▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/safety/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – LIBTAYO® (CEMIPLIMAB)

1 NAME OF THE MEDICINE

LIBTAYO 350 mg concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of concentrate contains 50 mg of cemiplimab.

Each vial contains 350 mg of cemiplimab in 7 mL of solution.

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

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colourless to pale yellow solution with a pH of 6.0 and osmolality between 300 and 360 mmol/kg. The solution may contain trace amounts of translucent to white particles in a single-use vial.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Cutaneous Squamous Cell Carcinoma

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

Non-Small Cell Lung Cancer

LIBTAYO as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 tumour proportion score (TPS) ≥50% as determined by a validated test, with no EGFR, ALK or ROS1 aberrations, who have:

- locally advanced NSCLC and who are not candidates for surgical resection or definitive chemoradiation, or
- metastatic NSCLC.

LIBTAYO in combination with platinum-based chemotherapy is indicated for the first-line treatment of patients with NSCLC whose tumours have no EGFR, ALK or ROS1 aberrations and is:

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

Basal Cell Carcinoma

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

Patient Selection for NSCLC

Select patients for treatment with cemiplimab based on PD-L1 expression confirmed by a validated test in locally advanced or metastatic NSCLC (see Section 5.1).

Posology

Recommended dose

The recommended dose is 350 mg cemiplimab every 3 weeks (Q3W) administered as an intravenous infusion over 30 minutes. Treatment may be continued until disease progression or unacceptable toxicity.

Dose modifications

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.

Detailed guidelines for the management of immune-related adverse reactions are described in Table 1 (see also Section 4.4 and Section 4.8).

Table 1 - Recommended treatment modifications

Adverse Reaction[a]	Severity[b]	Dose modification	Additional intervention
Immune-Mediated Adverse Reactions			
Pneumonitis	Grade 2	Withhold LIBTAYO	Initial dose of 1 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	Initial dose of 2 to 4 mg/kg/day prednisone or equivalent followed by a taper
Colitis	Grade 2 or 3	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if colitis or diarrhoea 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	Initial dose of 1 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 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	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Hypothyroidism	Grade 3 or 4	Withhold LIBTAYO	Initiate thyroid hormone replacement as clinically indicated

Adverse Reaction[a]	Severity[b]	Dose modification	Additional intervention
Immune-Mediated Adverse Reactions			
		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 symptomatic management
		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 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 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 (hyperglycaemia)	Withhold LIBTAYO	Initiate treatment with anti-hyperglycaemics 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 suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if skin reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	

Adverse Reaction[a]	Severity[b]	Dose modification	Additional intervention
Immune-Mediated Adverse Reactions			
	Grade 4 or confirmed SJS or TEN	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-mediated skin reaction or other immune-mediated adverse reactions in patients with prior treatment with idelalisib	Grade 2	Withhold LIBTAYO	Initiate management immediately, including initial dose of 1 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	Initiate management immediately, including initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Nephritis with renal dysfunction	Grade 2 creatinine increased	Withhold LIBTAYO	Initial dose of 1 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	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Other immune-mediated adverse reactions	Grade 2 or 3 based on type of reaction	Withhold LIBTAYO	Initiate symptomatic management including initial dose of 1 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	

Adverse Reaction[a]	Severity[b]	Dose modification	Additional intervention
Immune-Mediated Adverse Reactions			
	Grade 3 based on 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	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent as clinically indicated followed by a taper
Haemophagocytic 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 [a]			
Infusion-related reaction	Grade 1 or 2	Interrupt or slow rate of infusion	Initiate symptomatic management
	Grade 3 or 4	Permanently discontinue	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.
[a] See also Warnings and Precautions (Section 4.4) and Adverse Reactions (Section 4.8)
[b] Toxicity should be graded with the current version of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

Patient Alert Card

All prescribers of LIBTAYO should be familiar with the educational materials and inform the patients about the Patient Alert Card explaining what to do should they experience any symptom of immune-related adverse reactions and infusion-related reactions. The physician will provide the Patient Alert Card to each patient.

Special populations

Paediatric population

The safety and efficacy of LIBTAYO in children and adolescents below 18 years of age have not been established.

The efficacy, safety and pharmacokinetics of cemiplimab were evaluated in 57 paediatric and young adult patients with relapsed or refractory solid and CNS tumours, newly diagnosed diffuse intrinsic pontine glioma (DIPG), newly diagnosed high-grade glioma (HGG) or recurrent HGG in Study 1690. The study, an open-label, multi-centre study, consisted of two phases, Phase 1 and Efficacy phase, conducted in parallel.

In Phase 1, the safety and pharmacokinetics of cemiplimab monotherapy were evaluated in 25 patients (0 to less than 18 years): 8 patients with relapsed or refractory solid tumours and 17 patients with relapsed or refractory CNS tumours. Sixteen patients with solid or CNS tumours received a cemiplimab dose of 3 mg/kg every 2 weeks and 9 patients with CNS tumours received a cemiplimab dose of 4.5 mg/kg every 2 weeks. In Efficacy phase, the efficacy and safety of cemiplimab in combination with radiotherapy were evaluated in 32 patients (3 to 25 years) with CNS tumours: 11 patients with newly diagnosed DIPG, 12 patients with newly diagnosed HGG and 9 patients with recurrent HGG. All patients 12 years and older received a cemiplimab dose of 3 mg/kg and patients aged 3 to less than 12 years received a cemiplimab dose of 4.5 mg/kg every 2 weeks. Cemiplimab was administered via a 30-minute intravenous infusion.

Efficacy of cemiplimab in combination with radiotherapy was not established in studied populations as an improvement in OS or PFS was not demonstrated over historical control data.

No new risks or safety signals were identified.

Elderly

No dose adjustment is recommended for elderly patients. Cemiplimab exposure is similar across all age groups (see Section 5.1 and Section 5.2).

Renal impairment

No dose adjustment of LIBTAYO is recommended for patients with renal impairment. There are limited data for LIBTAYO in patients with severe renal impairment CL_{cr} 15 to 29 ml/min (see Section 5.2).

Hepatic impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. LIBTAYO has not been studied in patients with severe hepatic impairment. There are insufficient data in patients with severe hepatic impairment for dosing recommendations (see Section 5.2).

Method of administration

LIBTAYO is for intravenous use. It is administered by intravenous infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding, in-line or add-on filter (0.2 micron to 5 micron pore size).

Other medicinal products should not be co-administered through the same infusion line.

For instructions on dilution of the medicinal product before administration, see Section 6.6.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Immune-mediated adverse reactions

Severe and fatal immune-mediated adverse reactions have been observed with cemiplimab (see Section 4.2 and Section 4.8). These immune-mediated reactions may involve any organ system. Immune-mediated reactions can manifest at any time during treatment with cemiplimab; however, immune-mediated adverse reactions can occur after discontinuation of cemiplimab.

The guidance for immune-mediated adverse reactions applies to LIBTAYO monotherapy and in combination with chemotherapy.

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

Monitor patients for signs and symptoms of immune-mediated adverse reactions. Immune-mediated adverse reactions should be managed with cemiplimab treatment modifications, hormone replacement therapy (if clinically indicated), and corticosteroids. For suspected immune-mediated adverse reactions, patients should be evaluated to confirm an immune-mediated adverse reaction and to exclude other possible causes, including infection. Depending upon the severity of the adverse reaction, cemiplimab should be withheld or permanently discontinued (see Section 4.2).

Immune-mediated pneumonitis

Immune-mediated pneumonitis, defined as requiring use of corticosteroids with no clear alternate aetiology, including fatal cases, has been observed in patients receiving cemiplimab (see Section 4.8). Patients should be monitored for signs and symptoms of pneumonitis and causes other than immune-mediated pneumonitis should be ruled out. Patients with suspected pneumonitis should be evaluated with radiographic imaging as indicated based on clinical evaluation and managed with cemiplimab treatment modifications and corticosteroids (see Section 4.2).

Immune-mediated colitis

Immune-mediated diarrhoea or colitis, defined as requiring use of corticosteroids with no clear alternate aetiology, has been observed in patients receiving cemiplimab (see Section 4.8) Patients should be monitored for signs and symptoms of diarrhoea or colitis and managed with cemiplimab treatment modifications, anti-diarrhoeal agents, and corticosteroids (see Section 4.2).

Immune-mediated hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids with no clear alternate aetiology, including fatal cases, has been observed in patients receiving cemiplimab (see Section 4.8). Patients should be monitored for abnormal liver tests prior to and periodically during treatment as indicated based on clinical evaluation and managed with cemiplimab treatment modifications and corticosteroids (see Section 4.2).

Immune-mediated endocrinopathies

Immune-mediated endocrinopathies, defined as treatment-emergent endocrinopathies with no clear alternate aetiology, have been observed in patients receiving cemiplimab (see Section 4.8).

Thyroid disorders (Hypothyroidism/Hyperthyroidism/Thyroiditis)

Thyroid disorders have been observed in patients receiving cemiplimab. 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. Patients should be monitored for changes in thyroid function at the start of treatment and periodically

during the treatment as indicated based on clinical evaluation (see Section 4.8). Patients should be managed with hormone replacement therapy (if indicated) and cemiplimab treatment modifications. Hyperthyroidism should be managed according to standard medical practice (see Section 4.2).

Hypophysitis

Hypophysitis has been observed in patients receiving cemiplimab (see Section 4.8). Patients should be monitored for signs and symptoms of hypophysitis and managed with cemiplimab treatment modifications, corticosteroids and hormone replacement, as clinically indicated (see Section 4.2).

Adrenal insufficiency

Adrenal insufficiency has been observed in patients receiving cemiplimab (see Section 4.8). Patients should be monitored for signs and symptoms of adrenal insufficiency during and after treatment and managed with cemiplimab treatment modifications, corticosteroids and hormone replacement, as clinically indicated (see Section 4.2).

Type 1 Diabetes mellitus

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been observed in patients receiving cemiplimab (see Section 4.8). Patients should be monitored for hyperglycaemia and signs and symptoms of diabetes as indicated based on clinical evaluation and managed with oral anti-hyperglycaemics or insulin and cemiplimab treatment modifications (see Section 4.2).

