PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr LIBTAYO®

cemiplimab for injection
Solution for infusion, 50 mg/mL

Antineoplastic Agent, Monoclonal Antibody

sanofi-aventis Canada Inc.
2905 Place Louis-R.-Renaud
Laval, Quebec, H7V 0A3

Distributed by Sanofi Genzyme,
a division of sanofi-aventis Canada Inc.
800-2700 Matheson Blvd East
Mississauga, Ontario, L4W 4V9

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS	04/2023
1 INDICATIONS	03/2022
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	12/2023
4 DOSAGE AND ADMINISTRATION, 4.4 Administration	04/2023
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Cutaneous Squamous Cell Carcinoma

Libtayo (cemiplimab for injection) is indicated for:

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

Non-Small Cell Lung Cancer

Libtayo (cemiplimab for injection) is indicated:

- as monotherapy for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 in ≥ 50% of tumour cells (Tumour Proportion Score [TPS] ≥ 50%), as determined by a validated test, with no EGFR, ALK or ROS1 aberrations, who have:
    - locally advanced NSCLC who are not candidates for surgical resection or definitive chemoradiation, or
    - metastatic NSCLC.

- in combination with platinum-based chemotherapy for the first-line treatment of adult patients with NSCLC whose tumors have no EGFR, ALK or ROS1 aberrations and is:
    - locally advanced where patients are not candidates for surgical resection or definitive chemoradiation, or
    - metastatic NSCLC.

Basal Cell Carcinoma

Libtayo (cemiplimab for injection) is indicated for:

- the treatment of patients with locally advanced basal cell carcinoma (BCC) previously treated with a hedgehog pathway inhibitor.

Cervical Cancer

Libtayo (cemiplimab for injection) is indicated for:

- the treatment of adult patients with cervical cancer who have progressed on or after prior platinum-based chemotherapy and who require additional systemic therapy to treat recurrent or metastatic disease.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): No overall differences in efficacy were observed between younger patients (< 65 years of age) and elderly patients (≥ 65 years of age) (see 7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

Libtayo is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Treatment with Libtayo must be initiated and supervised by health professionals experienced in the treatment of cancer.

Patient Selection for NSCLC

Patients should be selected for treatment with Libtayo based on PD-L1 expression confirmed by a validated test in locally advanced or metastatic NSCLC (see 14 CLINICAL TRIALS).

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of Libtayo is 350 mg every three (3) weeks administered as an intravenous infusion over 30 minutes.

- CSCC, NSCLC and BCC
  Treatment is until disease progression or unacceptable toxicity, whichever occurs first.

- Cervical Cancer
  Treatment is for 96 weeks or until disease progression or unacceptable toxicity, whichever occurs first.

No dose reductions are recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Recommended modifications to manage adverse reactions are provided in Table 1 (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

When Libtayo is to be administered in combination with other agents, refer to the Product Monograph for these agents for recommended dosing information prior to administration.

Table 1: Recommended Treatment Modifications for Adverse Reactions

Adverse Reaction	Severity[a]	Dose modification	Additional Intervention
Immune-Mediated Adverse Reactions			
Pneumonitis	Grade 2	Withhold Libtayo	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume Libtayo if pneumonitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue Libtayo	Initial dose of 2 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by a taper
Colitis	Grade 2 or 3	Withhold Libtayo	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume Libtayo if colitis or diarrhea improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 4 or recurrent Grade 3	Permanently discontinue Libtayo	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
Hepatitis	Grade 2 with AST or ALT >3 and ≤5×ULN or total bilirubin >1.5 and ≤3×ULN	Withhold Libtayo	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume Libtayo if hepatitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or returns to baseline AST or ALT after completion of corticosteroid taper	
	Grade ≥3 with AST or ALT >5×ULN or total bilirubin >3×ULN	Permanently discontinue Libtayo	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper

Adverse Reaction	Severity[a]	Dose modification	Additional Intervention
Hypothyroidism	Grade 3 or 4	Withhold Libtayo	Initiate thyroid hormone replacement as clinically indicated
		Resume Libtayo when hypothyroidism returns to Grade 0 to 1 or is otherwise clinically stable	
Hyperthyroidism	Grade 3 or 4	Withhold Libtayo	Initiate symptomatic management
		Resume Libtayo when hyperthyroidism returns to Grade 0 to 1 or is otherwise clinically stable	
Thyroiditis	Grade 3 to 4	Withhold Libtayo	Initiate hormone management as clinically indicated
		Resume Libtayo when thyroiditis returns to Grade 0 to 1 or is otherwise clinically stable	
Hypophysitis	Grade 2 to 4	Withhold Libtayo	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
		Resume Libtayo if hypophysitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or is otherwise clinically stable	
Adrenal insufficiency	Grade 2 to 4	Withhold Libtayo	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
		Resume Libtayo if adrenal insufficiency improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or is otherwise clinically stable	
Type 1 Diabetes Mellitus	Grade 3 or 4 (hyperglycemia)	Withhold Libtayo	Initiate treatment with anti-hyperglycemics as clinically indicated
		Resume Libtayo when diabetes mellitus returns to Grade 0 to 1 or is otherwise clinically stable	
Skin Adverse Reactions	Grade 2 lasting longer than 1 week, Grade 3 or	Withhold Libtayo	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper

Adverse Reaction	Severity[a]	Dose modification	Additional Intervention
	suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Resume Libtayo if skin reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 4 or confirmed SJS or TEN	Permanently discontinue Libtayo	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
Skin Reaction or other Adverse Reactions in patients with prior treatment with idelalisib	Grade 2	Withhold Libtayo	Initiate management immediately, including initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume Libtayo if skin reaction or other immune-mediated adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 3 or 4 (excluding endocrinopathies) or recurrent Grade 2	Permanently discontinue Libtayo	Initiate management immediately, including initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
Nephritis	Grade 2 creatinine increased	Withhold Libtayo	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume Libtayo if nephritis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	Grade 3 or 4 creatinine increased	Permanently discontinue Libtayo	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper

Adverse Reaction	Severity[a]	Dose modification	Additional Intervention
Other (see 8 ADVERSE REACTIONS, Other Immune-Mediated Adverse Reactions)	Grade 2 or 3 based on severity or type of reaction	Withhold Libtayo	Initiate symptomatic management, including initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent as clinically indicated followed by a taper
		Resume Libtayo if other immune-mediated adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	• Grade 3 based on the type of reaction or grade 4 (excluding endocrinopathies) • Grade 3 or 4 neurologic toxicity • Grade 3 or 4 myocarditis or pericarditis • Recurrent Grade 3 immune-mediated adverse reaction • Persistent Grade 2 or 3 immune-mediated adverse reactions lasting 12 weeks or longer (excluding endocrinopathies) • Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks	Permanently discontinue Libtayo	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent as clinically indicated followed by a taper
Hemophagocytic lymphohistiocytosis (HLH)	Suspected	Withhold LIBTAYO	Initiate treatment
		Resume LIBTAYO at physician's discretion if diagnosis of HLH is excluded	
	Confirmed	Permanently discontinue	Initiate/continue treatment for HLH
Infusion-related reactions			
Infusion-Related Reaction	Grade 1 or 2	Interrupt or slow rate of infusion	Initiate symptomatic management
	Grade 3 or 4	Permanently discontinue Libtayo	

Adverse Reaction	Severity[a]	Dose modification	Additional Intervention

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.
[a] Toxicity was graded as per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4 (NCI CTCAE v4).

Pediatrics:
Health Canada has not authorized an indication for pediatric use.

Renal Impairment:
No formal studies of Libtayo in patients with renal impairment have been conducted. Based on population pharmacokinetic analyses, no dose adjustment of Libtayo is recommended for patients with renal impairment (see 10 CLINICAL PHARMACOLOGY).

Hepatic Impairment:
No formal studies of Libtayo in patients with hepatic impairment have been conducted. Based on population pharmacokinetic analyses, no dose adjustment of Libtayo is recommended for patients with mild to moderate hepatic impairment (see 10 CLINICAL PHARMACOLOGY).

4.3 Reconstitution

Preparation and Reconstitution

Visually inspect drug product for particulate matter and discolouration prior to administration. Libtayo is clear to slightly opalescent, colourless to pale yellow solution that may contain trace amounts of translucent to white particles.

Discard the vial if the solution is cloudy, discoloured or contains extraneous particulate matter other than trace amounts of translucent-to-white particles.

Do not shake the vial.

Withdraw the required volume from the vial(s) of Libtayo and transfer into an intravenous (IV) infusion bag containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Mix diluted solution by gentle inversion. Do not shake the solution. The final concentration of the diluted solution should be between 1mg/mL to 20mg/mL.

Libtayo is for single use only. Dispose of any unused medicinal product or waste material in accordance with local requirements.

No compatibility studies have been performed. Do not mix with other medicinal products.

Storage of Infusion

Once prepared, administer the diluted solution immediately. If diluted solution is not administered immediately, it may be stored temporarily either:

- At room temperature up to 25°C for no more than 8 hours from the time of infusion preparation to the end of infusion.

Or

- Under refrigeration at 2°C to 8°C for no more than 24 hours from the time of infusion preparation to the end of infusion. Allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

Do not shake.

4.4 Administration

Libtayo is administered by intravenous infusion over 30 minutes through an intravenous line containing a sterile, in-line or add-on filter (0.2-micron to 5-micron pore size)

Do not co-administer with other drugs through the same infusion line.

When administered in combination with platinum-based doublet chemotherapy agents, the chemotherapy agents should be infused first, followed by cemiplimab, on the same day. Use separate infusion bags and filters for each infusion.

4.5 Missed Dose

If a planned dose of Libtayo is missed, it should be administered as soon as possible; do not wait until the next planned dose. Maintain the planned schedule of administration of subsequent doses.

5 OVERDOSAGE

There is no information on overdosage with Libtayo (cemiplimab for injection). In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intravenous (IV) Infusion	Sterile solution for infusion/	L-Histidine, L-Histidine Monohydrochloride

	350 mg cemiplimab / 7mL (10mL single use vial) 250 mg cemiplimab / 5mL (10mL single use vial)	Monohydrate, Sucrose, L-Proline, Polysorbate 80, Water for Injection

Libtayo is a clear to slightly opalescent, colorless to pale yellow sterile solution with a pH of 6.0 that may contain trace amounts of translucent to white particles.

Libtayo is provided in a 10 mL glass vial with a 20 mm finish made of clear Type 1 glass, equipped with a 20 mm grey chlorobutyl elastomeric liquid stopper. The 350mg vial has a violet flip-off button and the 250 mg vial has a light green flip-off button.

7 WARNINGS AND PRECAUTIONS

General

Libtayo should be administered under the supervision of health care practitioners experienced in the treatment of cancer.

Driving and Operating Machinery

Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Immune

Severe and fatal immune-mediated adverse reactions have been observed in patients treated with Libtayo (see 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS). These immune-mediated reactions may involve any organ system and may affect more than one body system simultaneously. Immune-mediated reactions can manifest at any time during treatment with Libtayo; however, immune-mediated adverse reactions can occur after discontinuation of Libtayo.

The warnings and precautions for immune-mediated adverse reactions applies to the use of Libtayo as monotherapy and also in combination with platinum-based chemotherapy.

Immune-mediated adverse reactions affecting more than one body system can occur simultaneously, such as myositis and myocarditis and/or myasthenia gravis in patients treated with Libtayo or other PD-1/PD-L1 inhibitors.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Evaluate suspected immune-mediated adverse reactions to exclude other causes. Monitor patients continuously (even after the last dose) for signs and symptoms of immune-mediated adverse reactions and manage immune-mediated adverse reactions with Libtayo treatment modifications, hormone replacement therapy (as clinically indicated), and corticosteroids. Depending upon the severity of the adverse reaction, withhold or permanently discontinue Libtayo (see 4 DOSAGE AND ADMINISTRATION).

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis, defined as requiring use of corticosteroids with no clear alternate etiology, including fatal cases, has been observed in patients receiving Libtayo (see 8 ADVERSE REACTIONS).

Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and manage with treatment modifications and corticosteroids (see 4 DOSAGE AND ADMINISTRATION).

Immune-Mediated Colitis

Immune-mediated diarrhea or colitis, defined as requiring use of corticosteroids with no clear alternate etiology, has been observed in patients receiving Libtayo (see 8 ADVERSE REACTIONS).

Monitor patients for signs and symptoms of diarrhea or colitis and manage with treatment modifications, anti-diarrheal agents, and corticosteroids (see 4 DOSAGE AND ADMINISTRATION).

Immune-Mediated Hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids with no clear alternate etiology, including fatal cases, has been observed in patients receiving Libtayo (see 8 ADVERSE REACTIONS).

Monitor patients for abnormal liver tests prior to and periodically during treatment, and manage with treatment modifications and corticosteroids (see 4 DOSAGE AND ADMINISTRATION).

Immune-Mediated Endocrinopathies

Immune-mediated endocrinopathies, defined as treatment emergent endocrinopathies with no clear alternate etiology, have been observed in patients receiving Libtayo (see 8 ADVERSE REACTIONS).

Thyroid Disorders (Hypothyroidism/Hyperthyroidism/Thyroiditis)

Immune-mediated thyroid disorders have been observed in patients receiving Libtayo. Thyroiditis can present with or without an alteration in thyroid function tests. Hypothyroidism can follow hyperthyroidism. Thyroid disorders can occur at any time during the treatment.

Monitor patients for changes in thyroid function at the start of the treatment, periodically during treatment, and as indicated based on clinical evaluation. Manage patients with hormone replacement therapy (if indicated) and treatment modifications. Initiate medical management for control of hyperthyroidism (see 4 DOSAGE AND ADMINISTRATION).

Hypophysitis

Immune-mediated hypophysitis has been observed in patients receiving Libtayo.

Monitor patients for signs and symptoms of hypophysitis and manage with treatment modifications, corticosteroids and hormone replacement, as clinically indicated (see 4 DOSAGE AND ADMINISTRATION).

Adrenal Insufficiency

Adrenal insufficiency has been observed in patients receiving Libtayo.

Monitor patients for signs and symptoms of adrenal insufficiency during and after treatment and manage with treatment modifications, corticosteroids and hormone replacement, as clinically indicated (see 4 DOSAGE AND ADMINISTRATION).

Type 1 Diabetes Mellitus

Immune-mediated type 1 diabetes mellitus, including diabetic ketoacidosis, has been observed in patients receiving Libtayo.

Monitor patients for hyperglycemia and signs and symptoms of diabetes and manage with oral anti-hyperglycemics or insulin and treatment modifications (see 4 DOSAGE AND ADMINISTRATION).

Immune-Mediated Skin Adverse Reactions

Immune-mediated skin adverse reactions, defined as requiring use of systemic corticosteroids with no clear alternate etiology, including rash, erythema multiforme, pemphigoid, and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (some cases with fatal outcome) have been observed (see 8 ADVERSE REACTIONS).

Monitor patients for signs and symptoms of suspected severe skin reactions and exclude other causes. Manage patients with treatment modifications and corticosteroids.

For symptoms or signs of SJS or TEN, refer the patient for specialized care for assessment and treatment and manage patient with treatment modifications (see 4 DOSAGE AND ADMINISTRATION).

Cases of SJS/TEN/stomatitis including fatal TEN occurred following dosing of Libtayo in patients with prior exposure to idelalisib, who were participating in a clinical trial evaluating Libtayo in Non Hodgkin Lymphoma (NHL), and who had recent exposure to sulfa containing antibiotics. Two patients experienced fatal mucocutaneous toxicity after a single dose of cemiplimab monotherapy, and a third patient developed myositis and myasthenia gravis following 2 doses of cemiplimab. Manage patients immediately with treatment modifications and corticosteroids as described above (see 4 DOSAGE AND ADMINISTRATION, Table 1).

Immune-Mediated Nephritis

Immune-mediated nephritis, defined as requiring use of corticosteroids with no clear alternate etiology, including a fatal case, has been observed in patients receiving Libtayo (see 8 ADVERSE REACTIONS).

Monitor patients for changes in renal function. Manage patients with treatment modifications and corticosteroids (see 4 DOSAGE AND ADMINISTRATION).

Other Immune-Mediated Adverse Reactions

Other fatal and life-threatening immune-mediated adverse reactions have been observed in patients receiving Libtayo including paraneoplastic encephalomyelitis, meningitis, myositis, and myocarditis (see 8 ADVERSE REACTIONS).

Cases of solid organ transplant rejection have been reported in the postmarketing setting with Libtayo. Solid organ transplant rejection has been reported in patients treated with other PD-1 inhibitors. Patients with history of solid organ transplant were excluded from Libtayo clinical studies. Treatment with Libtayo may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with Libtayo versus the risk of possible organ rejection in these patients.

Cases of graft-versus-host disease have been reported in the postmarketing setting in patients treated with other PD-1/PD-L1 inhibitors in association with allogeneic hematopoietic stem cell transplant.

Evaluate suspected immune-mediated adverse reactions to exclude other causes. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions and managed with Libtayo treatment modifications and corticosteroids as clinically indicated (see 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS).

Hemophagocytic lymphohistiocytosis (HLH) has been reported in the postmarketing setting with LIBTAYO (see 8.5 Post-Market Adverse Reaction). Patients should be monitored for clinical signs and symptoms of HLH. If HLH is suspected, administration of LIBTAYO should be withheld and treatment initiated (see 4.2 Recommended Dose and Dosage Adjustment). If HLH is confirmed, administration of LIBTAYO should be permanently discontinued.

Infusion-Related Reactions

Libtayo can cause severe or life-threatening infusion-related reactions (see 8 ADVERSE REACTIONS).

Monitor patients for signs and symptoms of infusion-related reactions and manage with treatment modifications and corticosteroids.

Interrupt or slow the rate of infusion or permanently discontinue Libtayo based on the severity of reaction (see 4 DOSAGE AND ADMINISTRATION).

Reproductive Health: Female and Male Potential

- **Fertility**

No clinical data are available on the possible effects of cemiplimab on fertility. No effects on fertility assessment parameters or in the male and female reproductive organs were observed in a 3-month repeat dose fertility assessment study with sexually mature cynomolgus monkeys (see 16 NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

Based on its mechanism of action, Libtayo can cause fetal harm when administered to a pregnant woman. There are no available data on the use of cemiplimab in pregnant women. Blockade of PD-1/PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. Animal reproduction studies have not been conducted with cemiplimab (see 16 NON-CLINICAL TOXICOLOGY).

Human IgG4 is known to cross the placental barrier and cemiplimab is an IgG4; therefore, cemiplimab has the potential to be transmitted from the mother to the developing fetus.

Cemiplimab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Effective contraception should be used in women of childbearing potential during treatment with cemiplimab and for at least 4 months following the last dose of Libtayo.

7.1.2 Breast-feeding

It is unknown whether cemiplimab is secreted in human milk. It is known that antibodies (including IgG4) are secreted in human milk; a risk to the newborn/infant cannot be excluded.

Breast-feeding women should be advised not to breast-feed during treatment and for at least 4 months after the last dose due to the potential risks to newborns/infants.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of Libtayo in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): No overall differences in efficacy were observed between elderly patients and younger patients. There was a trend towards a higher frequency of serious adverse events and discontinuations due to adverse events in patients 65 years and older compared with patients aged less than 65 years.

Initially, of the 163 patients with metastatic CSCC (mCSCC) or locally advanced CSCC (laCSCC) who received Libtayo in clinical studies, 63.2% (103/163) were younger than 75 years. Grade ≥3 treatment-

related adverse reactions occurred in 8.7%% (9/103) of patients younger than 75 years and 18.3% (11/60) of patients 75 years or older. Grade ≥3 treatment-related Serious TEAEs occurred in 3.9% (4/103) of patients younger than 75 years, and 13.3% (8/60) of patients 75 years or older. In the 108 patients evaluable for efficacy, the objective response rate in patients 65 years or older was 46.1% (35/76) and in patients 75 years or older was 44% (17/38).

