrinopathies	Grades 2, 3, or 4	Withhold if clinically necessary
Other immune-mediated adverse reactions involving a major organ	Grade 3	Withhold†
	Grade 4	Permanently discontinue
Recurrent or persistent immune mediated adverse reactions	• Recurrent Grade 3 or 4 • Grade 2 or 3 persistent for 12 weeks or longer after last LIBTAYO dose • Requirement for 10 mg per day or greater prednisone or equivalent lasting 12 weeks or longer after last LIBTAYO dose	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

*Toxicity graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
†Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

2.3 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 binds to the programmed death receptor-1 (PD-1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response with the potential for breaking of peripheral tolerance and induction of immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under Warnings and Precautions may not be inclusive of all possible immune-mediated reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Early identification and management are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor for symptoms and signs of immune-mediated adverse reactions. Evaluate clinical chemistries, including liver tests and thyroid function tests, at baseline and periodically during treatment. Institute medical management promptly to include specialty consultation as appropriate.

In general, withhold LIBTAYO for Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions. Permanently discontinue LIBTAYO for Grade 4 and certain Grade 3 immune-mediated adverse reactions *[see Dosage and Administration (2.2)]*. For Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions, administer corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy until improvement to Grade 1 or less followed by a corticosteroid taper over one month *[see Dosage and Administration (2.2)]*. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids. Institute hormone replacement therapy for endocrinopathies as warranted.

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis occurred in 2.4% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 3 (0.7%) and Grade 2 (1.3%) *[see Adverse Reactions (6.1)]*. Pneumonitis led to permanent discontinuation of LIBTAYO in 1.3% of patients. Systemic corticosteroids were required in all patients with pneumonitis, including 85% who received prednisone ≥ 40 mg per day or equivalent. Pneumonitis resolved in 62% of patients.

Immune-Mediated Colitis

Immune-mediated colitis occurred in 0.9% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.6%) *[see Adverse Reactions (6.1)]*. Colitis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with colitis, including 50% who received prednisone ≥ 40 mg per day or equivalent. Colitis resolved in 80% of patients.

Immune-Mediated Hepatitis

Immune-mediated hepatitis occurred in 2.1% of 534 patients receiving LIBTAYO, including Grade 5 (0.2%), Grade 4 (0.2%), and Grade 3 (1.7%) *[see Adverse Reactions (6.1)]*. Hepatitis led to permanent discontinuation of LIBTAYO in 0.9% of patients. Systemic corticosteroids were required in all patients with hepatitis, including 91% who received prednisone ≥ 40 mg per day or equivalent. Hepatitis resolved in 64% of patients.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

Adrenal insufficiency occurred in 0.4% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%), and Grade 2 (0.2%) *[see Adverse Reactions (6.1)]*.

Hypophysitis

Hypophysitis, which can result in hypopituitarism, occurred in 0.2% of 534 patients receiving LIBTAYO, which consisted of one patient with Grade 3 hypophysitis.

Hypothyroidism

Hypothyroidism occurred in 6% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (5.6%). No patients discontinued hormone replacement therapy.

Hyperthyroidism

Hyperthyroidism occurred in 1.5% of 534 patients receiving LIBTAYO, including Grade 3 (0.2%) and Grade 2 (0.4%). Hyperthyroidism resolved in 38% of patients.

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in 0.7% of 534 patients, including Grade 4 (0.4%) and Grade 3 (0.4%). Type 1 diabetes mellitus led to permanent discontinuation of LIBTAYO in 0.2% of patients.

Immune-Mediated Nephritis with Renal Dysfunction

Immune-mediated nephritis occurred in 0.6% of 534 patients receiving LIBTAYO, including Grade 3 (0.4%) and Grade 2 (0.2%) *[see Adverse Reactions (6.1)]*. Nephritis led to permanent discontinuation of LIBTAYO in 0.2% of patients. Systemic corticosteroids were required in all patients with nephritis, including 67% who received prednisone ≥ 40 mg per day or equivalent. Nephritis resolved in all patients.

Immune-Mediated Dermatologic Adverse Reactions

Immune-mediated dermatologic reactions, including erythema multiforme and pemphigoid, occurred in 1.7% of 534 patients receiving LIBTAYO, including Grade 3 (1.1%) and Grade 2 (0.6%) *[see Adverse Reactions (6.1)]*. In addition, SJS and TEN have been observed with LIBTAYO and with other products in this class. Systemic corticosteroids were required in all patients with dermatologic reactions, including 89% who received prednisone ≥ 40 mg per day or equivalent. Dermatologic reactions resolved in 33% of patients. Approximately 22% of patients had recurrence of dermatologic reactions after re-initiation of LIBTAYO.

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: 09/2018

INDICATIONS AND USAGE

LIBTAYO is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation. (1)

DOSAGE AND ADMINISTRATION

The recommended dosage of LIBTAYO is 350 mg as an intravenous infusion over 30 minutes every 3 weeks. (2.1)

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

- Severe and Fatal Immune-Mediated Adverse Reactions: Immune-mediated adverse reactions 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 and immune-mediated nephritis and renal dysfunction. Monitor for symptoms and signs of immune-mediated adverse reactions. Evaluate clinical chemistries, including liver and thyroid function, at baseline and periodically during treatment. Withhold or permanently discontinue LIBTAYO and administer corticosteroids based on the severity of reaction. (2.2, 5.1)
- Infusion-Related Reactions: Interrupt, slow the rate of infusion or permanently discontinue based on severity of reaction. (2.2, 5.2)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.3, 8.1, 8.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 20%) were fatigue, rash and diarrhea. (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 FDA-approved Medication Guide.

Revised: 09/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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