Immune-mediated skin adverse reactions

Immune-mediated skin adverse reactions, defined as requiring use of systemic corticosteroids with no clear alternate aetiology, including severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (some cases with fatal outcome), and other skin reactions such as rash, erythema multiforme, pemphigoid, have been reported in association with cemiplimab treatment (see Section 4.8).

Patients should be monitored for evidence of suspected severe skin reactions and exclude other causes. Patients should be managed with cemiplimab treatment modifications and corticosteroids (see Section 4.2). For symptoms or signs of SJS or TEN, refer the patient for specialised care for assessment and treatment and manage patient with treatment modifications (see section 4.2).

Cases of SJS, fatal TEN and stomatitis occurred following 1 dose of cemiplimab in patients with prior exposure to idelalisib, who were participating in a clinical trial evaluating cemiplimab in Non-Hodgkin Lymphoma (NHL), and who had recent exposure to sulfa containing antibiotics (see Section 4.8). Patients should be managed with cemiplimab treatment modifications and corticosteroids as described above (see Section 4.2). For symptoms or signs of SJS or TEN, refer the patient for specialised care for assessment and treatment and manage patient with treatment modifications (see Section 4.2).

Immune-mediated nephritis

Immune-mediated nephritis defined as requiring use of corticosteroids with no clear alternate aetiology, including a fatal case, has been observed in patients receiving cemiplimab (see Section 4.8). Monitor patients for changes in renal function. Patients should be managed with cemiplimab treatment modifications and corticosteroids (see Section 4.2).

Other Immune-mediated adverse reactions

Other fatal and life-threatening immune-mediated adverse reactions have been observed in patients receiving cemiplimab including paraneoplastic encephalomyelitis meningitis, myositis, myocarditis and pancreatitis (see Section 4.8 for other immune-related adverse reactions).

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 cemiplimab treatment modifications and corticosteroids as clinically indicated (see Section 4.2 and Section 4.8).

Cases of solid organ transplant rejection have been reported in the post-marketing setting with cemiplimab and other PD-1/PD-L1 inhibitors. Cases of graft-versus-host disease have been reported in the post-marketing setting in patients treated with other PD-1/PD-L1 inhibitors in association with allogeneic hematopoietic stem cell transplant.

Haemophagocytic lymphohistiocytosis (HLH) has been reported in the postmarketing setting with LIBTAYO (see Section 4.8). 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 Section 4.2). If HLH is confirmed, administration of LIBTAYO should be permanently discontinued.

Patients with pre-existing autoimmune disease (AID)

In patients with pre-existing autoimmune disease (AID), data from observational studies suggest that the risk of immune-mediated adverse reactions following immune checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.

Infusion-related reactions

Cemiplimab can cause severe or life-threatening infusion-related reactions (see Section 4.8). Patients should be monitored for signs and symptoms of infusion-related reactions and managed with cemiplimab treatment modifications and corticosteroids. Cemiplimab should be interrupted or the rate of infusion slowed for mild or moderate infusion-related reactions. The infusion should be stopped and cemiplimab should be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions (see Section 4.2).

Patients excluded from clinical studies

Patients that had active infections or that were immunocompromised were not included in the main study. For a full list of patients excluded from clinical trials, see Section 5.1.

In the absence of data, cemiplimab should be used with caution in these populations after careful evaluation of the balance of benefits and risks for the patient.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

The use of systemic corticosteroids or immunosuppressants before starting cemiplimab, except for physiological doses of systemic corticosteroid (≤10 mg/day prednisone or equivalent), should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of cemiplimab. However, systemic corticosteroids or other immunosuppressants can be used after starting cemiplimab to treat immune-related adverse reactions (see Section 4.2).

4.6 FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment with cemiplimab and for at least 4 months after the last dose of cemiplimab.

Effects on fertility

No clinical data are available on the possible effects of cemiplimab on fertility. No effects on fertility assessment parameters (menstrual cycle and semen analysis) or male and female reproductive organs were observed in a 3-month repeat dose fertility assessment study with sexually mature cynomolgus monkeys at doses up to the highest dose studied of 50 mg/kg/week IV, resulting in exposures (AUC and C_{max}) approximately 20 times that expected in patients.

Use in pregnancy (Category D)

Animal reproduction studies have not been conducted with cemiplimab. There are no available data on the use of cemiplimab in pregnant women. As reported in the literature, PD-1/PD-L1 signalling pathway plays a role in sustaining pregnancy by maintaining immunological tolerance and animal studies have shown that PD-1 receptor blockade can result in an increase in foetal loss.

The increase of spontaneous abortion and/or resorption in animals with restricted PD-L1 expression (knock-out or anti-PD1/PD-L1 monoclonal antibodies) has been shown in both mice and monkeys. These animal species have similar maternal foetal interface to that in humans.

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 foetus. Cemiplimab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk.

Use in lactation

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 breast-feeding newborn/infant cannot be excluded.

If a woman chooses to be treated with cemiplimab, she should be instructed not to breast-feed while being treated with cemiplimab and for at least 4 months after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Cemiplimab has no or negligible influence on the ability to drive and use machines. Fatigue has been reported following treatment with cemiplimab (see Section 4.8).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

Immune-mediated adverse reactions can occur with cemiplimab. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of cemiplimab (see *Description of selected adverse reactions* below).

LIBTAYO as monotherapy

The safety of cemiplimab monotherapy has been evaluated in 1281 patients with advanced solid malignancies who received cemiplimab in 5 clinical studies. These studies included 384 patients with advanced CSCC, 138 patients with advanced BCC, 355 patients with advanced NSCLC, 300 patients with recurrent or metastatic cervical cancer and 104 patients with other solid tumours. The median duration of exposure to cemiplimab was 27 weeks (range: 2 days to 144 weeks). Among the 1281 patients, 53% were exposed for ≥ 6 months and 26% were exposed for ≥ 12 months

Immune-mediated adverse reactions occurred in 20.8% of patients treated with cemiplimab in clinical trials including Grade 5 (0.3%), Grade 4 (0.6%), Grade 3 (5.7%) and Grade 2 (11.2%). Immune-mediated adverse reactions led to permanent discontinuation of cemiplimab in 4.6% of patients. The most common immune-mediated adverse reactions were hypothyroidism (6.8%), hyperthyroidism (3.0%), immune-mediated pneumonitis (2.6%), immune-mediated hepatitis (2.4%), immune-mediated colitis (2.0%) and immune-mediated skin adverse reactions (1.9%) (see *Description of selected adverse reactions* below, *Special warnings and precautions for use* in Section 4.4 and *Recommended treatment modifications* in Section 4.2).

Adverse events were serious in 32.4% of patients.

Adverse events led to permanent discontinuation of cemiplimab in 9.4% of patients.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with cemiplimab treatment (see Section 4.4).

Tabulated list of adverse reactions

Listed in Table 2 are adverse reactions by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2 - Tabulated list of adverse reactions in patients with solid tumours treated with cemiplimab in studies 1423, 1540, 1620, 1624 and 1676 (N = 1281)

System organ class preferred term	Grades 1-5 (Frequency category)	Grades 1-5 (%)	Grades 3-4 (%)	Grade 5 (%)
Infections and infestations				
Upper respiratory tract infection [a]	Very Common	10.9	0.4	0
Urinary tract infection [b]	Common	8.4	2.3	<0.1
Blood and lymphatic system disorders				
Anaemia	Very Common	15.0	5.2	0
Immune system disorders				
Infusion-related reaction	Common	3.3	<0.1	0
Sjogren's syndrome	Uncommon	0.2	0	0
Thrombocytopenia [c]	Uncommon	0.9	0	0
Endocrine disorders				
Hypothyroidism [d]	Common	6.8	<0.1	0
Hyperthyroidism	Common	3.0	<0.1	0
Adrenal insufficiency	Uncommon	0.5	0.5	0
Thyroiditis [e]	Uncommon	0.6	0	0
Hypophysitis [f]	Uncommon	0.5	0.2	0
Type 1 diabetes mellitus [g]	Rare	<0.1	<0.1	0
Nervous system disorders				
Headache	Common	8.0	0.3	0
Peripheral neuropathy [h]	Common	1.3	<0.1	0
Meningitis [i]	Rare	<0.1	<0.1	0
Encephalitis	Rare	<0.1	<0.1	0
Myasthenia gravis	Rare	<0.1	0	0
Paraneoplastic encephalomyelitis	Rare	<0.1	0	<0.1

System organ class preferred term	Grades 1-5 (Frequency category)	Grades 1-5 (%)	Grades 3-4 (%)	Grade 5 (%)
Chronic inflammatory demyelinating polyradiculoneuropathy	Rare	<0.1	0	0
Eye disorders				
Keratitis	Rare	<0.1	0	0
Cardiac disorders				
Myocarditis [j]	Uncommon	0.5	0.2	<0.1
Pericarditis [k]	Uncommon	0.3	0.2	0
Vascular disorders				
Hypertension [l]	Common	5.7	2.6	0
Metabolism and nutrition disorders				
Decreased appetite	Very common	13.0	0.6	0
Respiratory, thoracic and mediastinal disorders				
Cough [m]	Very common	10.8	0.2	0
Dyspnoea [n]	Common	9.7	1.2	<0.1
Pneumonitis [o]	Common	3.3	1.1	0.2
Gastrointestinal disorders				
Nausea	Very common	14.7	0.2	0
Diarrhoea	Very common	16.3	0.7	0
Constipation	Very common	12.3	0.2	0
Abdominal pain [p]	Very common	11.5	0.7	0
Vomiting	Common	9.9	0.2	0
Stomatitis	Common	1.8	<0.1	0
Colitis [q]	Common	2.0	0.8	0
Gastritis [r]	Uncommon	0.2	0	0
Pancreatitis [s]	-	-	-	-
Hepatobiliary disorders				
Hepatitis [t]	Common	2.7	1.7	<0.1
Skin and subcutaneous skin disorders				
Rash [u]	Very common	21.4	1.6	0
Pruritus [v]	Very common	12.7	0.2	0
Actinic keratosis	Common	3.7	0	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain [w]	Very Common	28.3	1.8	0
Arthritis [x]	Uncommon	0.9	0.2	0
Muscular weakness	Uncommon	0.2	0	0