In a subsequent update of the 219 patients with mCSCC and laCSCC treated with Libtayo in the safety analysis, 25.1% (55/219) were less than 65 years, 34.2% (75/219) were 65 to less than 75 years, and 40.6% (89/219) were 75 years or older. Grade ≥3 treatment-related adverse reactions occurred in 11.5% (15/130) of patients younger than 75 years and 16.9% (15/89) of patients 75 years or older. Grade ≥3 treatment-related Serious TEAEs occurred in 20.8% (27/130) of patients younger than 75 years, and 38.2% (34/89) of patients 75 years or older. In the 219 patients evaluable for efficacy, the objective response rate in patients 65 years or older was 45.7% (75/164) and in patients 75 years or older was 44.9% (40/89).

Libtayo as Monotherapy (Studies 1423, 1540, 1620, 1624 and 1676)

Of the 1116 patients treated with Libtayo monotherapy in clinical studies, 57.3% (640/1116) were less than 65 years, 25.9% (289/1116) were 65 to less than 75 years, and 16.8% (187/1116) were 75 years or older. Grade ≥3 adverse events occurred in 39.8% (115/289) of patients 65 to less than 75 years and 51.3% (96/187) of patients 75 years or older. Serious TEAEs occurred in 26.9% (172/640) of patients less than 65 years, 30.1% (87/289) of patients 65 to less than 75 years and 40.6% (76/187) of patients 75 years or older. TEAEs leading to study treatment discontinuation occurred in 7.3% (47/640) of patients less than 65 years, 7.6% (22/289) of patients 65 to less than 75 years, and 12.3% (23/187) of patients 75 years or older.

Libtayo in Combination with Platinum-Based Chemotherapy (Study 16113)

Among 466 advanced NSCLC patients in the efficacy analysis, 312 were treated with Libtayo in combination with platinum-based chemotherapy and 154 were treated with platinum-based chemotherapy. Of the 312 patients receiving Libtayo and platinum-based chemotherapy, 59% (184/312) were less than 65 years, 35.3% (110/312) were 65 to less than 75 years, and 5.8% (18/312) were 75 years or older. Grade ≥3 adverse events occurred in 44.6% (82/184) of patients less than 65 years, 40% (44/110) of patients 65 to less than 75 years and 55.6% (10/18) of patients 75 years or older. Serious TEAEs occurred in 24.5% (45/184) of patients less than 65 years, 29.1% (32/110) of patients 65 to less than 75 years and 11.1% (2/18) of patients 75 years or older. TEAEs leading to study treatment discontinuation occurred in 7.1% (13/184) of patients less than 65 years, 1.8% (2/110) of patients 65 to less than 75 years, and 5.6% (1/18) of patients 75 years or older.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Cutaneous Squamous Cell Carcinoma (Studies 1423 and 1540)

Libtayo has been evaluated as a monotherapy or as a combination therapy in two uncontrolled clinical studies (Study 1423 [Phase 1] and Study 1540 [Phase 2]). Initial enrollment (out of 534 patients total) included 98 patients with metastatic (nodal or distant) cutaneous squamous cell carcinoma (metastatic CSCC), 65 patients with locally advanced cutaneous squamous cell carcinoma (locally advanced CSCC) and 371 patients with other advanced solid malignancies.

Advanced CSCC patients with locally advanced and metastatic disease in Studies 1423 and 1540 received Libtayo as an intravenous infusion over 30 minutes until unequivocal progression of disease, unacceptable toxicity or completion of planned treatment. Study 1423 was an open-label, multi-center study in 397 patients with a variety of advanced solid tumours. It included 16 patients with mCSCC and 10 patients with laCSCC. Study 1540 was an open-label, multi-center study that initially enrolled 137 patients with mCSCC or laCSCC at the time of data cut-off. In the advanced CSCC patients, the initial median duration of exposure to Libtayo was 20 weeks (range: 3 days to 71 weeks).

In a subsequent update with a later data cut-off, 56 more patients with mCSCC or laCSCC were enrolled in Study 1540 (for a total of 193 patients). Updated safety data reflect exposure to Libtayo in 219 patients with advanced CSCC (mCSCC (131 subjects) and laCSCC (88 subjects)) from both Study 1423 and Study 1540. In the 219 patients with advanced CSCC, the median duration of exposure to Libtayo was 38 weeks (range: 2 weeks to 110 weeks).

Initially, among the 534 patients treated with Libtayo in Studies 1423 and 1540, 4 (0.7%) died due to treatment-related adverse events: pneumonitis (n=1), hepatic failure (n=1) and paraneoplastic encephalomyelitis (n=1) and death of unknown cause.

In a subsequent update, among the 591 patients treated with Libtayo in Studies 1423 and 1540, one more death was attributed to the study drug (pneumonitis) bringing the total to 5 (0.8%) that died due to treatment-related adverse events.

The data described below reflect exposure to Libtayo in 163 patients with advanced CSCC (metastatic CSCC and locally advanced CSCC) in Study 1423 and Study 1540. Initially, Libtayo was permanently discontinued due to adverse reactions in 8/163 (4.9%) CSCC patients; the only adverse reaction resulting in permanent discontinuation in more than 1 patient was pneumonitis. Serious adverse reactions occurred in 13/163 (8%) patients. The only serious adverse reaction that occurred in more than 1 patient was pneumonitis. There were no Grade 4 adverse reactions. The Grade 3 adverse reactions reported in more than 1 patient were hepatitis, rash, increased aspartate aminotransferase, and pneumonitis.

After a subsequent update, it was observed that Libtayo was permanently discontinued due to adverse reactions in 16/219 (7.3%) CSCC patients; the only adverse reaction resulting in permanent discontinuation in more than 1 patient was pneumonitis. Serious adverse reactions occurred in 19/219 (8.7%) patients. The only serious adverse reaction that occurred in more than 1 patient was pneumonitis. The Grade 4 adverse reaction that occurred in more than 1 patient was pneumonitis. The

Grade 3 adverse reactions reported in more than 1 patient were pneumonitis, hepatitis, rash, increased aspartate aminotransferase, anemia and fatigue.

There were no new safety signals identified at the final analysis.

Libtayo as Monotherapy (Studies 1423, 1540, 1620, 1624, and 1676)

The safety data reflect exposure to Libtayo monotherapy in 1116 patients with advanced solid malignancies in 5 clinical studies. Three clinical studies were single-arm, open-label, multicohort studies (Studies 1423, 1540 and 1620) and two were open-label, randomized, multi-center studies (Studies 1624 and 1676). These studies included 219 patients with advanced CSCC (Studies 1540 and 1423), 138 patients with advanced BCC (Study 1620), 355 patients with NSCLC (Study 1624), 300 patients with recurrent or metastatic cervical cancer, and 104 patients with other advanced solid tumours (Study 1423). Libtayo was administered intravenously at doses of 3 mg/kg every 2 weeks (n=235), 350 mg every 3 weeks (n=849), or other doses (n=32; 1 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, 200 mg every 2 weeks). The median duration of exposure to Libtayo was 27 weeks (range: 2 days to 144 weeks). Among the 1116 patients, 51% were exposed for ≥ 6 months and 23% were exposed for ≥ 12 months.

The overall safety population characteristics were: median age of 62 years (range: 22 to 96 years), 656 (58.8%) male, 900 (80.6%) white, European Cooperative Oncology Group (ECOG) performance score (PS) of 0 in 457 patients (40.9%) and 1 in 658 patients (59.0%); 633 (56.7%) patients had at least 1 prior systemic anti cancer therapy, and 605 (54.2%) had prior radiotherapy.

In the 1116 monotherapy patients, the most common adverse reactions (occurring in ≥15% of patients) were musculoskeletal pain, fatigue, rash, anemia, and diarrhea. The most common Grade 3-4 laboratory abnormalities (occurring in ≥2% of patients) were lymphopenia, anemia, hyponatremia, hypophosphatemia, increased aspartate aminotransferase, hyperkalemia, increased alkaline phosphatase, hypokalemia, and increased alanine aminotransferase.

Adverse events were serious in 30.0% of patients. The most common serious adverse reactions (occurring in ≥1% of patients) were pneumonia, urinary tract infections, and pneumonitis.

Adverse events led to permanent discontinuation of cemiplimab in 8.2% of patients. The most common adverse events leading to discontinuation (occurring in >2 patients) were pneumonitis, autoimmune hepatitis, immune-mediated hepatitis, hepatitis, pneumonia, colitis, acute kidney injury, increased alanine aminotransferase, and increased aspartate aminotransferase.

Immune-mediated adverse reactions occurred in 20.5% of patients treated with cemiplimab in clinical trials including Grade 5 (0.4%), Grade 4 (0.6%), Grade 3 (5.4%), and Grade 2 (10.9%). Immune-mediated adverse reactions led to permanent discontinuation of cemiplimab in 4.6% of patients. The most common immune-mediated adverse reactions were hypothyroidism (7.1%), hyperthyroidism (3.2%), immune-mediated pneumonitis (2.7%), immune-mediated hepatitis (2.4%), immune-mediated colitis (2.1%) and immune-mediated skin adverse reactions (1.6%) (see “Description of Selected Adverse Reactions (Monotherapy; Studies 1423, 1540, 1620, 1624 and 1676)” below, 7 WARNINGS AND PRECAUTIONS, and 4 DOSAGE AND ADMINISTRATION).

In a subsequent pooled analysis of monotherapy studies (1423, 1540, 1620, 1624, and 1676) in 1281 patients, no new safety signals have been identified.

Libtayo as Combination with Platinum-Based Chemotherapy (Study 16113)

In patients with advanced or metastatic NSCLC treated with Libtayo in combination with platinum-based chemotherapy, immune-mediated adverse reactions occurred in 18.9% of patients including Grade 5 (0.3%), Grade 3 (2.6%), and Grade 2 (7.4%). Immune-mediated adverse reactions led to permanent discontinuation of cemiplimab in 1.0% of patients. The most common immune-mediated adverse reactions were hypothyroidism (7.7%), hyperthyroidism (5.1%), increased blood thyroid stimulating hormone (4.2%), immune-mediated skin reaction (1.9%), immune-mediated pneumonitis (1.9%), and decreased blood thyroid stimulating hormone (1.6%) (see "Description of Selected Adverse Reactions (Monotherapy; Studies 1423, 1540, 1620, 1624 and 1676)" below, 7 WARNINGS AND PRECAUTIONS, and 4 DOSAGE AND ADMINISTRATION).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Cutaneous Squamous Cell Carcinoma (Studies 1423 and Study 1540)

The initial study population characteristics were: median age of 71.0 years (range: 38 to 96), 84.7% male, 96.3% white, ECOG performance score of 0 (44.2%) or 1 (55.8%), and 42.9% of patients had at least 1 prior anti-cancer therapy, and 73.0% had prior radiotherapy.

Table 2: Adverse Reactions that Occurred in ≥1% of Advanced CSCC Patients in Study 1423 and Study 1540

Adverse Reactions*	Cemiplimab N = 163	
SOC/ PT	All Grades N (%)	Grade 3-4 N (%)
Endocrine Disorders		
Hypothyroidism	12 (7.4%)	0
Hyperthyroidism	3 (1.8%)	0
Gastrointestinal Disorders		
Diarrhea[a]	20 (12.3%)	1 (0.6%)
General Disorders and Administration Site Conditions		
Fatigue[b]	34 (20.9%)	1 (0.6%)
Hepatobiliary Disorders		
Hepatitis	3 (1.8%)	3 (1.8%)
Injury, Poisoning and Procedural Complications		
Infusion related reaction	7 (4.3%)	0
Investigations		
Alanine aminotransferase increased	8 (4.9%)	1 (0.6%)
Aspartate aminotransferase increased	6 (3.7%)	2 (1.2%)
Blood alkaline phosphatase increased	3 (1.8%)	0
Blood creatinine increased	3 (1.8%)	0
Musculoskeletal and Connective Tissue Disorders		
Arthritis	2 (1.2%)	1 (0.6%)
Myalgia	4 (2.5%)	1 (0.6%)
Respiratory, Thoracic, and Mediastinal Disorders		
Pneumonitis	6 (3.7%)	2 (1.2%)
Skin and Subcutaneous Tissue Disorders		
Rash[c]	32 (19.6%)	2 (1.2%)
Pruritus[d]	17 (10.4%)	0

* Version 4.03 of the NCI CTCAE was used to grade toxicity.

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

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

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

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

In a subsequent update to Studies 1423 and 1540 (N=219), the study population characteristics in advanced CSCC patients were: median age of 72 years (range: 38 to 96 years), 182 (83.1%) male, 211 (96.3%) white, ECOG performance score of 0 in 96 patients (43.8%) and 1 in 123 patients (56.2%); 80 (36.5%) patients had at least 1 prior systemic anti-cancer therapy, and 152 (69.4%) had prior radiotherapy. The incidence of the following adverse events (as defined above) increased: pruritus (All Grades: 17.8%, Grade 3+: 0%), diarrhea (All Grades: 24.2%, Grade 3+: 0.5%), fatigue (All Grades: 32.4%, Grade 3+: 2.3%), myalgia (All Grades: 4.6%, Grade 3+: 0%), alanine aminotransferase increased (All Grades: 6.4%, Grade 3+: 0.5%), aspartate aminotransferase increased (All Grades: 5.5%; Grade 3+: 0.9%), blood alkaline phosphatase levels increased (All Grades: 5.0%, Grade 3+: 0%), blood creatinine increased (All Grades: 6.8%, Grade 3+: 0.5%), hypothyroidism (All Grades: 10.0%, Grade 3+: 0%), hyperthyroidism (All Grades: 2.7%; Grade 3+: 0%), pneumonitis (All Grades: 5.9%; Grade 3+: 2.3%), and infusion related reaction (All Grades: 4.6%; Grade 3+: 0%). Furthermore, the following adverse events were also noted in ≥1% of Advanced CSCC Patients: cough (All Grades: 14.2%; Grade 3+: 0%), anemia

(All Grades: 11.4%; Grade 3+: 3.7%), hypertension (All Grades: 7.3%; Grade 3+: 3.2%), cellulitis (All Grades: 5.5%; Grade 3+ 3.7%), pneumonia (All Grades: 3.7%, Grade 3+: 2.7%), hyperglycemia (All Grades: 3.2%; Grade 3+: 1.8%) and sepsis (All Grades: 2.3%, Grade 3+: 2.3%).

No new safety signals were observed at the final analysis.

Non-Small Cell Lung Cancer

First-line treatment of NSCLC with Libtayo as monotherapy (Study 1624)
The safety of Libtayo was evaluated in 355 patients with locally advanced or metastatic NSCLC in Study 1624 (see CLINICAL TRIALS). 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.

In Study 1624, 28% of patients in the cemiplimab arm and 28% patients in the chemotherapy arm experienced at least 1 serious adverse event. The most common serious TEAE by PT (occurring in ≥5% of patients) was pneumonia in both the cemiplimab arm and the chemotherapy arm.

The most common TEAEs (occurring in ≥10% of patients) in the cemiplimab arm were anemia, decreased appetite and fatigue. In the chemotherapy arm, the most common TEAEs (occurring in ≥20% of patients) were anemia, nausea, and alopecia. Grade ≥3 TEAEs were reported in 37% of patients in the cemiplimab arm and 48% of patients in the chemotherapy arm. The most common Grade 3-4 adverse reactions (occurring in >2% of patients) in the cemiplimab arm were anemia, pneumonia, increased aspartate aminotransferase and dyspnea; the most common Grade 3-4 adverse reactions (occurring in >2% of patients) in the chemotherapy arm were anemia, neutropenia, thrombocytopenia, pneumonia, diarrhea and fatigue. Grade 5 TEAEs were reported in 9.6% of patients in the cemiplimab arm and 9.1% of patients in the chemotherapy arm. The most common Grade 5 adverse reactions in the cemiplimab arm were cardiac disorders (1 patient each for autoimmune myocarditis, cardiac failure, cardio-respiratory arrest, cardiopulmonary failure). The most common Grade 5 adverse reactions in the chemotherapy arm were pneumonia and pulmonary embolism (2 patients).

Table 3 summarizes the adverse reactions that occurred in ≥ 1% of patients and Table 10 summarizes Grade 3 or 4 laboratory abnormalities in patients receiving Libtayo.

Table 3: Adverse Reactions that Occurred in ≥1% of NSCLC Patients in Study 1624

Adverse Reactions*	Cemiplimab N = 355		Chemotherapy N = 342	
SOC/ PT	All Grades N (%)	Grade 3-5 N (%)	All Grades N (%)	Grade 3-5 N (%)
Blood and Lymphatic System Disorders				
Anemia	52 (14.6%)	12 (3.4%)	171 (50.0%)	56 (16.4%)
Thrombocytopenia	7 (2.0%)	0	52 (15.2%)	28 (8.2%)
Neutropenia	6 (1.7%)	2 (0.6%)	63 (18.4%)	35 (10.2%)
Endocrine Disorders				
Hypothyroidism	23 (6.5%)	0	0	0
Hyperthyroidism	16 (4.5%)	0	6 (1.8%)	0
Gastrointestinal Disorders				
Constipation	27 (7.6%)	0	52 (15.2%)	0
Diarrhea	25 (7.0%)	1 (0.3%)	32 (9.4%)	7 (2.0%)
Abdominal pain[a]	24 (6.8%)	1 (0.3%)	18 (5.3%)	1 (0.3%)
Nausea	22 (6.2%)	0	97 (28.4%)	4 (1.2%)
Vomiting	15 (4.2%)	0	49 (14.3%)	4 (1.2%)
Dry mouth	9 (2.5%)	0	0	0
Stomatitis	9 (2.5%)	0	13 (3.8%)	1 (0.3%)
Colitis[b]	6 (1.7%)	1 (0.3%)	0	0
General Disorders and Administration Site Conditions				
Fatigue[c]	48 (13.5%)	4 (1.1%)	89 (26.0%)	7 (2.0%)
Pyrexia[d]	25 (7.0%)	0	18 (5.3%)	0
Oedema[e]	17 (4.8%)	1 (0.3%)	11 (3.2%)	0
Hepatobiliary Disorders				
Hepatitis[f]	8 (2.3%)	4 (1.1%)	2 (0.6%)	1 (0.3%)
Infections and Infestations				
Pneumonia[g]	35 (9.9%)	19 (5.4%)	39 (11.4%)	21 (6.1%)
Upper respiratory tract infection[h]	22 (6.2%)	3 (0.8%)	21 (6.1%)	2 (0.6%)
Urinary tract infection	5 (1.4%)	0	5 (1.5%)	2 (0.6%)
Injury, Poisoning and Procedural Complications				
Infusion related reaction	10 (2.8%)	0	2 (0.6%)	0
Investigations				
Alanine aminotransferase increased	29 (8.2%)	5 (1.4%)	18 (5.3%)	1 (0.3%)
Aspartate aminotransferase increased	27 (7.6%)	8 (2.3%)	15 (4.4%)	1 (0.3%)
Blood creatinine increased	21 (5.9%)	1 (0.3%)	24 (7.0%)	1 (0.3%)
Blood alkaline phosphatase increased	19 (5.4%)	3 (0.8%)	10 (2.9%)	1 (0.3%)
Weight decreased	16 (4.5%)	2 (0.6%)	22 (6.4%)	0
Amylase increased	14 (3.9%)	1 (0.3%)	3 (0.9%)	1 (0.3%)
Weight increased	10 (2.8%)	2 (0.6%)	1 (0.3%)	0
Blood lactate dehydrogenase increased	7 (2.0%)	1 (0.3%)	2 (0.6%)	0
Lipase increased	6 (1.7%)	1 (0.3%)	0	0
Metabolism and Nutrition Disorders				
Decreased appetite	42 (11.8%)	2 (0.6%)	63 (18.4%)	1 (0.3%)
Hypoalbuminemia	23 (6.5%)	2 (0.6%)	24 (7.0%)	3 (0.9%)
Hyperglycemia	18 (5.1%)	1 (0.3%)	14 (4.1%)	0
Hypokalemia	11 (3.1%)	3 (0.8%)	14 (4.1%)	5 (1.5%)
Hyperkalemia	11 (3.1%)	2 (0.6%)	5 (1.5%)	2 (0.6%)
Hypomagnesemia	8 (2.3%)	0	29 (8.5%)	2 (0.6%)
Musculoskeletal and Connective Tissue Disorders				

Adverse Reactions*	Cemiplimab N = 355		Chemotherapy N = 342	
SOC/ PT	All Grades N (%)	Grade 3-5 N (%)	All Grades N (%)	Grade 3-5 N (%)
Musculoskeletal pain[i]	92 (25.9%)	2 (0.6%)	93 (27.2%)	5 (1.5%)
Nervous System Disorders				
Headache	18 (5.1%)	1 (0.3%)	5 (1.5%)	0
Peripheral neuropathy[j]	9 (2.5%)	1 (0.3%)	65 (19.0%)	2 (0.6%)
Psychiatric Disorders				
Insomnia	21 (5.9%)	0	18 (5.3%)	0
Renal and Urinary Disorders				
Nephritis[k]	6 (1.7%)	1 (0.3%)	8 (2.3%)	2 (0.6%)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough[l]	38 (10.7%)	0	28 (8.2%)	1 (0.3%)
Dyspnea[m]	34 (9.6%)	7 (2.0%)	25 (7.3%)	6 (1.8%)
Pneumonitis[n]	13 (3.7%)	3 (0.8%)	2 (0.6%)	0
Skin and Subcutaneous Tissue Disorders				
Rash[o]	55 (15.5%)	5 (1.4%)	20 (5.8%)	0
Pruritus	27 (7.6%)	0	12 (3.5%)	0

* Version 4.03 of the NCI CTCAE was used to grade toxicity.