System organ class preferred term	Grades 1-5 (Frequency category)	Grades 1-5 (%)	Grades 3-4 (%)	Grade 5 (%)
Myositis [y]	Uncommon	0.3	<0.1	0
Polymyalgia rheumatica	Uncommon	0.2	0	0
Renal and urinary disorders				
Nephritis [z]	Common	1.2	<0.1	<0.1
General disorders and administration site conditions				
Fatigue [aa]	Very common	29.9	2.6	0
Pyrexia [bb]	Common	8.7	0.2	0
Oedema [cc]	Common	7.9	0.4	0
Investigations				
Aspartate aminotransferase increased	Common	4.4	0.7	0
Alanine aminotransferase increased	Common	4.6	0.5	0
Blood alkaline phosphatase increased	Common	1.9	0.2	0
Blood creatinine increased	Common	1.6	0	0
Blood thyroid stimulating hormone increased	Uncommon	0.8	0	0
Transaminases increased	Uncommon	0.4	<0.1	0
Blood bilirubin increased	Uncommon	0.4	<0.1	0
Blood thyroid stimulating hormone decreased	Rare	<0.1	0	0

System organ class preferred term	Grades 1-5 (Frequency category)	Grades 1-5 (%)	Grades 3-4 (%)	Grade 5 (%)
Version 4.03 of NCI CTCAE was used to grade toxicity. a. Upper respiratory tract infection includes upper respiratory tract infection, nasopharyngitis, sinusitis, respiratory tract infection, rhinitis, viral upper respiratory tract infection, respiratory tract infection viral, pharyngitis, laryngitis, viral rhinitis, acute sinusitis, tonsillitis, and tracheitis. b. Urinary tract infection includes urinary tract infection, cystitis, pyelonephritis, kidney infection, pyelonephritis acute, urosepsis, cystitis bacterial, Escherichia urinary tract infection, pyelocystitis, urinary tract infection bacterial, and urinary tract infection pseudomonal. c. Thrombocytopenia includes thrombocytopenia and immune thrombocytopenia. d. Hypothyroidism includes hypothyroidism and immune-mediated hypothyroidism. e. Thyroiditis includes thyroiditis and autoimmune thyroiditis. f. Hypophysitis includes hypophysitis and lymphocytic hypophysitis. g. Type 1 diabetes mellitus includes diabetic ketoacidosis and Type 1 diabetes mellitus. h. Peripheral neuropathy includes peripheral sensory neuropathy, peripheral neuropathy, paraesthesia, polyneuropathy, neuritis, and peripheral motor neuropathy. i. Meningitis includes aseptic meningitis. j. Myocarditis includes myocarditis, autoimmune myocarditis, and immune-mediated myocarditis. k. Pericarditis includes autoimmune pericarditis and pericarditis. l. Hypertension includes hypertension and hypertensive crisis. m. Cough includes cough, productive cough, and upper-airway cough syndrome. n. Dyspnoea includes dyspnoea and dyspnoea exertional. o. Pneumonitis includes pneumonitis, immune-mediated lung disease, interstitial lung disease, and pulmonary fibrosis. p. Abdominal pain includes abdominal pain, abdominal pain upper, abdominal distension, abdominal pain lower, abdominal discomfort, and gastrointestinal pain. q. Colitis includes colitis, autoimmune colitis, enterocolitis, and immune-mediated enterocolitis. r. Gastritis includes gastritis and immune-mediated gastritis. s. Pancreatitis includes pancreatitis and immune-mediated pancreatitis. Includes cases outside the pooled safety dataset, hence frequency cannot be estimated.t. Hepatitis includes autoimmune hepatitis, immune-mediated hepatitis, hepatitis, hepatotoxicity, hyperbilirubinaemia, hepatocellular injury, hepatic failure, and hepatic function abnormal. u. Rash includes rash, rash maculo-papular, dermatitis, erythema, rash pruritic, urticaria, rash erythematous, dermatitis bullous, dermatitis acneiform, rash macular, psoriasis, rash papular, dyshidrotic eczema, pemphigoid, autoimmune dermatitis, dermatitis allergic, atopic dermatitis, drug eruption, erythema nodosum, skin reaction, skin toxicity, dermatitis exfoliative, dermatitis exfoliative generalized, dermatitis psoriasiform, erythema multiforme, exfoliative rash, immune-mediated dermatitis, lichen planus, and parapsoriasis. v. Pruritus includes pruritus and allergic pruritus. w. Musculoskeletal pain includes arthralgia, back pain, pain in extremity, myalgia, neck pain, musculoskeletal chest pain, bone pain, musculoskeletal pain, spinal pain, musculoskeletal stiffness, and musculoskeletal discomfort. x. Arthritis includes arthritis, polyarthritis, and immune-mediated arthritis. y. Myositis includes myositis and dermatomyositis. z. Nephritis includes acute kidney injury, nephritis, renal failure, and nephropathy toxic. aa. Fatigue includes fatigue, asthenia, and malaise. bb. Pyrexia includes pyrexia, hyperthermia, and hyperpyrexia. cc. Oedema includes oedema peripheral, face oedema, peripheral swelling, swelling face, localised oedema, generalized oedema, and swelling.				

LIBTAYO in combination with platinum-based chemotherapy

The safety of LIBTAYO in combination with platinum-based chemotherapy has been evaluated in a clinical study of 465 patients with locally advanced or metastatic NSCLC. The median duration of exposure was 38.5 weeks (range: 10 days to 102.6 weeks) in the LIBTAYO and chemotherapy group, and 21.3 weeks (range: 4 days to 95 weeks) in the chemotherapy group.

The safety population characteristics were median age of 63 years (range: 25 to 82 years), 268 (85.9%) male, 267 (85.6%) White, ECOG PS of 0 in 51 patients (16.3%) and 1 in 259 patients (83%).

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" below, Section 4.8, and Section 4.2).

Adverse events were serious in 25.3% of patients.

Adverse events led to permanent discontinuation of cemiplimab in 5.1% of patients.

Table 3 summarises the incidence of adverse reactions that occurred in patients receiving LIBTAYO in combination with chemotherapy in Study 16113.

Table 3: Adverse Reactions in Patients Receiving LIBTAYO in Combination with Chemotherapy in Study 16113 (N=312)

System Organ Class Preferred Term	Grades 1-5 (Frequency category)	Grades 1-5 %	Grades 3-4 %	Grade 5 %
Blood and lymphatic system disorders				
Anaemia	Very common	43.6	9.9	0
Neutropenia	Very common	15.4	5.8	0
Thrombocytopenia	Very common	13.1	2.6	0
Immune system disorders				
Infusion related reaction	Uncommon	0.3	0	0
Endocrine disorders				
Hypothyroidism	Common	7.7	0.3	0
Hyperthyroidism	Common	5.1	0	0
Thyroiditis[a]	Uncommon	0.6	0	0
Type 1 diabetes mellitus[b]	Uncommon	0.3	0	0
Nervous system disorders				
Peripheral neuropathy[c]	Very common	21.2	1.28	0
Metabolism and nutrition disorders				
Hyperglycaemia	Very common	17.6	1.92	0
Decreased appetite	Very common	17.0	0.96	0
Hypoalbuminemia	Very common	10.3	0.64	0
Respiratory, thoracic and mediastinal disorders				
Dyspnoea[d]	Very common	12.8	2.2	0
Pneumonitis[e]	Common	4.2	5.8	0.6
Gastrointestinal disorders				
Nausea	Very common	25.0	0	0
Constipation	Very common	13.8	0.32	0
Vomiting	Very common	12.2	0	0
Diarrhoea	Very common	10.6	1.28	0

System Organ Class Preferred Term	Grades 1-5 (Frequency category)	Grades 1-5 %	Grades 3-4 %	Grade 5 %
Colitis[f]	Common	1.0	0.3	0
Psychiatric disorders				
Insomnia	Very common	10.9	0	0
Skin and subcutaneous skin disorders				
Alopecia	Very common	36.9	0	0
Rash[g]	Very common	12.5	1.3	0
Pruritus	Common	4.5	0	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[h]	Very common	26.9	1.3	0
Arthritis[i]	Common	1.0	0.3	0
Renal and urinary disorders				
Nephritis[j]	Common	2.6	0.6	0
General disorders and administration site conditions				
Fatigue[k]	Very common	23.4	3.8	0
Investigations				
Alanine aminotransferase increased	Very common	16.3	2.2	0
Aspartate aminotransferase increased	Very common	14.7	0.3	0
Weight decreased	Very common	11.2	1.3	0
Blood creatinine increased	Common	8.7	0.3	0
Blood alkaline phosphatase increased	Common	4.5	0	0
Blood thyroid stimulating hormone increased	Common	4.2	0	0
Blood bilirubin increased	Common	1.6	0.3	0
Blood thyroid stimulating hormone decreased	Common	1.6	0	0
Gamma-glutamyl transferase increased	Uncommon	0.6	0.3	0

System Organ Class Preferred Term	Grades 1-5 (Frequency category)	Grades 1-5 %	Grades 3-4 %	Grade 5 %
Version 4.03 of NCI CTCAE was used to grade toxicity. a. Thyroiditis includes autoimmune thyroiditis and immune-mediated thyroiditis. b. Type 1 diabetes mellitus includes diabetes mellitus. c. Peripheral neuropathy includes peripheral neuropathy, peripheral sensory neuropathy, paraesthesia, and polyneuropathy. d. Dyspnoea includes dyspnoea and dyspnoea exertional. e. Pneumonitis includes pneumonitis and immune-mediated pneumonitis. f. Colitis includes colitis and enterocolitis. g. Rash includes rash, rash maculo-papular, dermatitis, psoriasis, rash papular, urticaria, dermatitis allergic, erythema, lichen planus, rash macular, rash pruritic, skin reaction, skin toxicity, and dermatitis acneiform. h. Musculoskeletal pain includes arthralgia, back pain, pain in extremity, myalgia, bone pain, musculoskeletal pain, neck pain, musculoskeletal chest pain, and spinal pain. i. Arthritis includes arthritis and autoimmune arthritis. j. Nephritis includes acute kidney injury, renal impairment, immune-mediated nephritis, renal failure, and tubulointerstitial nephritis. k. Fatigue includes asthenia, fatigue, and malaise.				