[a] Abdominal pain is a composite term that includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, and epigastric discomfort.

[b] Colitis is a composite term that includes colitis, enterocolitis, and immune-mediated enterocolitis.

[c] Fatigue is a composite term that includes fatigue, asthenia, and malaise.

[d] Pyrexia is a composite term that includes pyrexia and hyperthermia.

[e] Oedema is a composite term that includes oedema peripheral, face oedema, generalised oedema, peripheral swelling, and swelling face.

[f] Hepatitis is a composite term that includes autoimmune hepatitis, hepatitis, immune-mediated hepatitis, hepatitis toxic, hepatotoxicity, and liver injury.

[g] Pneumonia is a composite term that includes pneumonia, lower respiratory tract infection, atypical pneumonia, and pneumonia bacterial.

[h] Upper respiratory tract infection is a composite term that includes nasopharyngitis, viral upper respiratory tract infection, pharyngitis, rhinitis, sinusitis, and respiratory tract infection.

[i] 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.

[j] Peripheral neuropathy is a composite term that includes peripheral neuropathy, paraesthesia, peripheral sensory neuropathy, and polyneuropathy.

[k] Nephritis is a composite term that includes acute kidney injury, nephritis, nephropathy toxic, renal failure, and renal impairment.

[l] Cough is a composite term that includes cough and productive cough.

[m] Dyspnea is a composite term that includes dyspnea and dyspnea exertional.

[n] Pneumonitis is a composite term that includes pneumonitis, immune-mediated pneumonitis, and interstitial lung disease.

[o] 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.

First-line treatment of NSCLC with Libtayo in Combination with Platinum-based Chemotherapy (Study 16113)

The safety of Libtayo in combination with platinum-based chemotherapy was evaluated in 465 patients with locally advanced or metastatic NSCLC in Study 16113 (see 14 CLINICAL TRIALS). Patients received Libtayo 350 mg every 3 weeks in combination with platinum-based chemotherapy every 3 weeks for 4 cycles (n=312; Libtayo and chemotherapy arm) or placebo every 3 weeks in combination with platinum-based chemotherapy every 3 weeks for 4 cycles (n=153; placebo and chemotherapy arm). The median duration of exposure was 38.5 weeks (range: 10 days to 102.6 weeks) in the Libtayo plus platinum-based chemotherapy group, and 21.3 weeks (range: 4 days to 95 weeks) in the placebo plus platinum-

based chemotherapy group. In the Libtayo plus platinum-based chemotherapy group, 71.8% of patients were exposed to Libtayo for ≥ 24 weeks and 27.9 % were exposed for ≥ 60 weeks.

The safety population characteristics were: median age of 63 years (range: 25 to 82 years), 188 (40.3%) were 65 or older, 268 (85.9%) male, 267 (85.6%) White, 397 (85.2%) had metastatic disease and 69 (14.8%) had locally advanced disease, and ECOG PS of 0 in 51 patients (16.3%) and 1 in 259 patients (83%).

Libtayo was permanently discontinued due to adverse reactions in 5.1% of patients; adverse reactions resulting in permanent discontinuation in at least 2 patients were anaemia and alanine aminotransferase increased.

Serious adverse events occurred in 25.3% of patients in the Libtayo and chemotherapy arm and 22.2% of patients in the placebo and chemotherapy arm. The most frequent serious adverse events that occurred in at least 2% of patients in the Libtayo and chemotherapy arm were pneumonia (2.9%) and anemia (2.9%) and in the placebo and chemotherapy arm were pneumonia (2.0%) and febrile neutropenia (2.6%).

The most common (≥20%) adverse reactions that occurred in the Libtayo and chemotherapy arm were anemia, alopecia, musculoskeletal pain, nausea, fatigue, and peripheral neuropathy. The most common (≥20%) adverse reactions that occurred in the placebo and chemotherapy arm were alopecia, musculoskeletal pain, and anemia. The most common Grade 3-4 adverse reactions (≥2%) that occurred in the Libtayo and chemotherapy arm were anemia, neutropenia, fatigue, white blood cell count decreased, hyponatremia, thrombocytopenia, neutrophil count decreased, pneumonia, alanine aminotransferase increased and dypnea. The most common Grade 3-4 adverse reactions (≥2%) that occurred in the placebo and chemotherapy arm were anemia, neutropenia, febrile neutropenia, pneumonia, fatigue, alanine aminotransferase increased, aspartate aminotransferase increased, white blood cell count decreased and neutrophil count decreased. Fatal (Grade 5) adverse reactions, regardless of causality, occurred in 6.1% of patients in the Libtayo and chemotherapy arm and in 7.8% of patients in the placebo and chemotherapy arm. The Grade 5 adverse reactions that occurred in the Libtayo and chemotherapy arm included death not otherwise specified, sudden death, pneumonitis and mesenteric artery thrombosis. The Grade 5 adverse reactions that occurred in the placebo and chemotherapy arm included pulmonary embolism and colitis.

Table 4 summarizes the incidence of adverse reactions that occurred in ≥1% patients receiving Libtayo in combination with chemotherapy in Study 16113.

Table 4: Adverse Reactions that Occurred in ≥1% of NSCLC Patients Receiving Libtayo in Combination with Chemotherapy in Study 16113

Adverse Reactions*	Cemiplimab + Chemotherapy N = 312		Placebo + Chemotherapy N = 153	
SOC/ PT	All Grades N (%)	Grade 3-5 N (%)	All Grades N (%)	Grade 3-5 N(%)
Blood and Lymphatic System Disorders				
Anemia	136 (43.6%)	31 (9.9%)	61 (39.9%)	10 (6.5%)
Neutropenia	48 (15.4%)	18 (5.8%)	19 (12.4%)	9 (5.9%)
Thrombocytopenia	41 (13.1%)	8 (2.6%)	19 (12.4%)	2 (1.3%)
Leukopenia	18 (5.8%)	3 (1.0%)	10 (6.5%)	2 (1.3%)
Thrombocytosis	7 (2.2%)	0	1 (0.7%)	0
Leukocytosis	5 (1.6%)	0	4 (2.6%)	0
Febrile neutropenia	4 (1.3%)	4 (1.3%)	4 (2.6%)	4 (2.6%)
Cardiac Disorders				
Tachycardia	4 (1.3%)	0	1 (0.7%)	0
Ear and Labyrinth Disorders				
Tinnitus	3 (1.0%)	0	1 (0.7%)	0
Endocrine Disorders				
Hypothyroidism	28 (9.0%)	1 (0.3%)	4 (2.6%)	0
Hyperthyroidism[a]	19 (6.1%)	1 (0.3%)	4 (2.6%)	0
Eye Disorders				
Lacrimation increased	6 (1.9%)	0	2 (1.3%)	0
Gastrointestinal Disorders				
Nausea	78 (25.0%)	0	25 (16.3%)	0
Constipation	43 (13.8%)	1 (0.3%)	17 (11.1%)	0
Vomiting	38 (12.2%)	0	15 (9.8%)	0
Diarrhea	33 (10.6%)	4 (1.3%)	10 (6.5%)	0
Abdominal pain[b]	16 (5.1%)	1 (0.3%)	4 (2.6%)	0
Stomatitis	10 (3.2%)	2 (0.6%)	1 (0.7%)	0
Gastritis	4 (1.3%)	0	0	0
Abdominal distension	3 (1.0%)	0	1 (0.7%)	0
Colitis	3 (1.0%)	1 (0.3%)	1 (0.7%)	1 (0.7%)
General Disorders and Administration Site Conditions				
Fatigue[c]	73 (23.4%)	12 (3.8%)	28 (18.3%)	3 (2.0%)
Pyrexia	19 (6.1%)	1 (0.3%)	9 (5.9%)	0
Oedema[d]	18 (5.8%)	1 (0.3%)	6 (3.9%)	0
Non-cardiac chest pain	14 (4.5%)	1 (0.3%)	9 (5.9%)	0
Hepatobiliary Disorders				
Hepatitis[e]	8 (2.6%)	3 (1.0%)	2 (1.3%)	0
Hyperbilirubinemia	5 (1.6%)	0	1 (0.7%)	0
Immune System Disorders				
Hypersensitivity	3 (1.0%)	1 (0.3%)	0	0
Infections and Infestations				
Conjunctivitis	4 (1.3%)	0	2 (1.3%)	0
Pneumonia[n]	25 (8.0%)	9 (2.9%)	8 (5.2%)	6 (3.9%)
Urinary tract infection[o]	6 (1.9%)	2 (0.6%)	1 (0.7%)	0
Investigations				
Alanine aminotransferase increased	51 (16.3%)	7 (2.2%)	22 (14.4%)	3 (2.0%)
Aspartate aminotransferase increased	46 (14.7%)	1 (0.3%)	18 (11.8%)	3 (2.0%)

Adverse Reactions*	Cemiplimab + Chemotherapy N = 312		Placebo + Chemotherapy N = 153	
SOC/ PT	All Grades N (%)	Grade 3-5 N (%)	All Grades N (%)	Grade 3-5 N(%)
Weight decreased	35 (11.2%)	4 (1.3%)	13 (8.5%)	0
Blood creatinine increased	31 (9.9%)	1 (0.3%)	8 (5.2%)	0
Weight increased	24 (7.7%)	0	2 (1.3%)	0
White blood cell count decreased	23 (7.4%)	10 (3.2%)	6 (3.9%)	3 (2.0%)
Amylase increased	22 (7.1%)	3 (1.0%)	5 (3.3%)	0
Blood lactate dehydrogenase increased	22 (7.1%)	0	6 (3.9%)	0
Blood urea increased	21 (6.7%)	0	7 (4.6%)	0
Blood alkaline phosphatase increased	17 (5.4%)	0	14 (9.2%)	0
Platelet count decreased	17 (5.4%)	3 (1.0%)	6 (3.9%)	0
Blood thyroid stimulating hormone increased	15 (4.8%)	0	1 (0.7%)	0
Blood uric acid increased	15 (4.8%)	0	7 (4.6%)	1 (0.7%)
Lipase increased	15 (4.8%)	1 (0.3%)	2 (1.3%)	0
Neutrophil count decreased	12 (3.8%)	8 (2.6%)	5 (3.3%)	3 (2.0%)
Lymphocyte count decreased	11 (3.5%)	3 (1.0%)	4 (2.6%)	0
Blood thyroid stimulating hormone decreased	7 (2.2%)	0	4 (2.6%)	0
Blood bilirubin increased	6 (1.9%)	1 (0.3%)	4 (2.6%)	0
Blood potassium increased	4 (1.3%)	1 (0.3%)	1 (0.7%)	1 (0.7%)
Bilirubin conjugated increased	3 (1.0%)	0	0	0
Metabolism and Nutrition Disorders				
Hyperglycemia	55 (17.6%)	6 (1.9%)	18 (11.8%)	0
Decreased appetite	53 (17.0%)	3 (1.0%)	18 (11.8%)	0
Hypoalbuminemia	32 (10.3%)	2 (0.6%)	9 (5.9%)	0
Hypokalemia	20 (6.4%)	3 (1.0%)	7 (4.6%)	2 (1.3%)
Hypocalcemia	19 (6.1%)	1 (0.3%)	11 (7.2%)	1 (0.7%)
Hyperkalemia	15 (4.8%)	0	7 (4.6%)	3 (2.0%)
Hyperuricemia	15 (4.8%)	1 (0.3%)	3 (2.0%)	0
Hyponatremia	15 (4.8%)	9 (2.9%)	3 (2.0%)	2 (1.3%)
Hypomagnesemia	13 (4.2%)	0	1 (0.7%)	1 (0.7%)
Hypercalcemia	9 (2.9%)	1 (0.3%)	5 (3.3%)	2 (1.3%)
Hypophosphatemia	3 (1.0%)	1 (0.3%)	2 (1.3%)	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[f]	84 (26.9%)	4 (1.3%)	49 (32.0%)	0
Muscular weakness	4 (1.3%)	1 (0.3%)	3 (2.0%)	0
Arthritis[g]	3 (1.0%)	0	0	0
Nervous System Disorders				
Peripheral neuropathy[h]	66 (21.2%)	0	29 (19.0%)	0
Hypoesthesia	4 (1.3%)	0	0	0
Psychiatric Disorders				
Insomnia	34 (10.9%)	0	11 (7.2%)	0
Mood altered	10 (3.2%)	0	1 (0.7%)	0
Renal and Urinary Disorders				
Nephritis[i]	13 (4.2%)	2 (0.6%)	4 (2.6%)	2 (1.3%)
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea[j]	40 (12.8%)	7 (2.2%)	10 (6.5%)	1 (0.7%)
Cough[k]	22 (7.1%)	1 (0.3%)	12 (7.8%)	0
Pneumonitis[l]	14 (4.5%)	2 (0.6%)	1 (0.7%)	0
Skin and Subcutaneous Tissue Disorders				
Alopecia	115 (36.9%)	0	66 (43.1%)	0

Adverse Reactions*	Cemiplimab + Chemotherapy N = 312		Placebo + Chemotherapy N = 153	
SOC/ PT	All Grades N (%)	Grade 3-5 N (%)	All Grades N (%)	Grade 3-5 N(%)
Rash[m]	39 (12.5%)	4 (1.3%)	9 (5.9%)	0
Pruritis	14 (4.5%)	0	3 (2.0%)	0
Dry skin	6 (1.9%)	0	4 (2.6%)	0

* Version 4.03 of the NCI CTCAE was used to grade toxicity.

[a] Hyperthyroidism is a composite term that includes hyperthyroidism, Basedow's disease, and toxic nodular goitre.

[b] Abdominal pain is a composite term that includes abdominal pain and abdominal pain upper.

[c] Fatigue is a composite term that includes asthenia, fatigue, and malaise.

[d] Oedema is a composite term that includes oedema peripheral, peripheral swelling, oedema, and face oedema.

[e] Hepatitis is a composite term that includes hepatic function abnormal, drug-induced liver injury, hepatitis, hepatitis acute, hepatotoxicity, and immune-mediated hepatitis.

[f] Musculoskeletal pain is a composite term that includes arthralgia, back pain, pain in extremity, myalgia, bone pain, musculoskeletal pain, neck pain, musculoskeletal chest pain, and spinal pain.

[g] Arthritis is a composite term that includes arthritis and autoimmune arthritis.

[h] Peripheral neuropathy is a composite term that includes peripheral sensory neuropathy, peripheral neuropathy, paraesthesia, and polyneuropathy.

[i] Nephritis is a composite term that includes acute kidney injury, renal failure, renal impairment, tubulointerstitial nephritis, and immune-mediated nephritis.

[j] Dyspnea is a composite term that includes dyspnea and dyspnea exertional.

[k] Cough is a composite term that includes cough and productive cough.

[l] Pneumonitis is a composite term that includes pneumonitis and immune mediated pneumonitis.

[m] Rash is a composite term that includes rash, rash maculo-papular, dermatitis, psoriasis, rash papular, urticaria, dermatitis allergic, erythema, lichen planus, rash macular, rash pruritic, skin reaction, and skin toxicity.

n Pneumonia is a composite term that includes pneumonia and lower respiratory tract infection.

o Urinary tract infection is a composite term that includes urinary tract infection and cystitis.

Basal Cell Carcinoma (Study 1620)

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 TRIALS). 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, which included acute kidney injury (1 patient) and cachexia (1 patient).

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

Table 5: Adverse Reactions that Occurred in ≥1% of BCC Patients in Study 1620

Adverse Reactions*	Cemiplimab N = 132	
SOC/ PT	All Grades N (%)	Grade 3-5 N (%)
Blood and Lymphatic System Disorders		
Anemia	17 (12.9%)	1 (0.8%)
Lymphopenia	5 (3.8%)	2 (1.5%)
Cardiac Disorders		
Myocarditis[a]	2 (1.5%)	2 (1.5%)
Endocrine Disorders		
Hypothyroidism[b]	12 (9.1%)	0
Hyperthyroidism	5 (3.8%)	0
Adrenal insufficiency	3 (2.3%)	2 (1.5%)
Thyroiditis	2 (1.5%)	0
Gastrointestinal Disorders		
Diarrhea	33 (25.0%)	0
Nausea	16 (12.1%)	1 (0.8%)
Constipation	14 (10.6%)	1 (0.8%)
Abdominal pain[c]	13 (9.8%)	2 (1.5%)
Vomiting	10 (7.6%)	0
Colitis[d]	9 (6.8%)	6 (4.5%)
Dry mouth	6 (4.5%)	0
Abdominal distension	4 (3.0%)	0
Stomatitis	2 (1.5%)	0
General Disorders and Administration Site Conditions		
Fatigue[e]	64 (48.5%)	5 (3.8%)
Oedema[f]	11 (8.3%)	1 (0.8%)
Pyrexia	11 (8.3%)	1 (0.8%)
Influenza like illness	7 (5.3%)	0
Chills	4 (3.0%)	0
Hepatobiliary Disorders		
Hepatitis[g]	6 (4.5%)	1 (0.8%)
Infections and Infestations		
Upper respiratory tract infection[h]	20 (15.2%)	0
Urinary tract infection	16 (12.1%)	3 (2.3%)
Rash pustular	2 (1.5%)	0
Injury, Poisoning and Procedural Complications		
Infusion related reaction	4 (3.0%)	0
Investigations		
Weight decreased	12 (9.1%)	2 (1.5%)
Blood creatinine increased	12 (9.1%)	0
Alanine aminotransferase increased	6 (4.5%)	0
Blood creatine phosphokinase increased	6 (4.5%)	0
Aspartate aminotransferase increased	5 (3.8%)	0
Gamma-glutamyltransferase increased	4 (3.0%)	2 (1.5%)
Blood thyroid stimulating hormone increased	3 (2.3%)	0
Lymphocyte count decreased	2 (1.5%)	0
Metabolism and Nutrition Disorders		
Decreased appetite	19 (14.4%)	2 (1.5%)
Hyperglycemia	7 (5.3%)	1 (0.8%)

Adverse Reactions*	Cemiplimab N = 132	
SOC/ PT	All Grades N (%)	Grade 3-5 N (%)
Hyperkalemia	5 (3.8%)	1 (0.8%)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[i]	43 (32.6%)	2 (1.5%)
Muscle spasms	6 (4.5%)	0
Nervous System Disorders		
Headache	16 (12.1%)	2 (1.5%)
Dizziness	13 (9.8%)	0
Peripheral neuropathy[j]	8 (6.1%)	0
Renal and Urinary Disorders		
Nephritis[k]	6 (4.5%)	1 (0.8%)
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea[l]	15 (11.4%)	0
Cough[m]	11 (8.3%)	0
Pneumonitis	5 (3.8%)	2 (1.5%)
Skin and Subcutaneous Tissue Disorders		
Rash[n]	29 (22.0%)	1 (0.8%)
Pruritus	26 (19.7%)	0
Eczema	10 (7.6%)	0
Actinic keratosis	9 (6.8%)	0
Dry Skin	8 (6.1%)	0
Vascular Disorders		
Hypertension[o]	14 (10.6%)	6 (4.5%)

* Version 4.03 of the NCI CTCAE was used to grade toxicity.

[a] Myocarditis is a composite term that includes autoimmune myocarditis and immune-mediated myocarditis.

[b] Hypothyroidism is a composite term that includes hypothyroidism and immune-mediated hypothyroidism.

[c] Abdominal pain is a composite term that includes abdominal pain, abdominal pain upper, abdominal pain lower, and gastrointestinal pain.

[d] Colitis is a composite term that includes colitis, autoimmune colitis, and enterocolitis.

[e] Fatigue is a composite term that includes fatigue, asthenia, and malaise.

[f] Oedema is a composite term that includes oedema peripheral, peripheral swelling, and swelling face.

[g] Hepatitis is a composite term that includes hepatocellular injury, autoimmune hepatitis, and immune-mediated hepatitis.

[h] Upper respiratory tract infection is a composite term that includes nasopharyngitis, viral upper respiratory tract infection, pharyngitis, rhinitis, sinusitis, and respiratory tract infection.

[i] Musculoskeletal pain is a composite term that includes arthralgia, back pain, myalgia, pain in extremity, musculoskeletal pain, neck pain, musculoskeletal stiffness, musculoskeletal chest pain, musculoskeletal discomfort, and spinal pain.

[j] Peripheral neuropathy is a composite term that includes paraesthesia, peripheral motor neuropathy, and peripheral sensory neuropathy.

[k] Nephritis is a composite term that includes acute kidney injury, renal failure, nephropathy toxic, and renal impairment.

[l] Dyspnea is a composite term that includes dyspnea and dyspnea exertional.

[m] Cough is a composite term that includes cough and productive cough.

[n] Rash is a composite term that includes rash maculo-papular, rash, dermatitis, dermatitis acneiform, erythema, rash pruritic, dermatitis bullous, dyshidrotic eczema, pemphigoid, rash erythematous, and urticaria.

[o] Hypertension is a composite term that includes hypertension and hypertensive crisis.

Cervical Cancer (Study 1676)

The safety of Libtayo was evaluated in 300 patients with recurrent or metastatic cervical cancer in Study 1676 (see 14 CLINICAL TRIALS). Patients received Libtayo 350 mg every 3 weeks (n=300) or investigator's choice of IV chemotherapy (n=290), consisting of pemetrexed; topotecan or irinotecan; gemcitabine; or vinorelbine. Treatment in both arms was for up to 96 weeks and continued until disease progression or unacceptable toxicity, or whichever occurred first.

Permanent discontinuation of Libtayo due to an adverse event occurred in 9% of patients, which included pneumonitis (1.7%).

Serious adverse events occurred in 30% of patients treated with Libtayo. The serious adverse event that occurred in at least 2% of patients treated with Libtayo was urinary tract infection.

Dosage delays of Libtayo due to an adverse event occurred in 25% of patients receiving Libtayo. Adverse reactions which required dosage delay in > 2% of patients receiving Libtayo included anemia, and urinary tract infection.

The most common Grade 3 or 4 adverse events (> 2%) were anemia, urinary tract infection, hypokalemia, asthenia, and hydronephrosis. The most common (> 3%) laboratory abnormality worsening from baseline to Grade 3 or 4 were anemia, lymphocyte count decreased, hyponatremia, hypokalemia, aspartate aminotransferase increased, alanine aminotransferase increased, alkaline phosphatase increased, creatinine increased, hypoalbuminemia.

Table 6 summarizes the adverse reactions that occurred in ≥ 1% of patients and Table 11 summarizes Grade 3 or 4 laboratory abnormalities worsening from baseline in ≥ 10% of patients receiving Libtayo.

Table 6: Adverse Reactions that Occurred in ≥1% of Cervical Cancer Patients in Study 1676

Adverse Reactions*	Cemiplimab N = 300		Chemotherapy N = 290	
SOC/ PT	All Grades N (%)	Grade 3-5 N (%)	All Grades N (%)	Grade 3-5 N (%)
Blood and Lymphatic System Disorders				
Anemia	75 (25.0%)	36 (12.0%)	129 (44.5%)	78 (26.9%)
Neutropenia	6 (2.0%)	3 (1.0%)	44 (15.2%)	26 (9.0%)
Endocrine Disorders				
Hypothyroidism	18 (6.0%)	1 (0.3%)	0	0
Hyperthyroidism	9 (3.0%)	0	0	0
Gastrointestinal Disorders				
Nausea	55 (18.3%)	1 (0.3%)	97 (33.4%)	6 (2.1%)
Vomiting	48 (16.0%)	2 (0.7%)	68 (23.4%)	7 (2.4%)
Abdominal pain[a]	45 (15.0%)	4 (1.3%)	53 (18.3%)	5 (1.7%)
Constipation	45 (15.0%)	0	59 (20.3%)	1 (0.3%)
Diarrhea	32 (10.7%)	3 (1.0%)	39 (13.4%)	4 (1.4%)
Stomatitis	12 (4.0%)	1 (0.3%)	22 (7.6%)	3 (1.0%)
Gastroesophageal reflux disease	7 (2.3%)	0	3 (1.0%)	0
Colitis	5 (1.7%)	1 (0.3%)	0	0
Dry mouth	4 (1.3%)	0	2 (0.7%)	0
General Disorders and Administration Site Conditions				
Fatigue[b]	83 (27.7%)	11 (3.7%)	97 (33.4%)	8 (2.8%)
Pyrexia[c]	40 (13.3%)	1 (0.3%)	65 (22.4%)	0
Influenza like illness	6 (2.0%)	1 (0.3%)	7 (2.4%)	0
Chills	4 (1.3%)	0	2 (0.7%)	0
Hepatobiliary Disorders				
Hepatitis[d]	12 (4.0%)	11 (3.7%)	2 (0.7%)	1 (0.3%)
Injury, Poisoning and Procedural Complications				
Infusion related reaction	8 (2.7%)	0	13 (4.5%)	1 (0.3%)
Investigations				
Blood creatinine increased	20 (6.7%)	4 (1.3%)	17 (5.9%)	1 (0.3%)
Weight decreased	14 (4.7%)	3 (1.0%)	11 (3.8%)	1 (0.3%)
Alanine aminotransferase increased	13 (4.3%)	2 (0.7%)	20 (6.9%)	2 (0.7%)
Aspartate aminotransferase increased	12 (4.0%)	2 (0.7%)	19 (6.6%)	0
Blood alkaline phosphatase increased	12 (4.0%)	4 (1.3%)	14 (4.8%)	2 (0.7%)
Gamma-glutamyltransferase increased	7 (2.3%)	0	6 (2.1%)	1 (0.3%)
Platelet count decreased	3 (1.0%)	2 (0.7%)	14 (4.8%)	5 (1.7%)
Metabolism and Nutrition Disorders				
Decreased appetite	45 (15.0%)	1 (0.3%)	46 (15.9%)	2 (0.7%)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[e]	72 (24.0%)	6 (2.0%)	54 (18.6%)	4 (1.4%)
Nervous System Disorders				
Headache	22 (7.3%)	1 (0.3%)	17 (5.9%)	0
Dizziness	12 (4.0%)	0	12 (4.1%)	0
Renal and Urinary Disorders				
Nephritis[f]	11 (3.7%)	3 (1.0%)	11 (3.8%)	2 (0.7%)
Proteinuria	3 (1.0%)	2 (0.7%)	2 (0.7%)	0
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnea[g]	28 (9.3%)	5 (1.7%)	18 (6.2%)	1 (0.3%)
Pneumonitis[h]	7 (2.3%)	2 (0.7%)	2 (0.7%)	1 (0.3%)

Adverse Reactions*	Cemiplimab N = 300		Chemotherapy N = 290	
SOC/ PT	All Grades N (%)	Grade 3-5 N (%)	All Grades N (%)	Grade 3-5 N (%)
Skin and Subcutaneous Tissue Disorders				
Rash[i]	37 (12.3%)	5 (1.7%)	28 (9.7%)	0
Pruritus	16 (5.3%)	0	15 (5.2%)	1 (0.3%)
Dry skin	10 (3.3%)	0	0	0

* Version 4.03 of the NCI CTCAE was used to grade toxicity.

[a] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.

[b] Fatigue includes fatigue, asthenia, and malaise.

[c] Pyrexia includes pyrexia, hyperthermia, and hyperpyrexia.

[d] Hepatitis includes autoimmune hepatitis, immune-mediated hepatitis, hepatic failure, hepatic function abnormal, hepatitis, hepatotoxicity, drug-induced liver injury, and hepatocellular injury.

[e] Musculoskeletal pain includes back pain, arthralgia, pain in extremity, myalgia, neck pain, musculoskeletal chest pain, bone pain, musculoskeletal pain, and spinal pain.

[f] Nephritis includes acute kidney injury, renal failure, nephritis, and renal impairment.

[g] Dyspnea includes dyspnea and dyspnea exertional.

[h] Pneumonitis includes pneumonitis and interstitial lung disease.

[i] Rash includes rash, rash maculo-papular, dermatitis, rash pruritic, urticaria, dermatitis allergic, dermatitis bullous, dermatitis exfoliative generalized, erythema, erythema multiforme, rash erythematous, rash macular, rash papular, skin toxicity, and dermatitis acneiform.

Description of Selected Adverse Reactions (Monotherapy; Studies 1423, 1540, 1620, 1624 and 1676)

The safety data described in 7 WARNINGS AND PRECAUTIONS and "Description of Selected Adverse Reactions (Monotherapy; Studies 1423, 1540, 1620, 1624 and 1676)" reflects exposure to 1281 patients from a pooled analysis with advanced solid malignancies receiving Libtayo monotherapy in 5 clinical studies. Identified imAEs were defined as potential imAEs requiring treatment with systemic corticosteroid or other immunosuppressants or events that were immune-mediated endocrinopathies. High-dose corticosteroids in the following sections are defined as ≥40 mg prednisone per day, or equivalent.

These selected adverse reactions were consistent when Libtayo was administered as - monotherapy or in combination with platinum-based chemotherapy.

Immune-mediated Adverse Reactions
(see 4 DOSAGE AND ADMINISTRATION, Table 1, and 7 WARNINGS AND PRECAUTIONS).

Immune-mediated pneumonitis
Immune-mediated pneumonitis occurred in 30 (2.7%) of 1116 patients receiving Libtayo, including 4 (0.4%) patients with Grade 4 and 6 (0.5%) patients with Grade 3 pneumonitis. Immune-mediated pneumonitis led to permanent discontinuation of Libtayo in 15 (1.3%) of 1116 patients. Among the 30 patients with immune-mediated pneumonitis, the median time to onset was 2.2 months (range: 7 days to 18 months) and the median duration of pneumonitis was 30 days (range: 5 days to 16.9 months). Twenty-five of the 30 patients (83.3%) received high-dose corticosteroids for a median of 12 days (range: 1 day to 5.9 months). Resolution of pneumonitis had occurred in 18 (60.0%) of the 30 patients at the time of data cutoff.

Immune-mediated colitis
Immune-mediated diarrhea or colitis occurred in 23 (2.1%) of 1116 patients receiving Libtayo including 9 (0.8%) with Grade 3 immune-mediated diarrhea or colitis. Immune-mediated diarrhea or colitis led to permanent discontinuation of Libtayo in 5 (0.4%) of 1116 patients. Among the 23 patients with immune-mediated diarrhea or colitis, the median time to onset was 3.8 months (range: 21 days to 15.5 months) and the median duration of immune-mediated diarrhea or colitis was 2.1 months (range: 6 days to 10.0 months). Eighteen patients (78.3%) with immune-mediated diarrhea or colitis received high-dose corticosteroids for a median of 27 days (range: 2 days to 5.2 months). Resolution of immune-mediated diarrhea or colitis had occurred in 13 (57%) of the 23 patients at the time of data cutoff.

Immune-mediated hepatitis
Immune-mediated hepatitis occurred in 27 (2.4%) of 1116 patients receiving Libtayo including 1 (<0.1%) patient with Grade 5, 4 (0.4%) patients with Grade 4, and 19 (1.7%) patients with Grade 3 immune-mediated hepatitis. Immune-mediated hepatitis led to permanent discontinuation of Libtayo in 18 (1.6%) of 1116 patients. Among the 27 patients with immune-mediated hepatitis, the median time to onset was 2.8 months (range: 7 days to 22.5 months) and the median duration of hepatitis was 2.1 months (range: 10 days to 7.6 months). Twenty-three patients (85.2%) with immune-mediated hepatitis received high-dose corticosteroids for a median of 26 days (range: 6 days to 3.1 months). Resolution of hepatitis had occurred in 9 (33.3%) of the 27 patients at the time of data cutoff.

Immune-mediated endocrinopathies
Hypothyroidism occurred in 79 (7.1%) of 1116 patients receiving Libtayo including 1 (<0.1%) patient with Grade 3 hypothyroidism. Three (0.3%) of 1116 patients discontinued Libtayo due to hypothyroidism. Among the 79 patients with hypothyroidism, the median time to onset was 3.8 months (range: 15 days to 18.9 months) with a median duration of 7.7 months (range: 1 day to 23.3 months). Resolution of hypothyroidism had occurred in 5 (6.3%) of the 79 patients at the time of data cutoff.

Hyperthyroidism occurred in 36 (3.2%) of 1116 patients receiving Libtayo including 11 (1.0%) patients with Grade 2 hyperthyroidism. No patient discontinued Libtayo due to hyperthyroidism. Among the 36 patients with hyperthyroidism, the median time to onset was 2.0 months (range: 20 days to 23.8 months) and the median duration was 2.0 months (range: 9 days to 24.5 months). Resolution of hyperthyroidism had occurred in 19 (52.8%) of the 36 patients at the time of data cutoff.

Thyroiditis occurred in 6 (0.5%) of 1116 patients receiving Libtayo including 3 (0.3%) patients with Grade 2 thyroiditis. No patient discontinued Libtayo due to thyroiditis. Resolution of thyroiditis had occurred in 1 (16.7%) of the 6 patients at the time of data cutoff.

Adrenal insufficiency occurred in 3 (0.3%) of 1116 patients receiving Libtayo including 3 (0.3%) patients with Grade 3 adrenal insufficiency. One (<0.1%) of 1116 patients discontinued Libtayo due to adrenal insufficiency. Among the 3 patients with adrenal insufficiency, the median time to onset was 11.5 months (range: 4.2 months to 18.3 months) and the median duration was 5.1 months (range: 4.9 months to 6.1 months). All 3 patients (100.0%) were treated with systemic corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.

Hypophysitis occurred in 3 (0.3%) of 1116 patients receiving Libtayo, including 2 (0.2%) patients with Grade 3 hypophysitis. One (<0.1%) of 1116 patients discontinued Libtayo due to hypophysitis. Among

the 3 patients with hypophysitis, the median time to onset was 4.6 months (range: 2.6 months to 7.4 months) and the median duration was 23 days (range: 9 days to 1.5 months). Two of the 3 patients (66.7%) were treated with systemic corticosteroids. Hypophysitis resolved in 1 of the 3 patients (33.3%) at the time of data cutoff.

Type 1 diabetes mellitus occurred in 1 (<0.1%) of 1116 patients (Grade 4).

Immune-mediated skin adverse reactions
Immune-mediated skin adverse reactions occurred in 18 (1.6%) of 1116 patients receiving Libtayo including 8 (0.7%) patients with Grade 3 immune-mediated skin adverse reactions. Immune-mediated skin adverse reactions led to permanent discontinuation of Libtayo in 1 (<0.1%) of 1116 patients. Among the 18 patients with immune-mediated skin adverse reactions, the median time to onset was 1.2 months (range: 2 days to 17.0 months) and the median duration was 2.6 months (range: 8 days to 12.5 months). Twelve patients (66.7%) with immune-mediated skin adverse reactions received high-dose corticosteroids for a median of 9 days (range: 1 day to 2.6 months). Resolution of skin reaction had occurred in 13 (72.2%) of 18 patients at the time of data cutoff.

Immune-mediated nephritis
Immune-mediated nephritis occurred in 7 (0.6%) of 1116 patients receiving Libtayo including 1 (<0.1%) patient with Grade 5 and 1 (<0.1%) patient with Grade 3 immune-mediated nephritis. Immune-mediated nephritis led to permanent discontinuation of Libtayo in 2 (0.2%) of 1116 patients. Among the 7 patients with immune-mediated nephritis, the median time to onset was 1.8 months (range: 14 days to 5.6 months) and the median duration of nephritis was 29 days (range: 9 days to 5.5 months). Six patients (85.7%) with immune-mediated nephritis received high-dose corticosteroids for a median of 16 days (range: 3 days to 1.3 months). Resolution of nephritis had occurred in 5 (71.4%) of the 7 patients at the time of data cutoff.

Other Immune-mediated Adverse Reactions
The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% of 1116 patients with advanced solid malignancies treated with Libtayo monotherapy in clinical trials. The events were Grade 3 or less unless stated otherwise:

Nervous System Disorders: Aseptic meningitis, paraneoplastic encephalomyelitis (Grade 5), chronic inflammatory demyelinating polyradiculoneuropathy, encephalitis, myasthenia gravis, peripheral neuropathy[a]

Cardiac Disorders: Myocarditis[b] (Grade 5), pericarditis[c]

Immune System Disorders: Immune thrombocytopenia

Musculoskeletal and Connective Tissue Disorders: Arthralgia, arthritis[d], muscular weakness, myalgia, myositis[e], polymyalgia rheumatica, Sjogren's syndrome

Eye Disorders: Keratitis

Gastrointestinal Disorders: Stomatitis

a. includes neuritis, peripheral neuropathy and polyneuropathy
b. includes autoimmune myocarditis, immune-mediated myocarditis and myocarditis
c. includes autoimmune pericarditis and pericarditis
d. includes arthritis and polyarthritis
e. includes myositis and dermatomyositis

The following additional immune-mediated adverse reactions were observed in patients receiving combination therapy in clinical trials: vasculitis, Guillain-Barre syndrome, central nervous system inflammation, and meningitis (Grade 4), each with the frequency of rare (≥ 1/10,000 to < 1/1,000).

Infusion-related Reactions
Infusion-related reactions occurred in 83 (7.4%) of 1116 patients treated with Libtayo including 1 (<0.1%) patient with Grade 3 infusion-related reaction. The most common symptoms of infusion-related reactions were nausea, pyrexia and vomiting.