Description of selected adverse reactions

The selected adverse reactions described below are based on safety of cemiplimab monotherapy in 1281 patients with advanced solid malignancies in five clinical studies.

These selected adverse reactions were consistent when LIBTAYO was administered in monotherapy or in combination with chemotherapy.

Immune-mediated adverse reactions (see Section 4.2 and Section 4.4)

Immune-mediated pneumonitis

Immune-mediated pneumonitis occurred in 33 (2.6%) of 1281 patients receiving cemiplimab, including 4 (0.3%) patients with Grade 4, 8 (0.6%) patients with Grade 3 pneumonitis. Immune-mediated pneumonitis led to permanent discontinuation of cemiplimab in 17 (1.3%) of 1281 patients. Among the 33 patients with immune-mediated pneumonitis, the median time to onset was 2.7 months (range: 7 days to 22.2 months) and the median duration of pneumonitis was 1.1 months (range: 5 days to 16.9 months). Twenty-seven of the 33 patients (81.8%) received high-dose corticosteroids for a median of 15 days (range: 1 day to 5.9 months). Resolution of pneumonitis had occurred in 20 (60.6%) of the 33 patients at the time of data cut-off.

Immune-mediated colitis

Immune-mediated diarrhoea or colitis occurred in 25 (2.0%) of 1281 patients receiving cemiplimab including 10 (0.8%) with Grade 3 immune-mediated diarrhoea or colitis. Immune-mediated diarrhoea or colitis led to permanent discontinuation of cemiplimab in 5 (0.4%) of 1281 patients. Among the 25 patients with immune-mediated diarrhoea or colitis, the median time to onset was 3.8 months (range: 1 day to 16.6 months) and the median duration of immune-mediated diarrhoea or colitis was 2.1 months (range: 4 days to 26.8 months). Nineteen patients (76.0%) with immune-mediated diarrhoea or colitis received high-dose corticosteroids for a median of 22 days (range: 2 days to 5.2 months). Resolution

of immune-mediated diarrhoea or colitis had occurred in 14 (56%) of the 25 patients at the time of data cut-off.

Immune-mediated hepatitis

Immune-mediated hepatitis occurred in 31 (2.4%) of 1281 patients receiving cemiplimab including 1 (<0.1%) patient with Grade 5, 4 (0.3%) patients with Grade 4, and 21 (1.6%) patients with Grade 3 immune-mediated hepatitis. Immune-mediated hepatitis led to permanent discontinuation of cemiplimab in 18 (1.4%) of 1281 patients. Among the 31 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 2.3 months (range: 5 days to 8.7 months). Twenty-seven (87.1%) patients with immune-mediated hepatitis received high-dose corticosteroids for a median of 24 days (range: 2 days to 3.8 months). Resolution of hepatitis had occurred in 12 (38.7%) of the 31 patients at the time of data cut-off.

Immune-mediated endocrinopathies

Hypothyroidism occurred in 87 (6.8%) of 1281 patients receiving cemiplimab including 1 (<0.1%) patient with Grade 3 hypothyroidism. Three (0.2%) of 1281 patients discontinued cemiplimab due to hypothyroidism. Among the 87 patients with hypothyroidism, the median time to onset was 4.0months (range: 15 days to 18.9 months) with a median duration of 9.2 months (range: 1 day to 37.1 months). Resolution of hypothyroidism had occurred in 5 (5.7%) of the 87 patients at the time of data cutoff.

Hyperthyroidism occurred in 39 (3.0%) of 1281 patients receiving cemiplimab including 1 (<0.1%) patient with Grade 3 and 11 (0.9%) patients with Grade 2 hyperthyroidism. No patient discontinued cemiplimab due to hyperthyroidism. Among the 39 patients with hyperthyroidism, the median time to onset was 1.9 months (range: 20 days to 23.8 months) and the median duration was 1.9 months (range: 9 days to 32.7 months). Resolution of hyperthyroidism had occurred in 22(56.4%) of the 39 patients at the time of data cutoff.

Thyroiditis occurred in 8 (0.6%) of 1281 patients receiving cemiplimab including 4 (0.3%) patients with Grade 2 thyroiditis. No patient discontinued cemiplimab due to thyroiditis. Resolution of thyroiditis had occurred in 1 (16.7 12.5%) of the 6 8 patients at the time of data cutoff.

Adrenal insufficiency occurred in 6 (0.5%) of 1281 patients receiving cemiplimab including 6 (0.5%) patients with Grade 3 adrenal insufficiency. One (<0.1%) of 1281 patients discontinued cemiplimab due to adrenal insufficiency. Among the 6 patients with adrenal insufficiency, the median time to onset was 7.5 months (range: 4.2 months to 18.3 months) and the median duration was 2.9 months (range: 22 days to 6.1 months). Five of the 6 patients (83.3%) were treated with systemic corticosteroids. Adrenal insufficiency resolved in 1 of the 6 patients (16.7%) at the time of data cutoff.

Hypophysitis occurred in 7 (0.5%) of 1281 patients receiving cemiplimab, including 3 (0.2%) patients with Grade 3 hypophysitis. One (<0.1%) of 1281 patients discontinued cemiplimab due to hypophysitis. Among the 7 patients with hypophysitis, the median time to onset was 7.4 months (range: 2.5 months to 10.4 months) with a median duration of 2.7 months (range: 9 days to 34.9 months). Six of the 7 patients (85.7%) were treated with corticosteroids. Hypophysitis resolved in 1 of the 7 patients (14.3%) at the time of data cutoff.

Type 1 diabetes mellitus without an alternative aetiology occurred in 1 (<0.1%) of 1281 patients (Grade 4).

Immune-mediated skin adverse reactions

Immune-mediated skin adverse reactions occurred in 24 (1.9%) of 1281 patients receiving cemiplimab including 11(0.9%) patients with Grade 3 immune-mediated skin adverse reactions. Immune-mediated skin adverse reactions led to permanent discontinuation of cemiplimab in 2 (0.2%) of 1281 patients. Among the 24 patients with immune-mediated skin adverse reactions, the median time to onset was 2.0 months (range: 2 days to 17.0 months) and the median duration was 2.9 months (range: 8 days to 38.8 months). Seventeen patients (70.8%) with immune-mediated skin adverse reactions received high-dose corticosteroids for a median of 10 days (range: 1 days to 2.9 months). Resolution had occurred in 17 (70.8%) of 24 patients at the time of data cut-off.

Immune-mediated nephritis

Immune-mediated nephritis occurred in 9 (0.7%) of 1281 patients receiving cemiplimab including 1 (<0.1%) patient with Grade 5, and 1 (<0.1%) patient with Grade 3 immune-mediated nephritis. Immune-mediated led to permanent discontinuation of cemiplimab in 2 (0.2%) of 1281 patients. Among the 9 patients with immune-mediated nephritis, the median time to onset was 2.1 months (range: 14 days to 12.5 months) and the median duration of nephritis was 1.5 months (range: 9 days to 5.5 months). Six (66.7%) patients with immune-mediated nephritis received high-dose corticosteroids for a median of 18 days (range: 3 days to 1.3 months). Resolution of nephritis had occurred in 7 (77.8%) of the 9 patients at the time of data cut-off.

Other Immune-mediated adverse reactions

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% (unless otherwise noted) of 1281 patients with advanced solid malignancies treated with cemiplimab 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 (1.2%), arthritis[d], muscular weakness, myalgia, myositis[e] (Grade 4), polymyalgia rheumatica, Sjogren's syndrome

Skin and Subcutaneous Tissue Disorders: Pruritus

Eye disorders: Keratitis, uveitis[f] (Grade 4)

Gastrointestinal disorders: Stomatitis, immune-mediated gastritis, pancreatitis (Grade 4)

[a] includes neuritis, peripheral neuropathy, peripheral sensory neuropathy, and polyneuropathy
[b] includes autoimmune myocarditis, immune-mediated myocarditis, and myocarditis
[c] includes autoimmune pericarditis and pericarditis
[d] includes arthritis, immune-mediated arthritis, and polyarthritis
[e] includes myositis and dermatomyositis
[f] reported in clinical studies outside the pooled safety dataset

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).

Immune checkpoint inhibitor class effects

There have been cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors, which might also occur during treatment with cemiplimab: coeliac disease, pancreatic exocrine insufficiency and aplastic anaemia.

Infusion-related reactions

Infusion-related reactions occurred in 94 (7.3%) of 1281 patients treated with cemiplimab including 2 (0.2%) patients with Grade 3 or 4 infusion-related reactions. Common symptoms of infusion-related reaction include nausea, pyrexia, and vomiting.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with cemiplimab. Approximately 2.1% of patients developed treatment-emergent antibodies to cemiplimab, with approximately 0.3% of patients exhibiting persistent antibody responses. No neutralising antibodies have been observed. There was no evidence of an altered PK or safety 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.

Postmarketing Experience

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 Section 4.4 Special Warnings and Precautions for Use).

Immune System Disorder: Solid organ transplant rejection, autoimmune haemolytic anaemia

Blood and lymphatic system disorders: Haemophagocytic lymphohistiocytosis (HLH)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

For general advice on overdose management, contact the Poisons Information Centre at telephone number 13 11 26.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, PD-1/PD-L1 (Programmed cell death protein 1/death ligand 1) inhibitors. ATC code: L01FF06.

Mechanism of action

Cemiplimab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with its ligands PD-L1 and PD-L2. Engagement of PD-1 with its ligands PD-L1 and PD-L2, which are expressed by antigen presenting cells and may be expressed by tumour cells and/or other cells in the tumour microenvironment, results in inhibition of T cell function such as proliferation, cytokine secretion, and cytotoxic activity. Cemiplimab potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Clinical efficacy

CSCC

The efficacy and safety of cemiplimab in patients with mCSCC (nodal or distant) or laCSCC who were not candidates for curative surgery or curative radiation were studied in clinical trial R2810-ONC-1540 (Study 1540). Study 1540 was a phase 2, open label, multi-centre study that enrolled 193 advanced CSCC patients in Groups 1 to 3: 59 patients with mCSCC treated with cemiplimab 3 mg/kg Q2W (Group 1), 78 patients with laCSCC treated with cemiplimab 3 mg/kg Q2W (Group 2), 56 patients with mCSCC treated with cemiplimab 350 mg Q3W (Group 3).