8.3 Less Common Clinical Trial Adverse Reactions

Cutaneous Squamous Cell Carcinoma (CSCC) (Studies 1423 and Study 1540)

Listing 1a: Adverse Reactions that Occurred in <1% of Advanced Cutaneous Squamous Cell Carcinoma Patients in Study 1423 and Study 1540

Cardiac Disorders: Autoimmune myocarditis

Endocrine Disorders: Adrenal insufficiency, hypophysitis

Infections and Infestations: Meningitis

Musculoskeltal and Connective Tissue Disorders: Sjogren's syndrome

Nervous System Disorders: Chronic inflammatory demyelinating polyradiculoneurophathy

Renal and Urinary Disorders: Nephritis

Listing 2b: Adverse Reactions that Occurred in <1% of Advanced Cutaneous Squamous Cell Carcinoma Patients in Study 1540

In the final analysis of study 1540 (n=358), the following other adverse reactions observed in ≤1% of advanced CSCC patients included:

Cardiac Disorders: Myocarditis, pericarditis

Endocrine Disorders: Thyroiditis, adrenal insufficiency

Gastrointestinal Disorders: Stomatitis, immune-mediated gastritis

Musculoskeletal and Connective Tissue Disorders: Myositis, myalgia, arthritis[a], polymyalgia rheumatica

Nervous System Disorders: Encephalitis, meningitis aseptic, neuropathy peripheral[b]

Renal and Urinary Disorders: Immune-mediated nephritis[c]

Skin and subcutaneous tissue disorders: Pruritus

a. includes polyarthritis, arthritis, immune-mediated arthritis
b. includes neuropathy peripheral, peripheral sensory neuropathy, neuritis
c. includes nephritis and blood creatinine increased

Non-Small Cell Lung Cancer (Study 1624) - Monotherapy

Listing 3: Adverse Reactions that Occurred in <1% of Locally Advanced and Metastatic Non-Small Cell Lung Cancer Patients in Study 1624

Cardiac Disorders: Myocarditis[a]

Endocrine Disorders: Thyroiditis[b], hypophysitis, blood thyroid stimulating hormone increased

Gastrointestinal Disorders: Stomatitis

Hepatobiliary Disorders: Blood alkaline phosphatase increased

Musculoskeletal and Connective Tissue Disorders: Arthritis[c], myositis

Nervous System Disorders: Peripheral neuropathy[d]

Renal and Urinary Disorders: Immune-mediated nephritis[e]

a. includes autoimmune myocarditis and myocarditis
b. includes thyroiditis and autoimmune thyroiditis
c. includes arthritis and polyarthritis
d. includes peripheral neuropathy and polyneuropathy
e. includes nephritis (Grade 5), acute kidney injury and blood creatinine increased

Non-Small Cell Lung Cancer (Study 16113) – Combination with Platinum-Based Chemotherapy

Listing 3: Adverse Reactions that Occurred in <1% of NSCLC Patients Receiving Libtayo in Combination with Chemotherapy in Study 16113

Endocrine Disorders: Thyroiditis[a], type 1 diabetes mellitus[b]

Immune System Disorders: Infusion related reaction

Investigations: Gamma-glutamyltransferase increased

a. includes autoimmune thyroiditis and immune-mediated thyroiditis.

b. includes diabetes mellitus.

Basal Cell Carcinoma (Study 1620)

Listing 4: Adverse Reactions that Occurred in <1% of Basal Cell Carcinoma Patients in Study 1620

Cardiac Disorders: Autoimmune pericarditis

Endocrine Disorders: Blood thyroid stimulating hormone decreased, hypophysitis

Skin and Subcutaneous Tissue Disorders: Rash maculo-papular, pruritus

Cervical Cancer (Study 1676)

Listing 5: Adverse Reactions that Occurred in <1% of Cervical Cancer Patients in Study 1676

Cardiac Disorders: Autoimmune pericarditis

Endocrine Disorders: Thyroiditis, blood thyroid stimulating hormone increased

Musculoskeletal and Connective Tissue Disorders: Arthritis[a]

Renal and Urinary Disorders: Immune-mediated nephritis[b]

a. includes arthritis and polyarthritis
b. includes nephtritis and acute kidney injury

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Cutaneous Squamous Cell Carcinoma (Studies 1423 and Study 1540)

Table 7: Selected Treatment-Emergent Laboratory Abnormalities in ≥15% of Advanced CSCC Patients in Study 1423 and Study 1540

Laboratory Tests*	Any Grade (N=163) n/N (%)†	Grade 3-4 (N=163) n/N (%)†
Chemistry		
Aspartate aminotransferase increased	25/156 (16.0)	5/156 (3.2)
Creatinine increased	37/157 (23.6)	1/157 (0.6)
Hematology		
Anemia	66/157 (42.0)	3/157 (1.9)
Lymphopenia	65/157 (41.4)	11/157 (7.0)

* Treatment-emergent consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality

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

In a subsequent update of Studies 1423 and 1540 (N=219), the incidence of the following laboratory abnormalities increased: aspartate aminostransferase increased (Any Grade: 48/215 (22.3%), Grade 3+: 5/215 (2.3%)), creatinine increased (Any Grade: 174/216 (80.6%), Grade 3+: 2/216 (0.9%)), anemia (Any Grade: 91/216 (42.1%), Grade 3+: 10/216 (4.6%)). Furthermore, the following treatment-emergent laboratory abnormalities were also observed in >15% of advanced CSCC patients: hypoalbumenia (Any Grade: 70/216 (32.4%), Grade 3+: 2/216 (0.9%)), hyponatremia (Any Grade: 61/216 (28.2%), Grade 3+: 10/216 (4.6%)), hypophosphatemia (Any Grade: 53/215 (24.7%), Grade 3+: 9/215 (4.2%)), hypocalcemia (uncorrected calcium) (Any Grade: 47/216 (21.8%), Grade 3+: 0/216 (0%)), hyperkalemia (Any Grade: 44/216 (20.4%), Grade 3+: 2/216 (0.9%)), hypokalemia (Any Grade: 39/216 (18.1%), Grade 3+: 1/216 (0.5%)), activated partial thromboplastin time (Any Grade: 32/177 (18.1%), Grade 3+: 1/177 (0.6%)), and alanine aminotransferase increased (Any Grade: 37/216 (17.1%), Grade 3+: 1/216 (0.5%)).

Non-Small Cell Lung Cancer (Study 1624) - Monotherapy

Table 8: Laboratory Abnormalities in ≥10% of Locally Advanced and Metastatic NSCLC Patients in Study 1624

Laboratory Tests*	Cemiplimab (N=355)		Chemotherapy (N=342)	
	Any Grade n/N (%)	Grade 3-4 n/N (%)	Any Grade n/N (%)	Grade 3-4 n/N (%)
Chemistry				
Alanine Aminotransferase (Alanine aminotransferase increased)	86/336 (25.6%)	9/336 (2.7%)	73/321 (22.7%)	1/321 (0.3%)
Albumin (Hypoalbuminemia)	110/336 (32.7%)	6/336 (1.8%)	84/320 (26.3%)	4/320 (1.3%)
Alkaline Phosphatase (Alkaline phosphatase increased)	86/335 (25.7%)	8/335 (2.4%)	74/321 (23.1%)	1/321 (0.3%)
Aspartate Aminotransferase (Aspartate aminotransferase increased)	92/336 (27.4%)	13/336 (3.9%)	76/321 (23.7%)	4/321 (1.2%)
Bilirubin (Blood bilirubin increased)	46/336 (13.7%)	7/336 (2.1%)	23/321 (7.2%)	1/321 (0.3%)
Calcium (Hypercalcemia (Uncorrected Calcium))	60/333 (18.0%)	4/333 (1.2%)	47/320 (14.7%)	7/320 (2.2%)
Calcium (Hypocalcemia (Uncorrected Calcium))	87/333 (26.1%)	13/333 (3.9%)	83/320 (25.9%)	11/320 (3.4%)
Creatinine (Creatinine increased)	267/336 (79.5%)	4/336 (1.2%)	246/321 (76.6%)	5/321 (1.6%)
Glucose (Hypoglycemia)	39/335 (11.6%)	0/335	23/321 (7.2%)	0/321
Magnesium (Hypomagnesemia)	55/334 (16.5%)	0/334	100/318 (31.4%)	5/318 (1.6%)
Phosphate (Hypophosphatemia)	53/334 (15.9%)	8/334 (2.4%)	52/317 (16.4%)	13/317 (4.1%)
Potassium (Hyperkalemia)	74/336 (22.0%)	14/336 (4.2%)	65/321 (20.2%)	6/321 (1.9%)
Potassium (Hypokalemia)	34/336 (10.1%)	5/336 (1.5%)	43/321 (13.4%)	7/321 (2.2%)
Sodium (Hyponatremia)	101/336 (30.1%)	21/336 (6.3%)	99/321 (30.8%)	24/321 (7.5%)
Hematology				
Hemoglobin (Anemia)	109/336 (32.4%)	9/336 (2.7%)	245/324 (75.6%)	52/324 (16.0%)
Lymphocytes (Lymphocyte count decreased)	79/335 (23.6%)	22/335 (6.6%)	116/324 (35.8%)	29/324 (9.0%)
Platelets (Platelet count decreased)	46/336 (13.7%)	1/336 (0.3%)	121/323 (37.5%)	25/323 (7.7%)

* Version 4.03 of the NCI CTCAE was used to grade toxicity.

Non-Small Cell Lung Cancer (Study 16113) – Combination with Platinum-Based Chemotherapy

Table 9 Laboratory Abnormalities in ≥10% of NSCLC Patients Receiving Libtayo in Combination with Chemotherapy in Study 16113

Laboratory Tests*	Cemiplimab + Chemotherapy (N=312)		Placebo + Chemotherapy (N=153)	
	Any Grade n/N (%)	Grade 3-4 n/N (%)	Any Grade n/N (%)	Grade 3-4 n/N (%)
Chemistry				
Creatinine (Creatinine increased)	95/298 (31.9%)	6/298 (2.0%)	32/146 (21.9%)	2/146 (1.4%)
Fasting Glucose (Hyperglycemia)	141/276 (51.1%)	11/276 (4.0%)	62/134 (46.3%)	2/134 (1.5%)
Liver Function				
Alanine Aminotransferase (Alanine aminotransferase increased)	118/299 (39.5%)	9/299 (3.0%)	49/146 (33.6%)	3/146 (2.1%)
Albumin (Hypoalbuminemia)	90/298 (30.2%)	3/298 (1.0%)	36/146 (24.7%)	0/146 (0%)
Alkaline Phosphatase (Alkaline phosphatase increased)	80/298 (26.8%)	2/298 (0.7%)	32/146 (21.9%)	1/146 (0.7%)
Aspartate Aminotransferase (Aspartate Aminotransferase increased)	120/299 (40.1%)	1/299 (0.3%)	40/146 (27.4%)	3/146 (2.1%)
Bilirubin (Blood bilirubin increased)	40/298 (13.4%)	2/298 (0.7%)	14/146 (9.6%)	1/146 (0.7%)
Electrolytes				
Calcium (Hypercalcemia (Uncorrected Calcium))	78/298 (26.2%)	5/298 (1.7%)	28/146 (19.2%)	1/146 (0.7%)
Calcium (Hypocalcemia (Uncorrected Calcium)	96/298 (32.2%)	9/298 (3.0%)	36/146 (24.7%)	3/146 (2.1%)
Magnesium (Hypermagnesemia)	41/297 (13.8%)	7/297 (2.4%)	14/144 (9.7%)	4/144 (2.8%)
Magnesium (Hypomagnesemia)	91/297 (30.6%)	2/297 (0.7%)	41/144 (28.5%)	2/144 (1.4%)
Phosphate (Hypophosphatemia)	52/298 (17.4%)	10/298 (3.4%)	18/146 (12.3%)	10/146 (6.8%)
Potassium (Hyperkalemia)	70/298 (23.5%)	8/298 (2.7%)	31/146 (21.2%)	4/146 (2.7%)
Potassium (Hypokalemia)	61/298 (20.5%)	7/298 (2.3%)	20/146 (13.7%)	2/146 (1.4%)
Sodium (Hyponatremia)	80/298 (26.8%)	18/298 (6.0%)	27/146 (18.5%)	6/146 (4.1%)
Hematology				
Hemoglobin (Anemia)	204/299 (68.2%)	31/299 (10.4%)	99/146 (67.8%)	10/146 (6.8%)
Leukocytes (White blood cell decreased)	108/299 (36.1%)	19/299 (6.4%)	49/146 (33.6%)	6/146 (4.1%)
Lymphocytes (Lymphocyte count decreased)	106/299 (35.5%)	22/299 (7.4%)	39/146 (26.7%)	11/146 (7.5%)
Neutrophils (Neutrophil count decreased)	103/299 (34.4%)	30/299 (10.0%)	48/145 (33.1%)	12/145 (8.3%)
Platelets (Platelet count decreased)	100/299 (33.4%)	14/299 (4.7%)	36/146 (24.7%)	1/146 (0.7%)

* Version 4.03 of the NCI CTCAE was used to grade toxicity, except for Creatinine which was coded using NCI CTCAE Version 5.0.

Basal Cell Carcinoma (Study 1620)

Table 10: Laboratory Abnormalities in ≥10% of BCC Patients in Study 1620

Laboratory Tests*	Any Grade (N=132) n/N (%)	Grade 3-4 (N=132) n/N (%)
Chemistry		
Alanine Aminotransferase (Alanine aminotransferase increased)	29/130 (22.3%)	1/130 (0.8%)
Albumin (Hypoalbuminemia)	35/130 (26.9%)	1/130 (0.8%)
Alkaline Phosphatase (Alkaline phosphatase increased)	20/130 (15.4%)	1/130 (0.8%)
Aspartate Aminotransferase (Aspartate aminotransferase increased)	43/130 (33.1%)	1/130 (0.8%)
Bilirubin (Blood bilirubin increased)	13/130 (10.0%)	1/130 (0.8%)
Calcium (Hypercalcemia (Uncorrected Calcium))	14/130 (10.8%)	0/130
Calcium (Hypocalcemia (Uncorrected Calcium))	23/130 (17.7%)	0/130
Creatinine (Creatinine increased)	42/130 (32.3%)	0/130
Potassium (Hyperkalemia)	30/130 (23.1%)	0/130
Potassium (Hypokalemia)	17/130 (13.1%)	2/130 (1.5%)
Sodium (Hyponatremia)	37/130 (28.5%)	4/130 (3.1%)
Hematology		
Hemoglobin (Anemia)	52/130 (40.0%)	0/130
Lymphocytes (Lymphocyte count decreased)	44/130 (33.8%)	3/130 (2.3%)

* Version 4.03 of the NCI CTCAE was used to grade toxicity, except for Creatinine which was coded using NCI CTCAE Version 5.0.

Cervical Cancer (Study 1676)

Table 11: Laboratory Abnormalities in ≥10% of Cervical Cancer Patients in Study 1676

Laboratory Tests*	Cemiplimab (N=300)		Chemotherapy (N=290)	
	Any Grade n/N (%)	Grade 3-4 n/N (%)	Any Grade n/N (%)	Grade 3-4 n/N (%)
Chemistry				
Creatinine (Creatinine increased)	200/294 (68.0%)	9/294 (3.1%)	188/272 (69.1%)	8/272 (2.9%)
Fasting Glucose (Hyperglycemia)	91/228 (39.9%)	2/228 (0.9%)	72/193 (37.3%)	3/193 (1.6%)
Hematology				
Hemoglobin (Anemia)	156/293 (53.2%)	49/293 (16.7%)	212/278 (76.3%)	83/278 (29.9%)
Leukocytes (White blood cell decreased)	45/293 (15.4%)	4/293 (1.4%)	151/277 (54.5%)	38/277 (13.7%)
Lymphocytes (Lymphocyte count decreased)	107/293 (36.5%)	42/293 (14.3%)	154/278 (55.4%)	61/278 (21.9%)
Platelets (Platelet count decreased)	38/293 (13.0%)	6/293 (2.0%)	78/278 (28.1%)	19/278 (6.8%)

* Version 4.03 of the NCI CTCAE was used to grade toxicity.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been reported during post approval use of Libtayo. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure (see 7 WARNINGS AND PRECAUTIONS).

Immune System Disorder: Solid organ transplant rejection

Blood and lymphatic system disorders: HLH

Musculoskeletal Disorder: Myositis

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No pharmacokinetic drug-drug interaction studies have been conducted with cemiplimab.

9.3 Drug-behavioural interactions

Interactions with behaviours have not been established.

9.4 Drug-drug interactions

Interactions with other drugs have not been established.

9.5 Drug-food interactions

Interactions with food have not been established.

9.6 Drug-herb interactions

Interactions with herbal products have not been established.

9.7 Drug-laboratory test interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Binding of the ligands PD-L1 and PD-L2, to PD-1 on T cells, inhibits T-cell proliferation and cytokine production. This pathway can contribute to inhibition of active T-cell immune surveillance of tumours.

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

Cemiplimab is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture.

10.2 Pharmacodynamics

No exposure-response relationships were found in patients treated with cemiplimab monotherapy and plus chemotherapy for all efficacy and safety endpoints in patients with NSCLC.

10.3 Pharmacokinetics

Concentration data were combined in a population pharmacokinetic (PK) analysis in 1063 patients with various solid tumours who received cemiplimab (including CSCC, BCC, NSCLC, and Cervical). At intravenous dosing regimens of 1 mg/kg to 10 mg/kg administered intravenously every 2 weeks (Q2W) and 350 mg Q3W, the pharmacokinetics of cemiplimab were linear and dose proportional, suggesting saturation of the systemic target-mediated pathway over the dosing interval.

At 350 mg Q3W, the mean (CV%) concentration of cemiplimab at steady-state ranged between C_{max} of 171 mg/L (27.1%) and C_{trough} of 59 mg/L (47.1%). Steady-state exposure is achieved after approximately 4 months of treatment. Cemiplimab exposure at steady-state in patients with solid tumours is similar at 350 mg Q3W and at 3 mg/kg Q2W.

Table 12: Summary of Libtayo Pharmacokinetic Parameters for Multiple Tumour Types[a]

	C_{max} (mg/L)	C_{trough} (mg/L)	T_{max}	t½ (days)	AUC3wk,ss (mg.day/L)	CL (L/day)	Vd (L)
350 mg Q3W	171 (27.1)	59 (47.1)	NA[b]	22 (41.9)	1864 (37.0%)	0.22 (43.7)	5. 9 (28.8)

Parameters are presented as geometric mean values (%CV) based on population PK analysis.
Abbreviations: AUC – area under the concentration time curve over a 3 week dosing interval at steady-state; Cmax – maximum concentration; Ctrough – trough concentration; Tmax – time to reach Cmax; t1/2 – terminal elimination half-life; CL – clearance; Vd – volume of distribution
[a] Solid tumors, CSCC, BCC, NSCLC
[b] Cemiplimab is administered IV and peak concentrations are typically reached at the end of infusion

Absorption
Cemiplimab is administered by intravenous route and is therefore immediately and completely bioavailable.

Distribution
Based on the population pharmacokinetic analysis, the volume of distribution parameter of cemiplimab at steady-state is 5.9 L.

Metabolism
Cemiplimab is entirely metabolized by proteolysis without formation of active metabolites.

Elimination
Based on the population pharmacokinetic analysis, cemiplimab clearance (CV%) after the first dose is approximately 0.25 L/day (40.9%). The total clearance parameter appears to decrease by approximately 11% over time, resulting in a steady state clearance parameter (CL_{ss}) of 0.22 L/day (43.7%). The within dosing interval half-life (CV%) at steady state is estimated to be 22 days (41.9%).

Special Populations and Conditions
A population pharmacokinetic analysis suggests that the following factors have no clinically significant effect on the exposure of cemiplimab: age (27-96 years), gender, body weight (31-172 kg), race (White,

Black, Asian), cancer type, albumin level (20-93 g/L), renal impairment (CLcr 30-89 mL/min), or mild hepatic impairment (total bilirubin > 1.0-1.5 times the ULN).