Patients with any of the following were excluded: autoimmune disease that required systemic therapy with immunosuppressant agents within 5 years; history of solid organ transplant; history of pneumonitis within the last 5 years; prior treatment with anti PD-1/PD-L1 or other immune checkpoint inhibitor therapy; active infection requiring therapy, including known

infection with human immunodeficiency virus, or active infection with hepatitis B or hepatitis C virus; chronic lymphocytic leukaemia (CLL); brain metastases or Eastern Cooperative Oncology Group (ECOG) performance score (PS) ≥2.

In Study 1540, patients received cemiplimab until progression of disease, unacceptable toxicity or completion of planned treatment (3 mg/kg Q2W for 96 weeks (Groups 1 and 2) or 350 mg Q3W for 54 weeks Group 3)). 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 (for patients receiving 3 mg/kg Q2W or 350 mg Q3W, respectively). The primary endpoint of Study 1540 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) by ICR. Other secondary endpoints included ORR and DOR by investigator assessment (IA), progression free survival (PFS) by ICR and IA, overall survival (OS), complete response rate (CR) by ICR, and change in scores in patient reported outcomes on the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30).

The efficacy analysis presents results from 193 advanced CSCC patients in Study 1540 Groups 1 to 3. Of these 193 patients, 115 had mCSCC (nodal or distant) and 78 had laCSCC. The median age was 72 years (range: 38 to 96): Seventy-eight (40.4%) patients were 75 years or older, 66 patients (34.2%) were 65 to less than 75 years, and 49 patients (25.4%) were less than 65 years. A total of 161 (83.4%) patients were male, and 187 (96.9%) patients were White; the ECOG PS was 0 in 86 patients (44.6%) and 1 in 107 patients (55.4%). Sixty-five (33.7%) of patients had received at least 1 prior anti-cancer systemic therapy, 157 (81.3%) patients had received prior cancer-related surgery, and 113 (67.9%) patients had received prior radiotherapy. Among patients with mCSCC, 88 (76.5%) had distant metastases, and 26 (22.6%) had only nodal metastases.

At the time of primary analysis, median duration of follow-up was 7.9 months, 9.3 months, and 8.1 months for Groups 1, 2, and 3, respectively. The CR rate and ORR for Group 1 were 6.8% and 47.5%, respectively. The CR rate and ORR for Group 2 were 12.8% and 43.6%, respectively The CR rate and ORR for Group 3 were 5.4% and 41.1%, respectively.

Efficacy results based on the final analysis for Study 1540 Groups 1 to 3 are presented in Table 4.

In the final analysis, with median duration of follow-up of 18.5 months, 15.5 months, and 17.3 months for Groups 1, 2, and 3, respectively, complete response rate increases over time for mCSCC patients (3 mg/kg Q2W and 350 mg Q3W groups). As for the primary analysis, similar ORR were reported in the final analysis across Groups 1 to 3.

Efficacy results based on the final analysis for Study 1540 Groups 1 to 3 are presented in Table 4 and Figure 1.

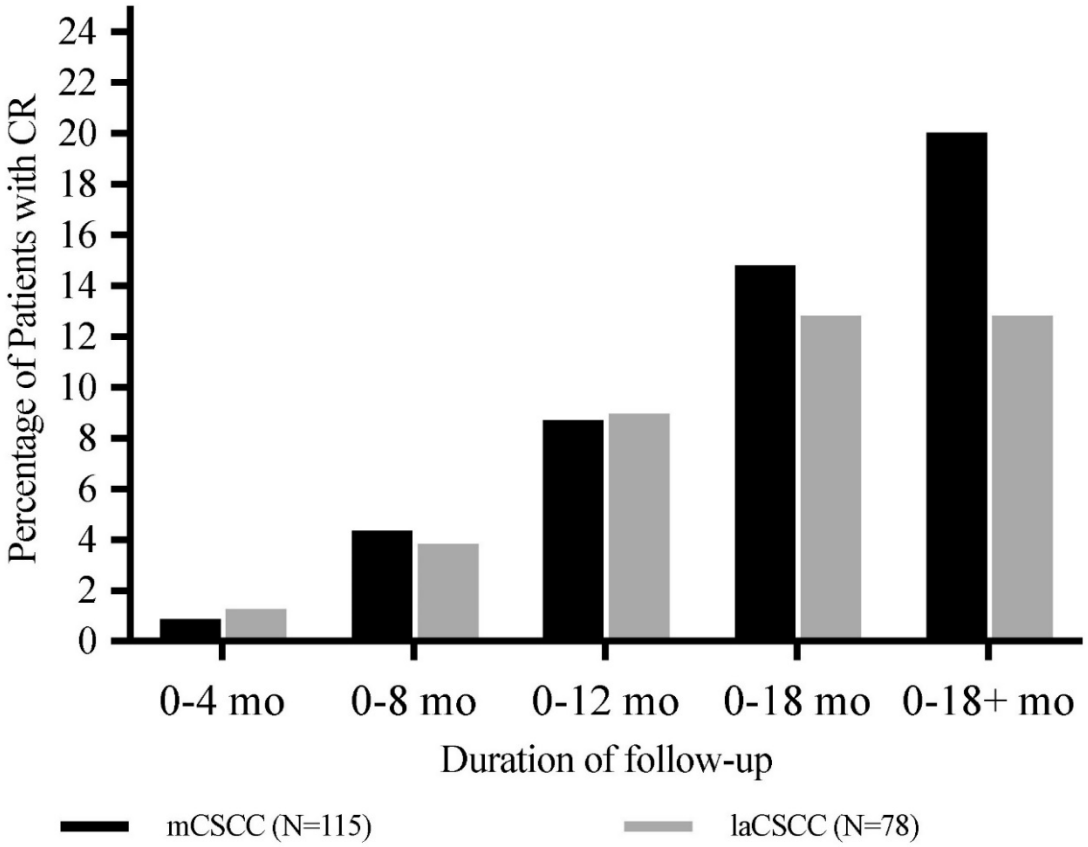
Table 4 - Efficacy results: Study 1540 (Final Analysis)

Efficacy Endpoints	Metastatic CSCC cemiplimab 3 mg/kg every 2 weeks (Group 1)	Locally Advanced CSCC cemiplimab 3 mg/kg every 2 weeks	Metastatic CSCC cemiplimab 350 mg every 3 weeks (Group 3)	Combined CSCC (Groups 1 to 3)
	N = 59	N = 78	N = 56	N = 193
Median Duration of Follow-Up (months) Range (months)	18.5 1.1 – 41.0	15.5 0.8 – 43.2	17.3 0.6 – 43.4	15.7 0.6 – 43.4
Best Overall Response (BOR)[a]				
Objective Response Rate (ORR) % (95% CI)	50.8% (37.5, 64.1)	44.9% (33.6, 56.6)	46.4% (33.0, 60.3)	47.2 (39.9, 54.4)
Complete response rate (CR)[b,c]	20.3%	12.8%	19.6%	17.1%
Partial response rate (PR)	30.5%	32.1%	26.8%	30.1%
Stable disease rate (SD)	15.3%	34.6%	14.3%	22.8%
Progressive disease rate (PD)	16.9%	12.8%	25.0%	17.6%
Duration of Response (DOR)				
Median[d] (months)	NR	41.9	41.3	41.3
Range (months)	2.8 – 38.9	1.9 – 54.6	4.2 – 46.3	1.9 – 54.6
Patients with observed DOR ≥ 6 months, n (%)[e]	28 (93.3%)	31 (88.6%)	25 (96.2%)	84 (92.3%)
Patients with observed DOR ≥ 12 months, n (%)[e]	23 (76.7%)	24 (68.6%)	23 (88.5%)	70 (76.9%)
Time to Response (months) (TTR)				
Median Range (months)	1.9 (1.7, 21.8)	2.1 (1.8, 8.8)	2.1 (2.0, 22.8)	2.1 (1.7, 22.8)

CI: Confidence interval; NR: Not reached

a. Non-evaluable and non-CR/non-PD patients are not presented in BOR results.
b. Only includes patients with complete healing of prior cutaneous involvement; laCSCC patients in Study 1540 required biopsy to confirm CR.
c. CR increased with further observation.
d. Based on Kaplan-Meier estimates.
e. The numerator includes the number of patients whose observed DOR reached at least the specified time. Patients who did not have the opportunity to reach the specified timepoint were included in the denominator only. Responses for some patients are ongoing at the time of final analysis.

Figure 1 - Percentage of Patients with Complete Response (CR) Over Time (Cumulative) – mCSCC Combined and laCSCC



Efficacy and PD-L1 status

Clinical activity was observed regardless of tumour PD-L1 expression status.

NSCLC

First-line treatment of NSCLC with LIBTAYO as monotherapy

The efficacy and safety of cemiplimab 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 were evaluated in Study 1624, a randomised, open-label, multi-centre study.

The study was designed to enrol patients with tumour PD-L1 expression ≥ 50%. A total of 710 patients (Intent-To-Treat [ITT] population) were enrolled, and an analysis was performed on the pre-specified population (n=563) who had PD-L1 expression ≥ 50% using the PD-L1 IHC 22C3 pharmDx assay according to its labelling.

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), or autoimmune

disease that required systemic therapy within 2 years of treatment. 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 randomisation. Radiological confirmation of stability or response was not required.

Randomisation was stratified by histology (non-squamous vs squamous). Patients were randomised (1:1) to receive cemiplimab 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 cemiplimab 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 cemiplimab therapy were permitted to continue treatment with cemiplimab 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 cemiplimab treatment until further progression, unacceptable toxicity or up to 108 weeks. Of the 203 patients randomised to receive chemotherapy who had IRC-assessed RECIST 1.1- defined disease progression, 150 (73.9%) patients crossed over to treatment with cemiplimab. Assessment of tumour status was performed every 9 weeks. The 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 5.

Table 5 - Summary of baseline patient and disease characteristics in the ITT population

	Cemiplimab N=356	**Chemotherapy N=354**
Patient characteristics		
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 (%)	308 (87)	305 (86)
ECOG performance status n (%)		
0	96 (27)	96 (27)
1	260 (73)	258 (73)
History of brain metastasis (%)	12	11

	Cemiplimab N=356	Chemotherapy N=354
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)

In the pre-specified population with PD-L1 ≥ 50%, baseline patient and disease characteristics were consistent with those in the ITT population.

The study demonstrated statistically significant improvement in OS and PFS for patients randomised to cemiplimab as compared with chemotherapy. In the ITT population, the median duration of response was 21 months (range: 1.9 – 23.3 months) in the cemiplimab group and 6 months (range 1.3 – 16.5 months) in the chemotherapy group. Median duration of follow-up was 13.1 months in the cemiplimab group and 13.1 months in the chemotherapy group.

Efficacy results for the ITT and the pre-specified population with PD-L1 ≥ 50% are presented in Table 6, and Figure 2, Figure 3, Figure 4, and Figure 5.

Table 6 - Efficacy results from study 1624 in non-small cell lung cancer

	Intent-to-treat (ITT) population (N=710)		Pre-specified PD-L1 ≥ 50% population (N=563)	
Efficacy endpoints	**Cemiplimab 350 mg every 3 weeks N=356**	**Chemotherapy N=354**	**Cemiplimab 350 mg every 3 weeks N=283**	**Chemotherapy N=280**
Overall survival (OS)				
Number of deaths (%)	108 (30.3)	141 (39.8)	70 (24.7)	105 (37.5)
Median in months (95% CI)[a]	22.1 (17.7, NE)	14.3 (11.7, 19.2)	NR (17.9, NE)	14.2 (11.2, 17.5)
Hazard ratio (95% CI)[b]	0.68 (0.53, 0.87)		0.57 (0.42, 0.77)	
p-Value[c]	0.0022		0.0002	
Progression-free survival (PFS)				
Number of events (%)	201 (56.5)	262 (74.0)	147 (51.9)	197 (70.4)
Median in months (95% CI)[a]	6.2 (4.5, 8.3)	5.6 (4.5, 6.1)	8.2 (6.1, 8.8)	5.7 (4.5, 6.2)
Hazard ratio (95% CI)[b]	0.59 (0.49, 0.72)		0.54 (0.43, 0.68)	
p-Value[c]	<0.0001		<0.0001	
Objective response rate (%)[d,e]				

	Intent-to-treat (ITT) population (N=710)		Pre-specified PD-L1 ≥ 50% population (N=563)	
ORR (95% CI)	36.5 (31.5, 41.8)	20.6 (16.5, 25.2)	39.2 (33.5, 45.2)	20.4 (15.8, 25.6)
Complete response (CR) rate	3.1	0.8	2.1	1.1
Partial response (PR) rate	33.4	19.8	37.1	19.3

[a.] Based on Kaplan-Meier method
[b.] Based on stratified proportional hazards model
[c.] Based on a two-sided p-value.
[d.] Not a pre-specified endpoint in the 563 pre-specified population with PD-L1 ≥ 50%
[e.] Based on Clopper-Pearson exact confidence interval

Figure 2 - Kaplan-Meier curve for OS in the ITT population

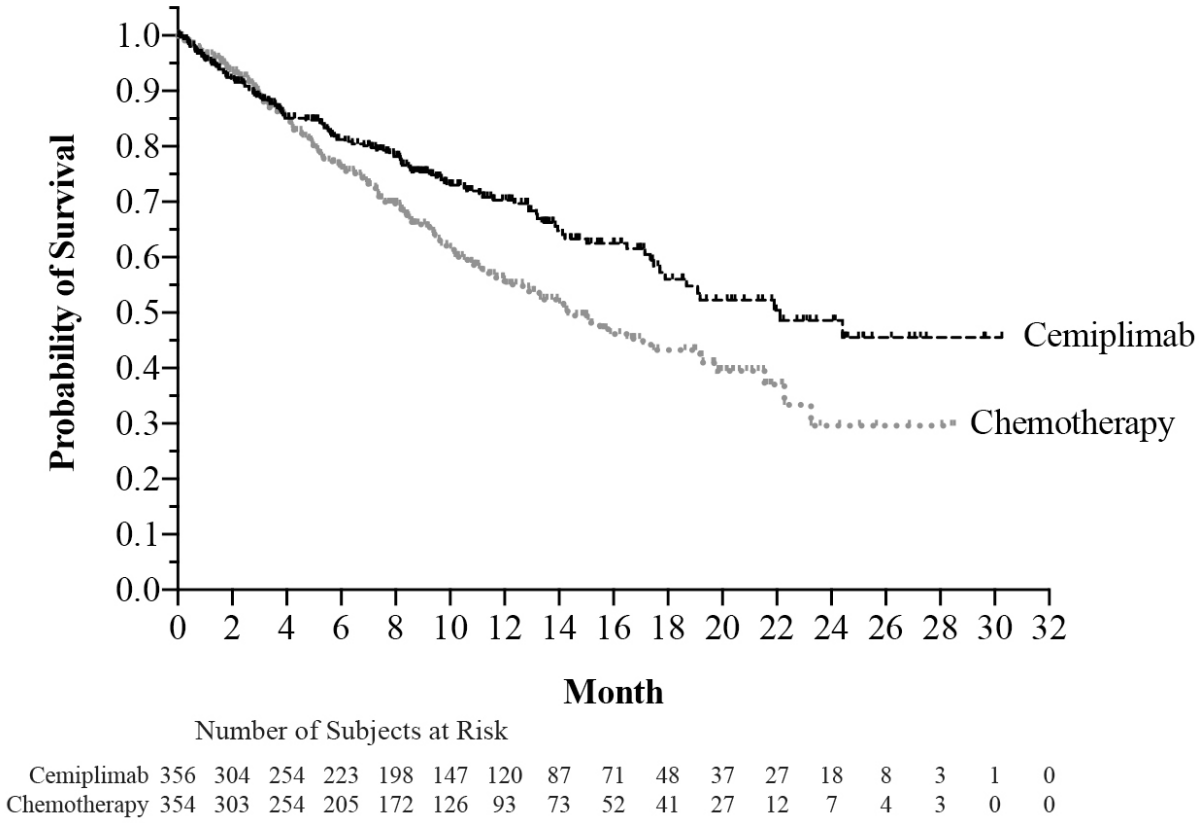
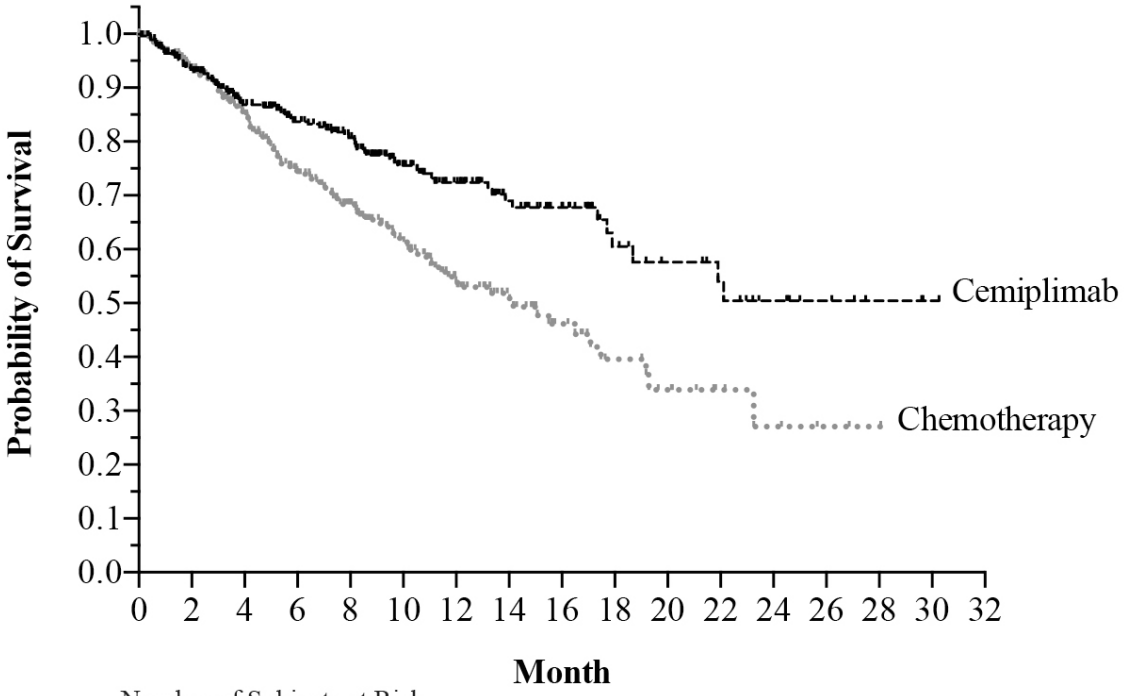