- **Hepatic Insufficiency:** The effect of hepatic impairment on the exposure of Libtayo was evaluated by population pharmacokinetic analysis in patients with mild hepatic impairment (n=22) (total bilirubin [TB] greater than 1.0 to 1.5 times the upper limit of normal [ULN] and any AST) and patients with moderate hepatic impairment (n=3) (total bilirubin >1.5-3 times the ULN and any AST). No clinically important differences in the exposure of Libtayo were found between patients with mild to moderate hepatic impairment and patients with normal hepatic function. Libtayo has not been studied in patients with severe hepatic impairment.

- **Renal Insufficiency:** The effect of renal impairment on the exposure of Libtayo was evaluated by a population pharmacokinetic analysis in patients with mild (CLcr 60-89 mL/min; n=396), moderate (CLcr 30-59 mL/min; n=166), or severe (CLcr 15-29 mL/min; n=7) renal impairment. No clinically important differences in the exposure of Libtayo were found between patients with renal impairment and patients with normal renal function.

11 STORAGE, STABILITY AND DISPOSAL

Store Libtayo (cemiplimab for injection) at 2 °C to 8 °C.

Protect Libtayo from light by storing in the original carton until time of use.

Do not freeze. Do not shake.

Do not use after the expiration date stamped in the carton and container label.

For storage conditions after reconstitution or dilution of the medicinal product, see 4 DOSAGE AND ADMINISTRATION.

12 SPECIAL HANDLING INSTRUCTIONS

Libtayo does not contain preservative.

Once opened, Libtayo should be diluted and infused immediately (see 4 DOSAGE AND ADMINISTRATION, 4.3 Reconstitution).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Cemiplimab for injection
Structure:	Cemiplimab (IgG4 isotype) is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each covalently linked through a disulfide bond to a human kappa light chain.
Molecular formula:	$C_{6380}H_{9808}N_{1688}O_{2000}S_{44}$
Molecular mass:	143,567.1 Da
Physicochemical properties	Clear to slightly opalescent, colourless to pale yellow liquid. Essentially free from visible particles

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Cutaneous Squamous Cell Carcinoma

Table 13: Summary of patient demographics for clinical trials in metastatic and locally advanced cutaneous squamous cell carcinoma (Studies 1423 and 1540)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
R2810-ONC-1423	Phase 1 First-in-human Open-label, repeat dose study with cemiplimab as monotherapy and combination therapy Adult patients (≥18 years old, males/females) with advanced solid malignancies	• 10mg/kg cemiplimab administered IV over 30 mins Q2W for 48 weeks • Cemiplimab 200mg dose IV infusion over 30 mins Q2W for 48 weeks • Cemiplimab at 1 or 3mg/kg administered IV over 30 minutes Q2W days for 48 weeks, alone or in combination with: radiotherapy, low-dose cyclophosphamide, or radiotherapy plus low-dose cyclophosphamide	Initial: 397 (26 with advanced CSCC) Subsequent update: 398 (26 with advanced CSCC)	Initial: 61 (27-88) Subsequent update: 61 (27-88)	Initial: 204 male 193 female Subsequent update: 204 male 194 female
R2810-ONC-1540	Phase 2 Pivotal Study Non-randomized multicentre study, with cemiplimab 3mg/kg or 350mg as monotherapy Adult patients (≥18 years old, males/females) with mCSCC or laCSCC	• Treatment duration (Groups 1 and 2): 96 weeks (twelve 56-day [8-week] treatment cycles); tumour assessment at the end of each 8-week cycle Treatment duration (Group 3): 54 weeks (six 63-day [9-week] treatment cycles); tumour assessment at the end of each 9-week cycle	Initial: 137 Subsequent update: 193	Initial: 70 (38-96) Subsequent update: 72 (38-96)	Initial: 117 male 20 female Subsequent update: 161 male 32 female

The efficacy and safety of Libtayo in patients with metastatic (nodal or distant) cutaneous squamous cell carcinoma or locally advanced cutaneous squamous cell carcinoma who were not candidates for curative surgery or curative radiation were initially evaluated in two prospective clinical trials, Study 1423 and Study 1540. Study 1423 was an open-label, multi-center study in 397 patients with a variety of advanced solid tumours. It included 26 advanced CSCC patients (16 patients with mCSCC and 10 patients with laCSCC) who were treated with cemiplimab monotherapy. Study 1540 was an open-label, multi-center study that enrolled 137 advanced CSCC patients in Groups 1 to 3: 59 patients with mCSCC treated with Libtayo 3 mg/kg Q2W (Group 1), 55 patients with laCSCC treated with Libtayo 3 mg/kg Q2W (Group 2), 23 patients with mCSCC treated with Libtayo 350 mg Q3W (Group 3).

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 or other immune checkpoint inhibitor therapy; infection with HIV, hepatitis B or hepatitis C; or ECOG performance score ≥ 2. Patients with anogenital squamous cell carcinoma (SCC) or SCCs arising on the dry red lip (vermillion) were not eligible.

Patients in both studies received Libtayo as an intravenous infusion over 30 minutes until unequivocal progression of disease, unacceptable toxicity or completion of planned treatment [3 mg/kg every 2 weeks for 48 weeks in Study 1423 or 96 weeks (Groups 1 and 2) in Study 1540 or 350 mg every 3 weeks for 54 weeks (Group 3) in Study 1540]. Patients could continue treatment beyond initial progression at the discretion of the investigator. If patients with locally advanced disease showed sufficient response to treatment, surgery with curative intent was permitted. Tumour response assessments were performed every 8 or 9 weeks. The primary endpoint was confirmed objective response rate (ORR), as assessed by independent central review (ICR). For patients with mCSCC without externally visible target lesions, ORR was determined by Response Evaluation Criteria in Solid Tumours (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). The key secondary endpoint was duration of response (DOR). Other secondary endpoints were progression free survival (PFS), overall survival (OS), complete response rate (CRR) and EORTC QLQ-C30. The primary efficacy analysis for each group was conducted when all patients had the opportunity for at least 6 months of follow-up.

Results are presented as a combined analysis of 26 CSCC patients from Study 1423 (1 patient in the dose escalation cohort received cemiplimab 1mg/kg Q2W), and 82 patients from Study 1540 who received cemiplimab 3mg/kg every 2 weeks. Of these 108 patients, 75 were metastatic CSCC and 33 locally advanced CSCC with a median age of 71 years (range: 38 to 96). Thirty-eight (35.2%) patients were 75 years or older. Ninety-two (85.2%) patients were male, and 105 (97.2%) were White; the ECOG performance score was 0 (42.6%) or 1 (57.4%). Fifty per cent (50%) of patients had received at least one prior anti-cancer systemic therapy, 96.3% of patients had received prior cancer related surgery, and 78.7% of patients had received prior radiotherapy. Among patients with metastatic CSCC, 69.3% had distant metastases, and 30.7% had only nodal metastases.

Initial efficacy results are presented in Table 14. Similar objective response rates (ORR) were observed in patients with metastatic CSCC (46.7%) and in patients with locally advanced CSCC (48.5%). At time of data cut-off, patients with advanced CSCC had been followed for a median duration of 8.9 months; the median duration of response (DOR) had not been reached. Fifty-one (47.2%) patients achieved response, defined as complete response (CR) or partial response (PR). At the time of data cut-off, 4 of these responding patients had subsequent progression.

Table 14: Combined Efficacy Results for Study 1423 and Study 1540 – metastatic CSCC, locally advanced CSCC and combined CSCC

Efficacy Endpoints[a]	metastatic CSCC (N = 75)	locally advanced CSCC (N = 33)	combined CSCC (N = 108)
Confirmed Objective Response Rate (ORR)			
ORR % 95% CI	46.7% (35.1%, 58.6%)	48.5% (30.8%, 66.5%)	47.2% (37.5%, 57.1%)
Complete response rate (CR)[b]	5.3%	0%	3.7%
Partial response rate (PR)	41.3%	48.5%	43.5%
Duration of Response (DOR)[c]			
Median DOR in months (range) (months)	NR (2.8 – 15.2+)	NR (1.0 – 12.9+)	NR (1.0 – 15.2+)
Patients with DOR ≥ 6 months, %	60.0% (21/35)	62.5% (10/16)	60.8% (31/51)
Time to Response (months)			
Median Range (months)	1.9 (1.7, 6.0)	3.7 (1.8, 7.6)	1.9 (1.7, 7.6)

CI: confidence interval; NR: Not reached; +: Denotes ongoing at last assessment.
[a] Median duration of follow up: metastatic CSCC: 8.1 months (range: 1.1 to 17.0); locally advanced CSCC: 10.2 months (range: 0.8 to 16.7); combined CSCC: 8.9 months (range: 0.8 to 17.0).
[b] Only includes patients with complete healing of prior cutaneous involvement; locally advanced CSCC patients in Study 1540 required biopsy to confirm complete response.
[c] 41 of 51 responses are on-going at last assessment.

Subsequent Update:

Study 1540

Among the 193 advanced CSCC patients enrolled in Study 1540 who received Libtayo at either 3 mg/kg every 2 weeks or 350 mg every 3 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 cancerrelated 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 15 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 15.

Table 15: Efficacy Results for Study 1540 – metastatic CSCC, locally advanced CSCC and combined CSCC

Efficacy Endpoints[a]	metastatic CSCC[c] (N = 59)	locally advanced CSCC (N = 78)	combined CSCC (N = 137)
Confirmed Objective Response Rate (ORR)			
ORR % 95% CI	49% (29/59) (36%, 63%)	44% (34/78) (32%, 55%)	46% (63/137) (37%, 55%)
Complete response rate (CR)[b]	17% (10/59)	13% (10/78)	15% (20/137)
Partial response rate (PR)	32% (19/59)	31% (24/78)	31% (43/137)
Duration of Response (DOR)			
Median DOR in months (range)	NR 2.8 – 21.6+	NR 1.0 – 24.2+	NR 1.0 – 24.2+
Patients with DOR ≥ 6 months, %	93% (27/29)	68% (23/34)	79% (50/63)

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

[a] Median duration of follow up: metastatic CSCC: 16.5 months (range: 1.1 to 26.6); locally advanced CSCC: 9.3 months (range: 0.8 to 27.9); combined CSCC: 11.1 months (range: 0.8 to 27.9)

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

[c] mCSCC data represent results from a post-hoc analysis with a longer duration of follow-up performed after the pre-specified primary analysis

In an additional cohort in Study 1540, 56 patients received cemiplimab 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 (range: 0.6 to 14.1 months), the confirmed ORR was 41% (23/56) (95% CI: 28, 55), and 65% (15/23) of responders had a DOR ≥ 6 months.

At the final analyses of Study 1540, the efficacy results remain consistent with the earlier reported data.

Study 1423

Among the 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 (range 1.1 to 21.0 months), for the combined total 26 CSCC patients, the confirmed ORR was 50% (13/26) (95% CI: 29.9, 70.1) (all responses were PRs) for mCSCC and laCSCC combined. The median DOR was not reached (range: 1.0 to 20.3 months). DOR was ≥ 6 months for 85% (11/13) of responders. The median time to response for all responding patients was 1.9 months (range: 1.7 to 7.3 months) and 85% of responders had a DOR ≥ 6 months.

Non-Small Cell Lung Cancer

First-line treatment of NSCLC with Libtayo as monotherapy (Study 1624)

Table 16: Summary of patient demographics for clinical trials in locally advanced and metastatic non-small cell lung cancer

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
R2810-ONC-1624	Open-label, randomized, multi-centre Adult patients (≥18 years old, males/females) with locally advanced or metastatic non-small cell lung cancer	• 350 mg/kg Q3W for 108 weeks, or investigator's choice of - Paclitaxel + cisplatin or carboplatin - Gemcitabine + cisplatin or carboplatin - Pemetrexed + cisplatin or carboplatin followed by optional pemetrexed maintenance	710	63 (31-79)	606 male 104 female

The efficacy of Libtayo in patients with locally advanced NSCLC who were not candidates for surgical resection or definitive chemoradiation, with locally advanced NSCLC who have progressed after treatment with chemoradiation, or with metastatic NSCLC was evaluated in Study 1624, a randomized, open-label, multi-center study.

The study was designed to enroll patients with tumour PD-L1 expression ≥ 50%. PD-L1 expression was evaluated using the PD-L1 IHC 22C3 pharmDx assay. A total of 710 patients (Intent-To-Treat [ITT] population) were enrolled in the study.

The study excluded patients with EGFR, ALK or ROS1 genomic tumour aberrations, medical conditions that required systemic immunosuppression, uncontrolled infection with hepatitis B (HBV) or hepatitis C (HCV) or human immunodeficiency virus (HIV), autoimmune disease that required systemic therapy within 2 years of treatment, or who have never smoked. Patients with type 1 diabetes mellitus or hypothyroidism only requiring hormone replacement were eligible. The study included patients who had not received prior systemic therapy for recurrent or metastatic NSCLC. Treatment of brain metastases was permitted, and patients could be enrolled if they had been adequately treated and had neurologically returned to baseline for at least 2 weeks prior to randomization. Radiological confirmation of stability or response was not required.

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 investigator's choice of the following platinum-doublet chemotherapy regimens for 4 to 6 cycles:

- Paclitaxel + cisplatin or carboplatin
- Gemcitabine + cisplatin or carboplatin
- Pemetrexed + cisplatin or carboplatin followed by optional pemetrexed maintenance (This regimen was not recommended for patients with squamous NSCLC.)

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 with an addition of 4 cycles of histology-specific chemotherapy until further progression was observed. Patients who experienced IRC-assessed RECIST 1.1-defined progressive disease on chemotherapy treatment were permitted to receive Libtayo treatment until further progression, unacceptable toxicity or up to 108 weeks. Of the 203 patients randomized to receive chemotherapy who had IRC-assessed RECIST 1.1- defined disease progression, 150 (73.9%) patients crossed over to treatment with Libtayo. Assessment of tumour status was performed every 9 weeks. The co-primary efficacy endpoints were overall survival (OS) and progression-free survival (PFS). An additional efficacy endpoint was objective response rate (ORR).

The study population characteristics of patients in the ITT population are included in Table 17.

Table 17: Summary of Baseline Patient and Disease Characteristics in the ITT population

	Libtayo N=356	**Chemotherapy N=354**
PATIENT DEMOGRAPHICS		
Median Age, Years (min, max)	63 (31, 79)	64 (40, 84)
Age < 65 Years, n (%)	200 (56)	190 (54)
Age ≥ 65 Years, n (%)	156 (44)	164 (46)
Gender: Male n (%)	312 (88)	294 (83)
Race: White n (%) Asian n (%)	308 (87) 39 (11)	305 (86) 38 (11)
ECOG Performance Status n (%)		
0	96 (27)	96 (27)
1	260 (73)	258 (73)
History of brain metastasis (%)	12	11
DISEASE CHARACTERISTICS		
Extent of Disease n (%)		
Locally Advanced	63 (18)	52 (15)
Metastatic	293 (82)	302 (85)
Histological Subtype n (%)		
Squamous	159 (45)	152 (43)
Non-squamous	197 (55)	202 (57)

The study demonstrated statistically significant improvement in OS and PFS for patients randomized to Libtayo as compared with chemotherapy. Median duration of follow-up was 13.1 months in the Libtayo group and 13.1 months in the chemotherapy group.

Efficacy results for the ITT population are presented in Table 18 and Figures 1 and 2.

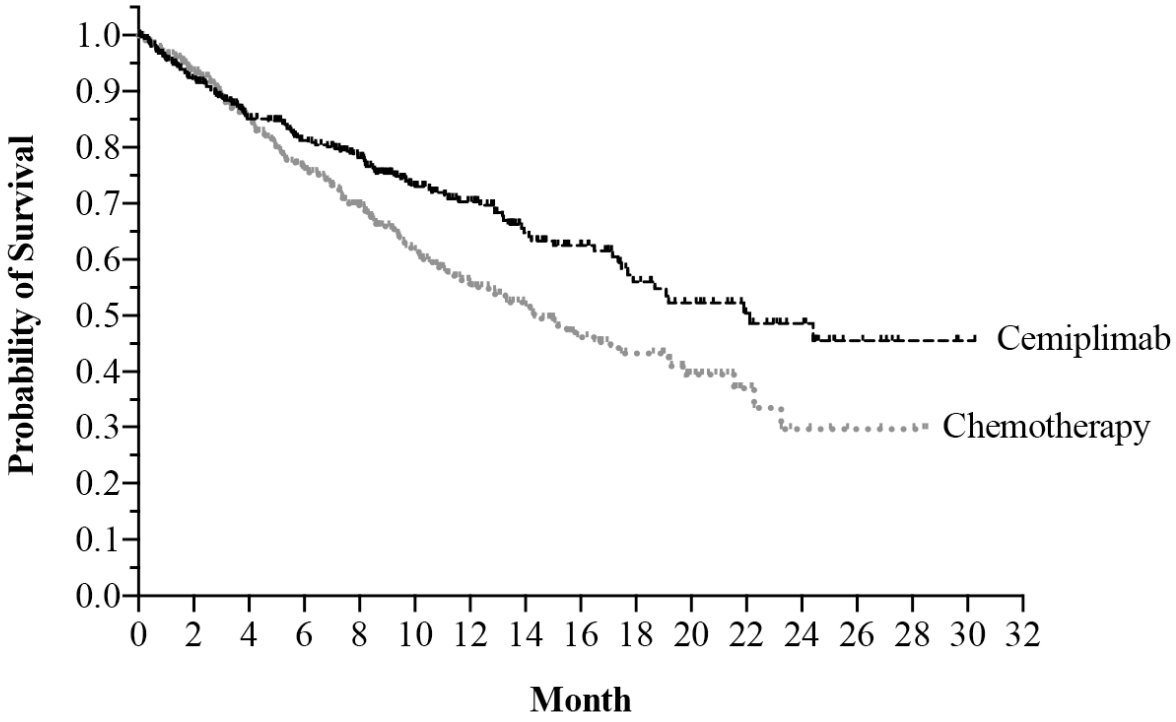
Table 18: Efficacy Results from Study 1624 in Non-Small Cell Lung Cancer

Efficacy Endpoints	**Intent-To-Treat (ITT) Population (N=710)**	
	Libtayo 350 mg every 3 weeks N=356	Chemotherapy N=354
Overall Survival (OS)		
Number of deaths (%)	108 (30.3)	141 (39.8)
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[c]	0.0022	
Progression-free survival (PFS) per BICR		
Number of events (%)	201 (56.5)	262 (74.0)
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[c]	<0.0001	
Objective Response Rate (ORR) (%) per BICR[d]		
ORR (95% CI)	36.5 (31.5, 41.8)	20.6 (16.5, 25.2)
Complete response (CR) rate	3.1	0.8
Partial response (PR) rate	33.4	19.8

BICR: Blinded Independent Central Review; CI: Confidence Interval; NE: Not evaluable

a. Based on Kaplan-Meier method
b. Based on stratified Cox proportional hazards model
c. Based on a two-sided p-value.
d. Based on Clopper-Pearson exact confidence interval

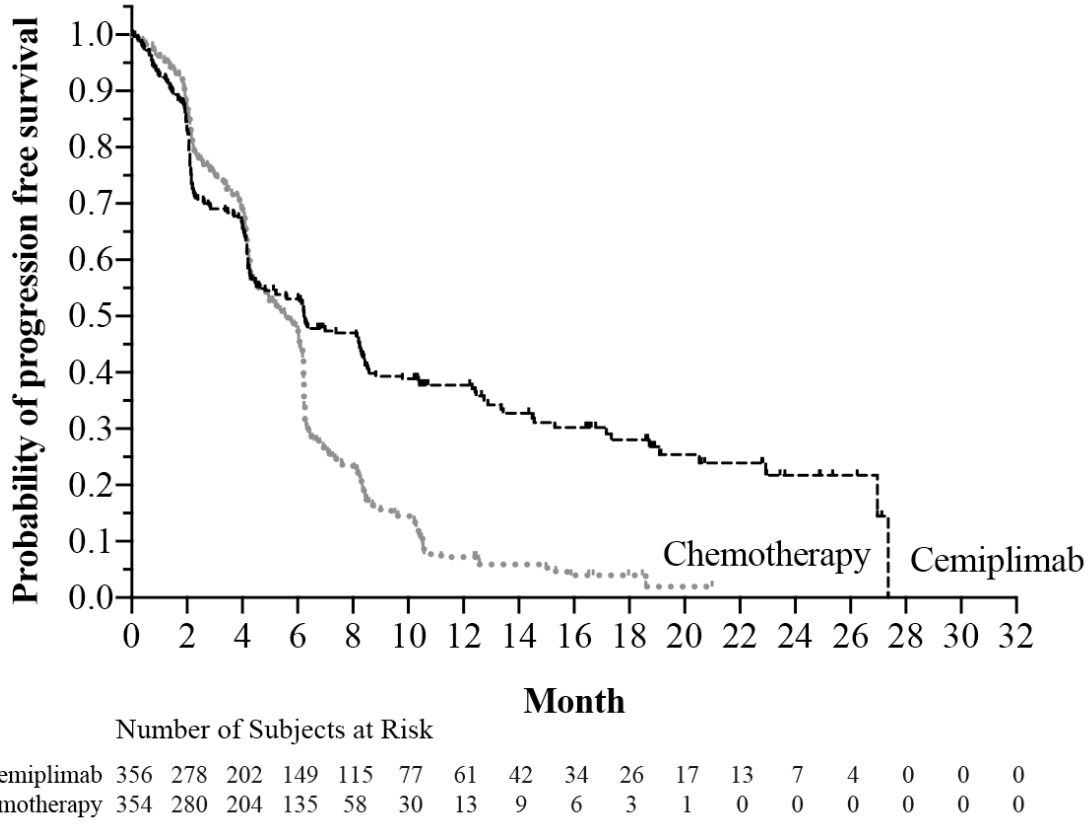
Figure 1: Kaplan-Meier Curve for OS in the ITT Population



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

Figure 2: **Kaplan-Meier Curve for PFS in the ITT Population**



For the ITT population, the median duration of response was 21.0 months (range: 1.9 to 23.3 months) for patients who received Libtayo and 6.0 months (range: 1.3 to 16.5 months) for patients treated with chemotherapy.

Out of 710 patients enrolled in Study 1624, 235 patients were impacted by PD-L1 testing not performed according to instructions for use. As a result 563 patients had confirmed PD-L1 expression ≥ 50% (283 in the Libtayo arms, and 280 in the chemo arm). An analysis of overall survival and progression-free survival was performed in the population of patients with confirmed PD-L1 expression ≥50%. For overall survival, the hazard ratio was 0.57 (95% CI: 0.42, 0.77) in favour of patients treated with Libtayo. For progression-free survival, the hazard ratio was 0.54 (95% CI: 0.43, 0.68) in favour of patients treated with Libtayo.

First-line treatment of NSCLC with Libtayo in Combination with Platinum-based Chemotherapy (Study 16113)

Table 19: Summary of patient demographics for clinical trials for non-small cell lung cancer in combination with platinum-based chemotherapy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
R2810-ONC-16113	Phase 3 Randomized (2:1), multicenter, double blind study Adult patients (≥18 years old, males/females) with histologically or cytologically documented squamous or non-squamous NSCLC with stage IIIB or IIIC disease who are not candidates for curative surgery, definitive chemoradiotherapy, or patients with stage IV disease if they have not received prior systemic treatment for advanced NSCLC	• 350 mg cemiplimab administered IV over 30 minutes Q3W for up to 108 weeks plus 4 cycles of platinum-based chemotherapy (n=312); or • Saline placebo administered IV over 30 minutes Q3W for up to 108 weeks plus 4 cycles of platinum-based chemotherapy (n=154)	466	61.8 (25-84)	391 male 75 female

The efficacy and safety of Libtayo in combination with platinum-based chemotherapy was evaluated in Study 16113, a randomized, multi-center, double-blind, active-controlled trial in 466 patients with locally advanced NSCLC who were not candidates for surgical resection or definitive chemoradiation, or with metastatic NSCLC, regardless of tumor PD-L1 expression status and who had not previously received systemic treatment for metastatic NSCLC.

Patients with EGFR, ALK or ROS1 genomic tumor aberrations; a medical condition that required systemic immunosuppression, active infection with hepatitis B (HBV) or hepatitis C (HCV), uncontrolled human immunodeficiency disease (HIV), or ongoing or recent autoimmune disease that required systemic therapy 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. Radiological confirmation of stability or response was not required.

Randomization was stratified by histology (non-squamous vs squamous) and PD-L1 expression (<1% versus 1% to 49% versus ≥ 50%) according to the VENTANA PD-L1 (SP263) assay. Patients were randomized (2:1) to receive either Libtayo 350 mg intravenously (IV) every 3 weeks for 108 weeks plus platinum-based chemotherapy every 3 weeks for 4 cycles, or placebo intravenously (IV) every 3 weeks for 108 weeks plus platinum-based chemotherapy every 3 weeks for 4 cycles. Platinum-based

chemotherapy in either arm consisted of carboplatin AUC of 5 or 6 and paclitaxel 200 mg/m^2; cisplatin 75 mg/m^2 and paclitaxel 200 mg/m^2; carboplatin AUC of 5 or 6 and pemetrexed 500 mg/m^2; or cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2. Maintenance pemetrexed was mandatory for patients with non-squamous NSCLC who received a pemetrexed containing chemotherapy regimen in the first 4 treatment cycles.

Treatment with Libtayo and platinum-based chemotherapy or placebo and platinum-based chemotherapy continued until RECIST 1.1-defined progressive disease, unacceptable toxicity, or 108 weeks. Assessment of tumor status was performed every 9 weeks beginning at week 9 during year 1 and every 12 weeks beginning at week 55 during year 2. The primary efficacy endpoint was overall survival (OS). Additional efficacy endpoints were progression-free survival (PFS) and objective response rate (ORR) as assessed by blinded independent central review (BICR).

The study population characteristics were: median age of 63 years (25 to 84 years), 40.3%% age 65 or older; 83.9% male; 86.9% White, 13.1% Asian; an ECOG PS 0 and 1 in 14.8% and 84.3% respectively; 85.6% were smokers and 14.4% were non-smokers; 85.2% had metastatic disease and 14.8% had stage IIIB or IIIC disease and were not candidates for surgical resection or definitive chemoradiation per investigator assessment; 57.1% had non-squamous and 42.9% had squamous histology; and 6.7% had history of treated brain metastases at baseline.

The study demonstrated a statistically significant improvement in OS for patients randomized to Libtayo in combination with chemotherapy compared with placebo in combination with chemotherapy. The median duration of follow-up was 16.3 months for the Libtayo plus platinum-based chemotherapy arm and 16.7 months for the placebo plus platinum-based chemotherapy arm.

Efficacy results, based on the prespecified second interim analysis for study 16113, are presented in Table 20 and Figure 3.

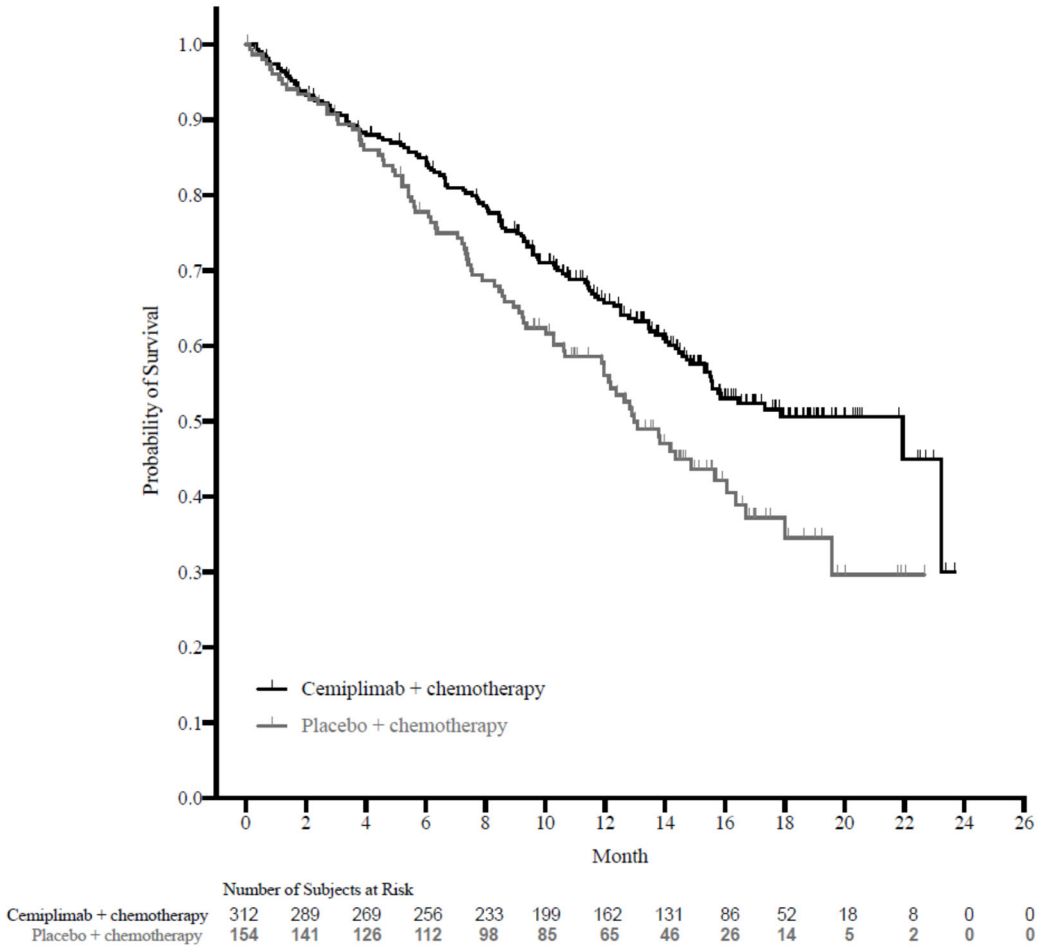
Table 20: Efficacy Results for Study 16113 in Non-Small Cell Lung Cancer

Efficacy Endpoints[a]	**Libtayo and Chemotherapy N=312**	**Placebo and Chemotherapy N=154**
Overall Survival (OS)		
Number of deaths (%)	132 (42)	82 (53)
Median in months (95% CI)[b]	21.9 (15.5, NE)	13.0 (11.9, 16.1)
Hazard ratio (95% CI)[c]	0.71 (0.53, 0.93)	
p-Value[d]	0.0140	
Progression-free survival (PFS)		
Number of events (%)	204 (65)	122 (79)
Median in months (95% CI)[b]	8.2 (6.4, 9.3)	5.0 (4.3, 6.2)
Hazard ratio (95% CI)[c]	0.56 (0.44, 0.70)	
p-Value[d]	<0.0001	
Objective Response Rate (ORR) (%)[e]		
ORR (95% CI)	43 (38, 49)	23 (16, 30)
Complete response (CR) rate	3	0
Partial response (PR) rate	41	23

CI: confidence interval; NE: Not evaluable; +: Ongoing response

a. Median duration of follow up: cemiplimab and chemotherapy: 16.3 months, placebo and chemotherapy: 16.7 months
b. Based on Kaplan-Meier method
c. Based on stratified proportional hazards model
d. Second interim analysis (primary). The two-sided p-value to declare statistical significance of OS is 0.01631. The two-sided p-value to declare statistical significance of PFS is 0.05.
e. Clopper-Pearson exact confidence interval

Figure 3: OS in Study 16113 in NSCLC



For the ITT population, the median duration of response was 15.6 months (range: 1.7 to 18.7 months) for patients who received Libtayo in combination with platinum-based chemotherapy and 7.3 months (range: 1.8 to 18.8 months) for patients treated with placebo plus platinum-based chemotherapy.

In an exploratory subgroup analyses, the HR for OS was 2.11 (95% CI: 0.89, 5.03) for females (n=75) and 1.28 (95% CI: 0.53, 3.08) for non-smokers (n=67). The results from an additional exploratory subgroup OS analysis with respect to tumor histology and PD-L1 expression are shown in Table 21.

Table 21: Overall Survival by Tumour Histology and PD-L1 Expression

	Overall Survival: n; HR (95% CI)	
	Squamous	**Non-squamous**
Any PD-L1 Expression	n=200; 0.56 (95% CI: 0.37, 0.84)	n=266; 0.79 (95% CI: 0.54, 1.14)
PD-L1 <1%	n=54; 0.67 (95% CI: 0.31, 1.49)	n=85; 1.32 (95% CI: 0.74, 2.35)
PD-L1 ≥1%	n=146, 0.52 (95% CI: 0.32, 0.84)	n=181; 0.57 (95% CI: 0.34, 0.94)

Basal Cell Carcinoma

Table 22: Summary of patient demographics for clinical trials in metastatic and locally advanced basal cell carcinoma (Study 1620)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
R2810-ONC-1620	Open-label, non-randomized, multi-centre Adult patients (≥18 years old, males/females) with locally advanced or metastatic basal cell carcinoma	• 350 mg/kg Q3W for 5 cycles of 9 weeks, followed by 4 cycles of 12 weeks, up to 93 weeks	132	68 (38-90)	89 male 43 female

The efficacy of Libtayo in patients with locally advanced, unrescectable basal cell carcinoma (BCC) who had progressed on hedgehog pathway inhibitor (HHI) therapy, were intolerant of prior HHI therapy, or had no better than stable disease (SD) after 9 months on HHI therapy (exclusive of treatment breaks), was evaluated in Study 1620, 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) ≥ 2.

Patients received Libtayo 350 mg intravenously (IV) every 3 weeks for 5 cycles of 9 weeks followed by 4 cycles of 12 weeks up to 93 weeks of treatment. Treatment continued until disease progression, unacceptable toxicity or completion of planned treatment. Tumour assessments were performed every 9 weeks during cycles 1 to 5 and every 12 weeks during cycles 6 to 9. The major efficacy endpoints were confirmed objective response rate (ORR) and duration of response (DOR) as assessed by independent central review (ICR). For patients with externally visible target lesions, 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 included 84 laBCC patients. See Table 23 for a summary of baseline patient and disease characteristics.

Table 23: Summary of Baseline Patient Characteristics and Prior Treatments in Study 1620

	laBCC N=84
PATIENT CHARACTERISTICS	
Median Age Years (Range)	70.0 (42 – 89)
<65	31 (37%)
≥65	53 (63%)
Gender: Male	56 (67%)
Race: White	57 (68%)
ECOG Performance Status	
0	51 (61%)
1	33 (39%)
PRIOR TREATMENTS	
Prior Cancer-related Surgery	
Patients with at least 1 prior cancer-related surgery, n (%)	70 (83%)
Patients with >3 prior cancer-related surgeries, n (%)	29 (35%)
Median number of prior cancer-related surgeries (Range)	3.0 (1 - 43)
Prior Anti-cancer Radiotherapy	
Patients with at least 1 prior anti-cancer radiotherapy, n (%)	42 (50%)
Median number of prior anti-cancer radiotherapy regimens (Range)	1.0 (1 - 6)
Prior Treatment with a HHI[a]	84 (100%)
Prior treatment with both vismodegib and sonidegib (as separate lines of therapy), n (%)	9 (11%)
Reason for Discontinuation of HHI	
Disease progression/lack of response[b], n (%)	63 (75%)
Intolerance to HHI therapy, n (%)	21 (25%)

a. Sums to greater than 100% as some patients switched from one HHI to another
b. Lack of response was defined as no better than stable disease after 9 months on HHI therapy

The median follow-up for patients with laBCC was 15.1 months (range: 0.5 to 25.1 months). The median time to response was 4.2 months (range: 2.1 to 13.4 months). Twenty-four patients (28.6%) with laBCC had complete response (CR) or partial response (PR).

Efficacy results are presented in Table 24.

Table 24: Efficacy Results for Study 1620 in Basal Cell Carcinoma

Efficacy Endpoints	**Locally Advanced BCC Libtayo 350 mg every 3 weeks**
	N=84
	ICR
Confirmed Objective Response Rate (ORR)	
Objective response rate (ORR: CR+ PR) (95% CI)	24 (28.6%)[a] (19.2, 39.5)
Complete response (CR), n (%)	5 (6.0%)
Partial response (PR), n (%)	19 (22.6 %)
Duration of Response (DOR)	
Median[b] (months) (Range in months)	NR (2.1 - 21.4)
Patients with observed DOR ≥ 6 months, n (%)	19 (79.2%)

ICR: Independent Central Review; CI: confidence interval; NR: Not reached; NE: Not evaluable; +: Denotes ongoing at last assessment

a. Locally advanced BCC patients in Study 1620 required biopsy to confirm complete response.
b. Based on Kaplan Meier estimates.

Cervical Cancer

Table 25: Summary of patient demographics for clinical trials in cervical cancer (Study 1676)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
R2810-ONC-1676	Phase 3 Randomized, open-label, multi-center study Adult patients (≥18 years old, females) who progressed on or after prior platinum based chemotherapy and who have recurrent or metastatic cervical cancer	350 mg/kg Q3W cemiplimab for up to 96 weeks, or investigator's choice of chemotherapy with pemetrexed; topotecan or irinotecan; gemcitabine; or vinorelbine; for up to 96 weeks	608	51 (22-87)	608 female

The efficacy and safety of Libtayo in adult patients with recurrent or metastatic cervical cancer who progressed on or after prior plantinum based chemotherapy was compared to investigator's choice chemotherapy in Study 1676, a randomized, open-label, multi-center study. Patients were enrolled regardless of PD-L1 tumour expression status.

To be enrolled on study, patients were required to have measurable disease, adequate hepatic function, adequate renal function (serum creatinine ≤1.5x ULN or estimated creatinine clearance >45 mL/min), hemoglobin ≥9.0 g/dL, absolute neutrophil counts ≥1.5x 10^9/L and platelet counts ≥75 x 10^9/L. Patients were excluded if they had prior treatment with any agent that blocks the PD-1/PD-L1 pathway, ongoing or recent evidence of autoimmune disease that required treatment with systemic immunosuppressive agents or treatment, or prior treatment with other systemic-modulating agents within 4 weeks of study enrollment. Patients were also excluded if they had an active bacterial, viral, fungal or mycobasterial infection, pneumonitis within five years prior to enrollment, a history of documented allergic reactions to antibody therapies, prior treatment with idelalisib (another anticancer agent), or were pregnant or breast-feeding.

The stratification factors for the efficacy analysis were geographic region (North America, Asia, Rest of World) and histology (squamous histology, adenocarcinoma / adenosquamous histologies). Randomization was also stratified by whether or not patients had received prior bevacizumab treatment and their ECOG performance status. Patients were randomized (1:1) to receive Libtayo 350 mg intravenously every 3 weeks or intravenous chemotherapy with pemetrexed; topotecan or irinotecan; gemcitabine; or vinorelbine.

Treatment was for up to 96 weeks and continued until disease progression or unacceptable toxicity. Patients who experienced progressive disease on Libtayo were permitted to continue treatment with Libtayo. Tumour assessments were performed every 6 weeks for the first 24 weeks and every 12 weeks

thereafter. The key efficacy outcome measure was overall survival (OS). Investigator-assessed progression-free survival (PFS) and overall response rates were secondary endpoints.

Table 26: Summary of Baseline Patient Characteristics and Prior Treatments in Study 1676

	N=608
PATIENT DEMOGRAPHICS	
Median Age Years (Range)	51.1 (22 – 87)
<65	533 (88%)
≥65	75 (12%)
Race: White	385 (63%)
Race: Asian	176 (29%)
Race: Black	21 (3.5%)
ECOG Performance Status	
0	283 (47%)
1	325 (54%)
PRIOR TREATMENTS	
Patients with prior bevacizumab treatment, n (%)	297 (49%)
Patients with 1 prior line of treatment in recurrent or metastatic setting, n (%)	346 (57%)
Patients with > 1 prior line of treatment in recurrent or metastatic setting, n (%)	259 (43%)
BASELINE DISEASE CHARACTERISTICS	
Squamous histology (SCC)	78%
Adenocarcinoma / Adenosquamous histology (AC)	22%
Metastatic disease	94%

Libtayo demonstrated a statistically significant improvement in OS and PFS compared to chemotherapy. Survival benefit compared to chemotherapy was seen regardless of prior bevacizumab treatment.