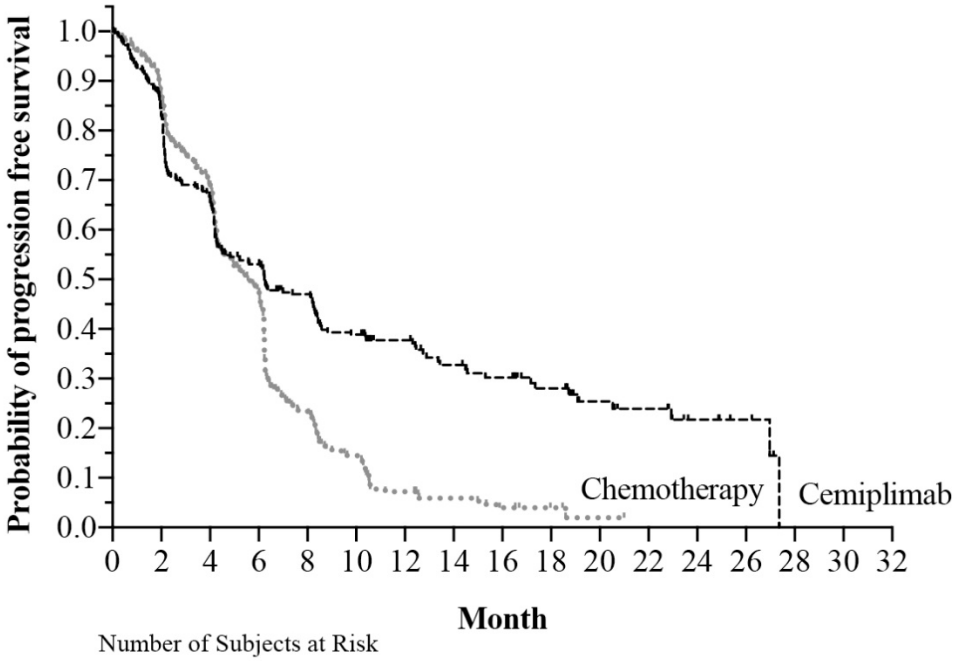
Figure 3 - Kaplan-Meier curve for OS in the pre-specified PD-L1 ≥ 50% population



Number of Subjects at Risk

Cemiplimab	283	244	203	177	154	108	83	55	42	24	18	15	10	6	3	1	0
Chemotherapy	280	239	198	153	125	87	57	41	25	15	11	6	4	2	1	0	0

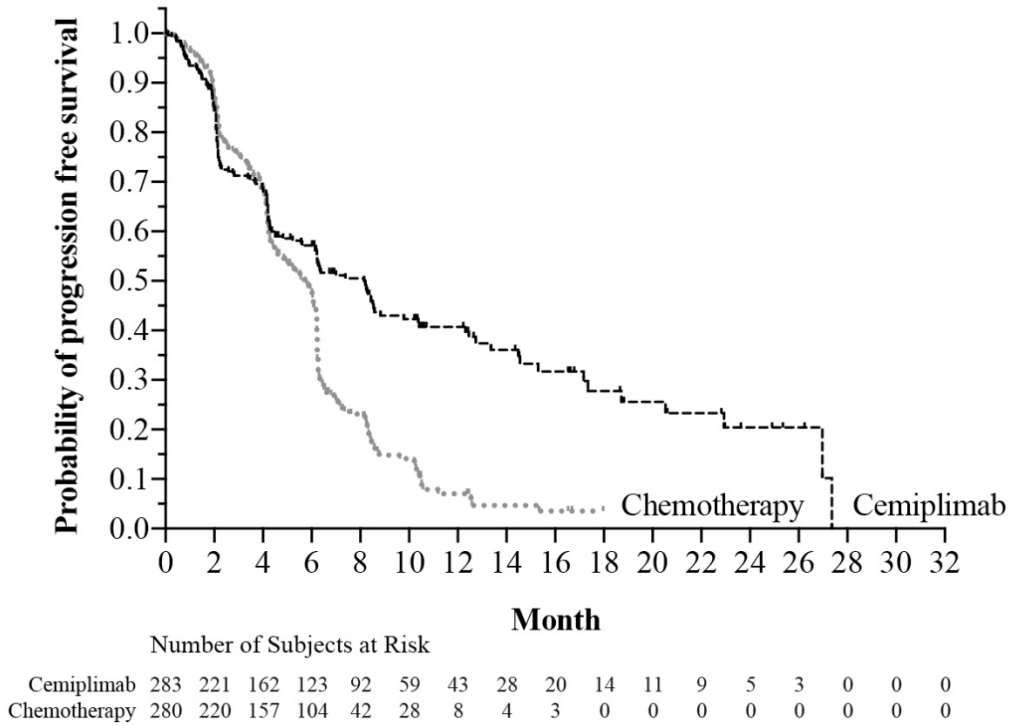
Figure 4 - Kaplan-Meier curve for PFS in the ITT population



Number of Subjects at Risk

Cemiplimab	356	278	202	149	115	77	61	42	34	26	17	13	7	4	0	0	0
Chemotherapy	354	280	204	135	58	30	13	9	6	3	1	0	0	0	0	0	0

Figure 5 - Kaplan-Meier curve for PFS in the pre-specified PD-L1 ≥ 50% population



First-line treatment of NSCLC with LIBTAYO in combination with platinum-based chemotherapy

The efficacy and safety of LIBTAYO in combination with platinum-based chemotherapy was evaluated in Study 16113, a randomised, multi-centre, 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 tumour PD-L1 expression status and who had not previously received systemic treatment for metastatic NSCLC.

Patients with EGFR, ALK or ROS1 genomic tumour 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 randomisation. Radiological confirmation of stability or response was not required.

Randomisation 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 randomised (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.

Treatment with LIBTAYO and chemotherapy or placebo and chemotherapy continued until RECIST 1.1-defined progressive disease, unacceptable toxicity, or 108 weeks. Assessment of tumour 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).

The study population characteristics were: median age of 63 years (25 to 82 years), 41% age 65 or older; 85.9% male; 85.6% White, 14.4% Asian; an ECOG PS 0 and 1 in 16.3% and 83% respectively; 85.6% had metastatic disease and 14.4% had stage IIIB or IIIC disease and were not candidates for surgical resection or definitive chemoradiation per investigator assessment; 57.4% had non-squamous and 42.6% had squamous histology; and 7.7% had history of treated brain metastases at baseline.

For the primary analysis (Table 7), the median duration of follow up for cemiplimab and chemotherapy arm was 16.3 months, and 16.7 months for placebo and chemotherapy arm. The overall median duration of exposure was 38.45 weeks (range: 1.4 to 102.6 weeks) for cemiplimab/chemotherapy and 21.30 weeks (range: 0.6 to 95.0 weeks) for placebo/chemotherapy. At the time of data cut off, 224 (71.8%) patients had been treated with cemiplimab for ≥24 weeks and 119 (38.1%) patients have been treated for ≥48 weeks.

The study demonstrated a statistically significant improvement in OS for patients randomised to LIBTAYO in combination with chemotherapy compared with placebo in combination with chemotherapy.

Efficacy results are presented in Table 7 and Figure 6.

Table 7 - Efficacy Results for Study 16113 in Non-Small Cell Lung Cancer

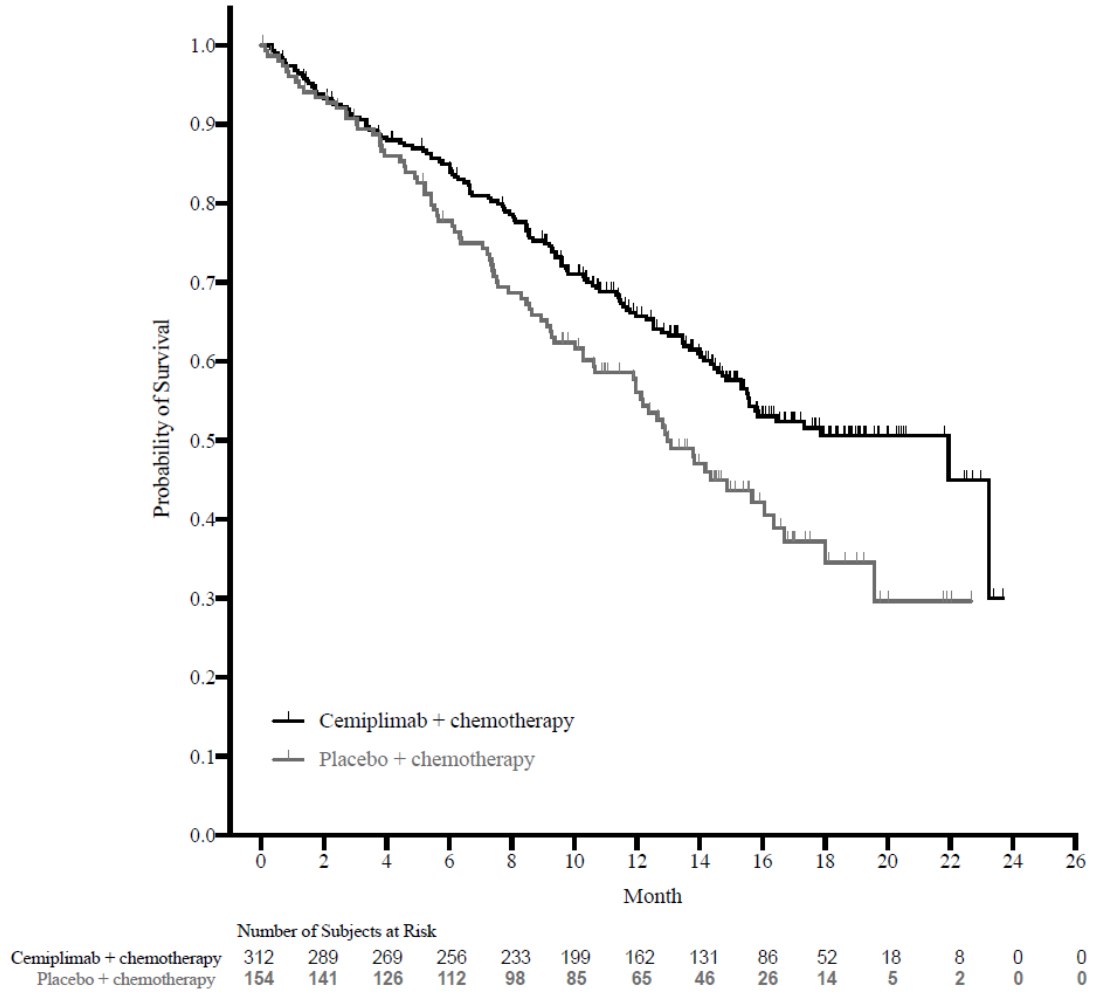
Endpoints[a]	LIBTAYO and Chemotherapy N=312	Placebo and Chemotherapy N=154
Overall Survival (OS)		
Deaths, n (%)	132 (42)	82 (53)
Median in months (95% CI)[b]	21.9 (15.5, NE)	13.0 (11.9, 16.1)
Hazard ratio (95% CI)[c]	0.71 (0.53, 0.93)	
p-value[d]	0.0140	
Progression-free Survival (PFS)		
Events, n (%)	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
p-value[d]	<0.0001	
Duration of Response (DOR)		
Median in months[b] (range)	15.6 (1.7, 18.7+)	7.3 (1.8, 18.8+)

Endpoints[a]	LIBTAYO and Chemotherapy N=312	Placebo and Chemotherapy N=154
Patients with DOR > 6 months[b], %	87	54

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. Based on a two-sided p-value
e. Clopper-Pearson exact confidence interval

Figure 6 - OS in Study 16113 in NSCLC



In a subgroup analysis relative to chemotherapy, OS benefit was shown in patients treated with LIBTAYO in combination with chemotherapy with squamous histology (median OS 21.9 in the cemiplimab plus chemotherapy group vs. 13.8 in the chemotherapy group, HR [95% CI] 0.557 [0.370, 0.840], n=200) and in patients with non-squamous histology (median OS 15.8 in the cemiplimab plus chemotherapy group vs. 13.0 in the chemotherapy group, HR [95% CI] 0.785 [0.539, 1.143], n=266).