Efficacy results are presented in Table 27, Figure 4 and Figure 5.

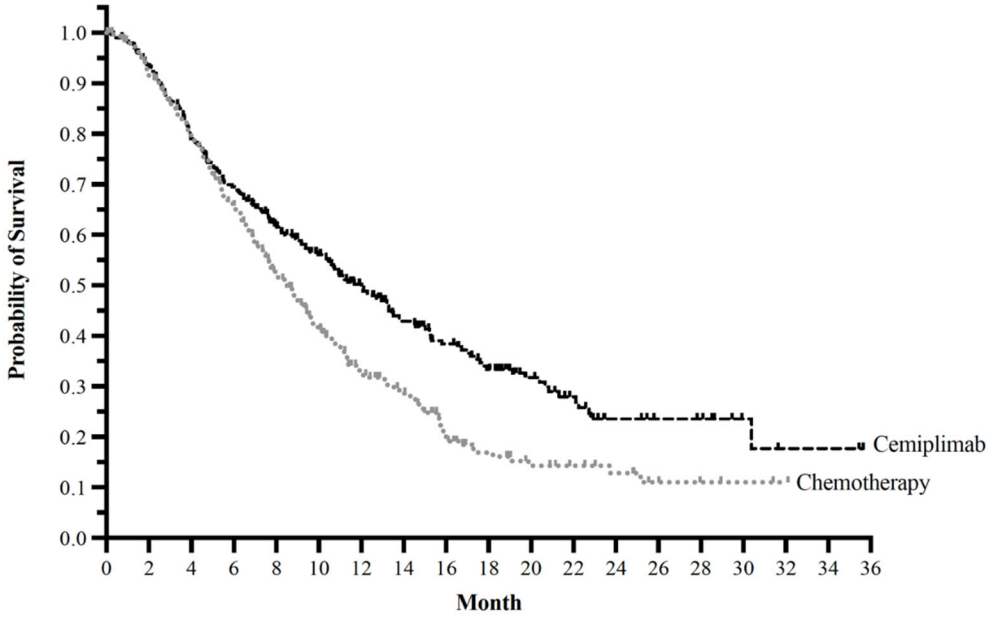
Table 27: Efficacy Results for Study 1676 in Cervical Cancer

	Total population (N=608)	
Efficacy Endpoint	**Libtayo 350 mg every 3 weeks (n=304)**	**Chemotherapy (n=304)**
Overall Survival (OS)		
Deaths n, (%)	184 (60.5%)	211 (69.4%)
Median in months[a] (95% CI)	12.0 (10.3, 13.5)	8.5 (7.5, 9.6)
Hazard Ratio[b] (95% CI)	0.69 (0.56, 0.84)	
p-value	0.0001[c]	
Progression-Free Survival (PFS)		
Hazard Ratio[b] (95% CI)	0.75 (0.63, 0.89)	
p-value	0.0005	
Overall Response Rate (ORR)		
Objective response rate n, % (ORR: CR+ PR) (95% CI)	50 (16.4%) (12.5, 21.1)	19 (6.3%) (3.8, 9.6)

CI: Confidence interval

a. Based on Kaplan-Meier method
b. Based on stratified proportional hazards model stratified by histology and geographic region
c. One-sided p-value (cemiplimab vs. chemotherapy)

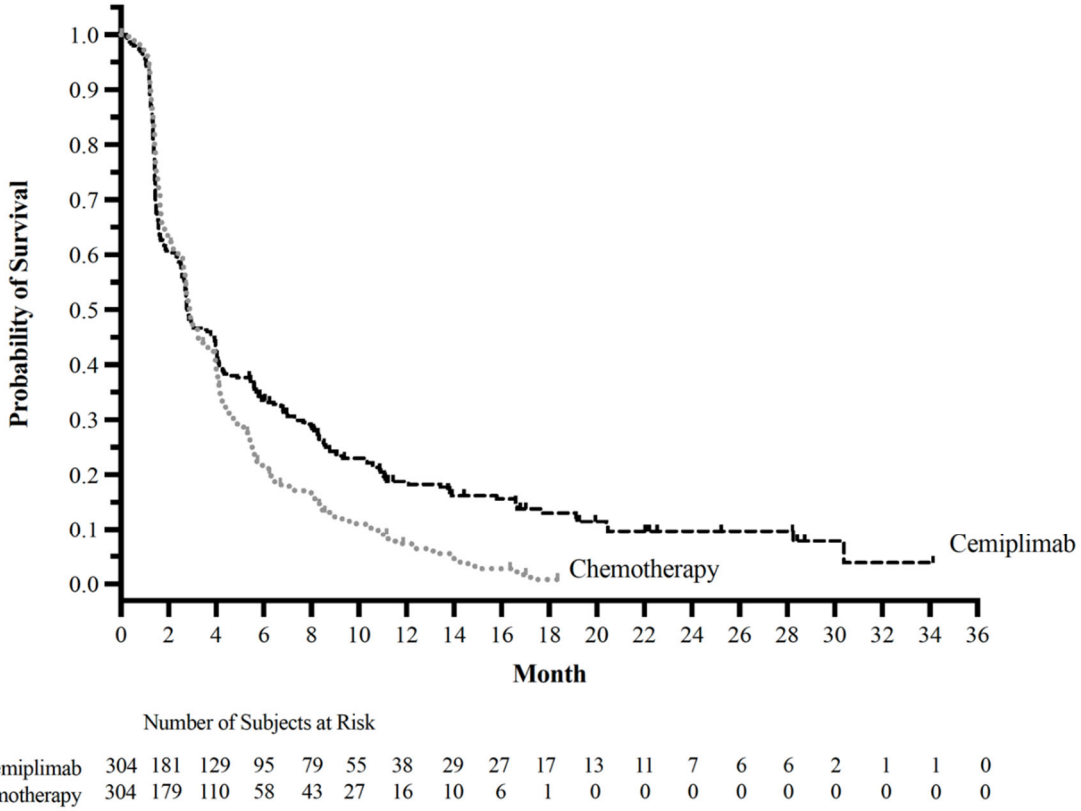
Figure 4: **OS in Study 1676 in Cervical Cancer**



Number of Subjects at Risk

Cemiplimab	304	281	236	206	167	139	110	83	65	52	35	26	13	10	9	4	2	2	0
Chemotherapy	304	264	224	183	132	99	70	54	32	22	15	12	9	5	3	2	1	0	0

Figure 5: **Investigator-assessed PFS in Study 1676 in Cervical Cancer**



Tumour PD-L1 biomarker analysis was available for 254 patients on study and 162 (64%) patients were considered positive for PD-L1 at the 1% level according to the Ventana kit using SP263 antibody. In an exploratory analysis, the Hazard Ratio for OS for Libtayo over IC chemotherapy was 0.70 [95% CI: 0.46,1.05] in PD-L1-positive patients, and 0.98 [95% CI: 0.59, 1.62] in PD-L1 negative patients.

14.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with Libtayo. Immunogenicity was assessed in 1029 patients who were treated with Libtayo. Approximately 2.1% of patients developed treatment-emergent antibodies to cemiplimab, with approximately 0.3% of patients exhibiting persistent antibody responses. There was no evidence of an altered pharmacokinetic profile with anti-cemiplimab antibody development.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay as well as other factors. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cemiplimab with the incidence of antibodies to other products may be misleading.

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:
The safety of cemiplimab was evaluated in a 1-month and a 6-month repeat-dose toxicity studies in cynomolgus monkeys. The no-observed adverse effect level (NOAEL) was the highest dose administered in these studies (50 mg/kg/week).

Carcinogenicity:
No carcinogenicity studies have been conducted with cemiplimab.

Genotoxicity:
No genotoxicity studies have been conducted with cemiplimab.

Reproductive and Developmental Toxicology:
Animal reproduction studies have not been conducted with cemiplimab.

In a 3-month repeat-dose fertility assessment study with sexually mature cynomolgus monkeys at the highest dose (50 mg/kg/week) tested, there were no cemiplimab-related effects on fertility assessment parameters (menstrual cycle, semen analysis, or testicular measurements) or in male or female reproductive organs.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
Libtayo

Cemiplimab for injection

Read this carefully before you start taking **Libtayo** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Libtayo**.

What is Libtayo used for?

Libtayo is a prescription medicine used to treat:

Cutaneous Squamous Cell Carcinoma

- adult patients with a type of skin cancer called cutaneous squamous cell carcinoma (CSCC) when your cancer:
    - has spread or grown, and
    - your tumour cannot be removed by surgery or treated with radiation.

Non-Small Cell Lung Cancer

- adult patients with a type of lung cancer called non-small cell lung cancer (NSCLC) and your cancer:
    - has spread, or grown and you are not a candidate to undergo surgery or be treated with chemotherapy and radiation
    - your tumour was tested, and found to express a specific protein called programmed death-ligand 1 (PD-L1) in 50% or more of the tumour cells, and
    - your tumour does not have an abnormal epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), or c-ROS oncogene 1 (ROS1) gene.
- adult patients with NSCLC, in combination with chemotherapy that contains platinum based medicine, and your cancer:
    - has spread or grown and you are not a candidate to undergo surgery or be treated with chemotherapy and radiation, and
    - your tumour does not have an abnormal EGFR, ALK, or ROS1 gene.

Basal Cell Carcinoma

- patients with a type of skin cancer called basal cell carcinoma (BCC) when your cancer:
    - has been previously treated with a drug called a hedgehog pathway inhibitor.

Cervical Cancer

- adult patients with cervical cancer when the cancer has worsened on or after chemotherapy.

How does Libtayo work?
Libtayo works by helping your immune system fight your cancer.

What are the ingredients in Libtayo?

Medicinal ingredients:	Cemiplimab
Non-medicinal ingredients:	L-histidine, L-histidine monohydrochloride monohydrate, L-proline, Polysorbate 80, Sucrose, Water for injection

Libtayo comes in the following dosage forms:
Libtayo comes in a 10mL glass vial containing either 250 mg or 350 mg of cemiplimab.

Do not use Libtayo if:

- You are allergic to cemiplimab or any of the other ingredients in this medicine. Talk to your health care professional if you are not sure.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Libtayo. Talk about any health conditions or problems you may have, including if you have:

- An autoimmune disease (a condition where your body attacks its own cells)
- Had an organ transplant, including stem cell transplant that uses donor stem cells (allogeneic)
- Lung or breathing problems
- Liver problems
- Kidney problems
- Diabetes
- Any other medical conditions
- A history of taking idelalisib (a medication to treat cancer)

Other warnings you should know about:

Pregnancy:

- If you are pregnant, or are planning to have a baby, tell your healthcare professional before taking this medicine. You must not use Libtayo if you are pregnant unless your healthcare professional specifically recommends it.
- Libtayo can cause harm to your unborn baby.
- If you are a woman who could become pregnant, you must use effective birth control while you are being treated with Libtayo and for at least 4 months after your last dose.

Breast-feeding:

- If you are breast-feeding, or plan to breast-feed, tell your healthcare professional
- Do not breast-feed while receiving Libtayo and for at least 4 months after your last dose
- It is unknown if Libtayo passes into your breast milk. A risk to the breast-fed infant cannot be excluded

Children and adolescents:
- Libtayo should not be used in children and adolescents below 18 years of age.

Driving and using machines
- It is not known whether Libtayo affects your ability to drive or use tools or machines. However, if you feel tired, do not drive or use tools or machines until you feel better.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Libtayo:
- There are no known drug-drug interaction with Libtayo.

How to take Libtayo:
- You will receive Libtayo in a hospital or clinic under the supervision of an experienced healthcare professional
- You will receive Libtayo as a drip into a vein (intravenous infusion)
- It will last about 30 minutes
- Libtayo is usually given every 3 weeks. Your doctor may choose to treat you with an every 2 week regimen if more appropriate for you.

Usual dose:
The recommended dose of Libtayo is 350 mg every 3 weeks. Your doctor will decide how much Libtayo you will receive, and how many treatments you will need.

Your doctor will test your blood for certain side effects during your treatment.

Overdose:

If you think you have taken too much Libtayo, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss any appointments, call your healthcare professional as soon as possible to reschedule your appointment. It is very important that you do not miss a dose of this medicine.

What are possible side effects from using Libtayo?
These are not all the possible side effects that you may feel when taking Libtayo. If you experience any side effects not listed here, contact your healthcare professional.

These may happen anytime during treatment or even after your treatment has ended. You may have more than one side effect at the same time.

The following side effects have been reported in clinical trials when Libtayo is given alone:

Very common (may affect more than 1 in 10 people)
- Abdominal pain

- Constipation
- Cough
- Decreased appetite
- Diarrhea
- Feeling tired (fatigue)
- Hair loss (alopecia)
- Itching (pruritus)
- Low red blood cell count (anemia)
- Muscle and bone pain
- Nausea
- Rash
- Upper respiratory tract infection

Common (may affect less than 1 in 10, but more than 1 in 100 people)

- Abdominal swelling
- Abnormal kidney function test
- Altered sense of taste (dysgeusia)
- Changes in blood, liver, and urine laboratory values
- Changes in weight
- Chest pain
- Chills
- Difficulty breathing
- Difficulty sleeping (insomnia)
- Dizziness
- Dry mouth
- Dry skin
- Eczema
- Fever
- Flu-like symptoms
- Gastric reflux
- Headache
- High blood pressure (hypertension)
- Hypersensitivity
- Infusion-related reactions
- Mood changes
- Mouth sores
- Muscle spasms
- Numbness, tingling or pain in your feet or hands (peripheral neuropathy)
- Rapid heartbeat (tachycardia)
- Ringing in the ears (tinnitus)
- Scaly patches on the skin (actinic keratosis)
- Swelling (oedema)
- Urinary tract infection
- Vomiting
- Watering eyes (lacrimation)

Uncommon (may affect less than 1 in 100, but more than 1 in 1000 people)

- Chest pain, shortness of breath, fatigue, abdominal or leg swelling (pericarditis)
- Eye redness or pain, blurred vision (keratitis)
- Stomach pain or upset (gastritis)
- Type 1 diabetes

The following side effects have been reported in clinical trials when Libtayo is given in combination with chemotherapy. Ask your doctor for more information regarding side effects of your chemotherapy.

Very common (may affect more than 1 in 10 people):

- decreased number of red blood cells
- hair loss
- muscle pain or bone pain
- nausea
- feeling tired
- inflammation of the nerves causing tingling, numbness, weakness or burning pain of the arms or legs
- high blood sugar
- feeling less hungry
- increased liver enzymes in blood
- decrease in the number of white blood cell (neutrophils)
- constipation
- decrease in the number of platelets
- shortness of breath
- rash
- vomiting
- weight loss
- trouble sleeping
- diarrhea (loose stools)
- low levels in the blood of a protein called ‘albumin’.

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
Very Common		
Itching		√
Rash		√
Respiratory tract (lung) infection: runny nose, shortness of breath, fever		√
Common		
Arthritis: pain or swelling in the joints		√
Colitis (inflammation of the colon): diarrhea, stools that are black, tarry, sticky, or have blood or mucous, severe abdominal pain		√
Conjunctivitis (inflammation of the eye or eyelid): eye redness, watering eyes		√
Dyspnea (shortness of breath)		√
Gastritis (inflammation of the stomach lining): stomach pain, nausea, vomiting, decreased appetite		√
Hepatitis (inflammation of the liver): yellowing of the skin or the whites of the eyes, severe nausea or vomiting, pain on the right side of the abdomen, feeling sleepy, dark urine, bleeding or bruising more easily than normal, decreased appetite		√
Hyperthyroidism (overactive thyroid gland): rapid or irregular heartbeat, high blood pressure, increased sweating, feeling more hot than usual, mood swings		√
Hypoesthesia: total or partial loss of sensation in a part of your body		√
Hypothyroidism (underactive thyroid gland): feeling tired, weight gain, constipation, feeling more cold than usual, hair loss, depression		√
Infusion-related reactions: chills or shaking, fever, itching or rash, flushing or swollen face, shortness of breath or wheezing, dizziness, back or neck pain		√
Muscle weakness	√	
Nephritis (inflammation of the kidneys): swelling of the ankles, decreased urination, decreased appetite		√
Peripheral neuropathy (damaged nerves): numbness, tingling or pain in your hands or feet		√
Pneumonia (infection in the lungs): new or worsening cough, fever, shortness of breath		√

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
Pneumonitis (inflammation of the lungs): new or worsening cough, shortness of breath, chest pain		√
Stomatitis (inflammation of the mouth): painful mouth ulcers, blisters, or peeling	√	
Urinary tract infection: pain or burning with urination, increased urination		√
Uncommon		
Adrenal insufficiency (underactive adrenal gland): feeling tired, dizzy or weak, nausea, vomiting, diarrhea, low blood pressure		√
Hypophysitis (inflammation of the pituitary gland): headache, nausea, vomiting, increased thirst, vision changes		√
Myocarditis (inflammation of heart muscles): chest pain, rapid or irregular heartbeat, shortness of breath		√
Myositis (inflammation of the muscles): muscle pain or weakness, which could be associated with a rash (dermatomyositis), feeling tired after standing or walking		√
Pericarditis (inflammation of heart membrane): chest pain, shortness of breath, feeling tired, swelling of the abdomen or legs		√
Skin blistering		√
Sjogren's syndrome (disease affecting salivary and tear glands): dry eyes, nose, mouth, and throat		√
Thyroiditis (inflammation of the thyroid gland): irritability, rapid heartbeat, changes in weight, feeling tired, constipation, depression		√
Type 1 diabetes (blood sugar problems): hunger or thirst, increased urination, weight loss		√
Ulcers in mouth or other mucous membranes		√
Rare		
Chronic inflammatory demyelinating polyradiculoneuropathy: tingling or loss of feeling in your arms and legs, weakness		√
Encephalitis (inflammation of the brain): headache, fever, pain in muscles or joints, feeling tired or weak		√
Meningitis (inflammation of the protective covering of the brain): headache, nausea,		√

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
vomiting, decreased appetite, confusion, fever, seizures		
Myasthenia gravis: feeling tired or weak, double vision, difficulty speaking, swallowing or chewing		√
Paraneoplastic encephalomyelitis: loss of muscle tone or coordination, muscle weakness		√
Polymyalgia rheumatica: pain in the shoulders, neck, upper arms, buttocks or hips, stiffness, feeling tired		√
Hemophagocytic lymphohistiocytosis: fever, enlargement of liver or spleen, swollen lymph nodes, skin rash, jaundice (yellow colour of your skin and eyes), coughing, trouble breathing, stomach ache, vomiting, diarrhea, headache, trouble walking, visual problems, and weakness		√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Libtayo should not be used after the expiry date which is stated on the label and carton.

Libtayo should be stored in a refrigerator (2°C to 8°) in its original package to protect from light.

Do not freeze.

Do not shake.

From time of preparation by diluting in an intravenous (IV infusion) bag, Libtayo can be stored before use for no more than 8 hours at temperatures up to 25°C, and no more than 24 hours in a refrigerator (2°C to 8°C). If refrigerated, the vials and/or intravenous bags must be allowed to reach room

temperature prior to use.

Do not store any unused portion of the infusion solution for re-use. Any unused portion of the infusion solution should not be re-used, and should be disposed in accordance with local requirements.

Keep out of reach and sight of children.

If you want more information about Libtayo:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the sanofi-aventis Canada website www.sanofi.ca, or by calling 1-800-265-7927.

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