Efficacy and PD-L1 status

Efficacy by PD-L1 status is shown in Table 8.

Table 8 - Efficacy Results by PD-L1 Expression in Study 16113

Endpoint	cemiplimab in combination with chemotherapy	Chemotherapy	cemiplimab in combination with chemotherapy	Chemotherapy	cemiplimab in combination with chemotherapy	Chemotherapy
	PD-L1 expression <1%		**PD-L1 expression 1-49%**		**PD-L1 expressions ≥ 50%**	
OS, Number of deaths (%)	54/95 (56.8%)	27/44 (61.4%)	40/114 (35.1%)	31/61 (50.8%)	38/103 (36.9%)	24/49 (49%)
Median OS (months)	12.8	14.2	21.9	12.1	17.9	13.8
OS Hazard ratio [a] (95% CI)	1.01 (0.63, 1.60)		0.52 (0.32, 0.83)		0.61 (0.37, 1.02)	
PFS, Number of events	70/95 (73.7%)	36/44 (81.8%)	77/114 (67.5%)	50/61 (82.0%)	57/103 (55.3%)	36/49 (73.5%)
Median PFS (months)	6.2	4.4	8.2	5.5	12.5	5.0
PFS Hazard ratio [a] (95% CI)	0.76 (0.51, 1.15)		0.47 (0.33, 0.68)		0.47 (0.31, 0.72)	
ORR %	32.6%	22.7%	43.0%	19.7%	53.4%	26.5%

[a.] Based on unstratified proportional hazards model

Table 9 - Follow up Overall Survival (12 months after primary analysis)[a]

	Deaths (n)		**mOS (months)**		**HR (95% CI)**
	Cemiplimab in combination with chemotherapy	Chemotherapy	Cemiplimab in combination with chemotherapy	Chemotherapy	
OS (n=466)	180/312	111/154	21.1	12.9	0.645 (0.507, 0.820)
PD-L1 <1%	66/95	34/44	12.8	14.2	0.939 (0.619, 1.423)
PD-L1 1-49%	62/114	43/61	23.2	12.0	0.496 (0.335, 0.735)
PD-L1 ≥50%	52/103	24/49	23.5	14.4	0.559 (0.362, 0.862)

[a.] Based on protocol-specified final OS analysis

BCC

The efficacy and safety of cemiplimab in patients with advanced basal cell carcinoma (BCC) [unresectable locally advanced (laBCC) or metastatic (nodal or distant) (mBCC)] who had

progressed on hedgehog pathway inhibitor (HHI) therapy, were intolerant of prior HHI therapy, or had no better than stable disease (SD) after 9 months on HHI therapy (exclusive of treatment breaks), were evaluated in Study 1620, an open-label, multi-centre, non-randomised 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 cemiplimab 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). Secondary efficacy endpoints included ORR and DOR by investigator assessment (IA), progression free survival (PFS), overall survival (OS), complete response (CR) by ICR, time to tumour response (TTR), disease control rate (DCR), durable DCR by ICR, EORTC QLQ-C30 and Skindex-16 scores. For patients with mBCC 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 (laBCC and mBCC), ORR was determined by a composite endpoint that integrated ICR assessments of radiologic data (RECIST 1.1) and digital medical photography (WHO criteria).

A total of 138 patients with advanced BCC were included in the efficacy analysis of Study 1620. Of these, 39% had mBCC and 61% had laBCC. See Table 10 for a summary of baseline patient and disease characteristics

Table 10 - Summary of baseline patient characteristics and prior treatments in Study 1620

	mBCC N=54	**laBCC N=84**
Patient characteristics		
Median age years (Range)	63.5 (38 – 90)	70.0 (42 – 89)
<65	27 (50%)	31 (37%)
≥65	27 (50%)	53 (63%)
Gender: Male	38 (70%)	56 (67%)
Race: White	47 (87%)	57 (68%)
ECOG performance status		
0	36 (67%)	51 (61%)
1	18 (34%)	33 (39%)
Prior treatments		
Prior cancer-related surgery		
Patients with at least 1 prior cancer-related surgery, n (%)	46 (85%)	70 (83%)
Patients with >3 prior cancer-related surgeries, n (%)	15 (28%)	29 (35%)

	mBCC N=54	laBCC N=84
Median number of prior cancer-related surgeries (Range)	2.0 (1 – 8)	3.0 (1 - 43)
Prior anti-cancer radiotherapy		
Patients with at least 1 prior anti-cancer radiotherapy, n (%)	32 (59%)	42 (50%)
Median number of prior anti-cancer radiotherapy regimens (Range)	1.0 (1 - 4)	1.0 (1 - 6)
Prior treatment with a HHI[a]	54 (100%)	84 (100%)
Prior treatment with both vismodegib and sonidegib (as separate lines of therapy), n (%)	7 (13%)	9 (11%)
Reason for discontinuation of HHI		
Disease progression/lack of response[b], n (%)	46 (85%)	63 (75%)
Intolerance to HHI therapy, n (%)	8 (14.8%)	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 c. Eight out of 1089 (79%) patients had lack of response		

The median time to response was 4.0 months (range 2.0 to 10.5 months) for the mBCC group, 4.3 months (range: 2.1 to 21 months) for the laBCC and 4.2 months overall (range: 2.0 to 21.4 months).

Forty patients (29.0%) with advanced BCC had complete response (CR) or partial response (PR).

ORR and PFS endpoints evaluated by investigator assessment (IA) were consistent with the independent central review results (ICR). Response rates were similar regardless of the reason for discontinuation of prior HHI therapy.

Efficacy results are presented in Table 11.

Table 11 - Efficacy results for Study 1620 in basal cell carcinoma

Efficacy Endpoints	mBCC N=54	laBCC N=84
	ICR	ICR
Median Duration of Follow-Up (months) (Range)	8.4 (1.5 - 36.2)	15.9 (0.5 – 39.7)
Best Overall Response (BOR)[a]		
Objective response rate (ORR: CR+ PR) (95% CI)	13 (24.1%) (13.5, 37.6)	27 (32.1%)[b] (22.4, 43.2)
Complete response (CR) rate[b] (95 % CI)	1 (1.9%) (0.0, 9.9)	6 (7.1%) (2.7, 14.9)
Partial response (PR) rate	12 (22.2%)	21 (25.0%)
Stable disease (SD) rate	16 (29.6%)	40 (47.6%)

Efficacy Endpoints	mBCC N=54	laBCC N=84
Progressive disease (PD) rate	16 (29.6%)	9 (10.7%)
Duration of Response (DOR)		
Median[c] (months) (95% CI)	16.7 (9.8, NE)	NR (15.5, NE)
Range (observed) (months)	4.8 - 25.8+	2.1 – 36.8+
Patients with DOR ≥ 6 months, % (95% CI)[c]	100% (NE, NE)	88.5% (68.4, 96.1)
Patients with DOR ≥12 months, % (95% CI)[c]	53.5% (21.2, 77.7)	83.8% (62.2, 93.6)
Time to Response (TTR)		
Median (months) (Range)	4.0 (2.0 - 10.5)	4.3 (2.1 - 21.4)

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

a. Non-evaluable and non-CR/non-PD patients are not presented in BOR results.
b. Locally advanced BCC patients in Study 1620 required biopsy to confirm complete response.
c. Based on Kaplan Meier estimates.

Efficacy and PD-L1 status

Clinical activity was observed regardless of tumour PD-L1 expression status.

Elderly population

No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

LIBTAYO as monotherapy

Of the 1281 patients treated with cemiplimab monotherapy in clinical studies, 52.2% (669/1281) were less than 65 years, 25.9% (332/1281) were 65 to less than 75 years, and 21.9% (280/1281) were 75 years or older. Grade ≥3 adverse events occurred in 42.2% (140/ 332) of patients 65 to less than 75 years and 50.7% (142/280) of patients 75 years or older.

In the 193 advanced CSCC patients from Study 1540 Groups 1 to 3 in the efficacy analysis, the ORR by ICR (95% CI) was 42.9% (28.8%, 57.8%) in 49 of 193 patients less than 65 years, 53.0% (40.3%, 65.4%) in 66 of 193 patients 65 to less than 75 years, and 44.9% (33.6%, 56.6%) in 78 of 193 patients 75 years or older.

In the 710 advanced NSCLC patients in the efficacy analysis, the median OS (95% CI) was 24.4 months (17.3, NE) in the cemiplimab group and 17.1 months (12.1, 23.3) in the chemotherapy group in patients less than 65 years, was not reached (13.4, NE) in the cemiplimab group and 14.3 months (10.6, 22.3) in the chemotherapy group in patients 65 to less than 75 years, and 19.2 months (17.7, NE) in the cemiplimab group and 8.5 months (5.4, 14.2) in the chemotherapy group in patients 75 years or older. The median PFS by ICR (95% CI) was 6.2 months (4.3, 8.5) in the cemiplimab group and 5.6 months (4.2, 6.1) in the

chemotherapy group in patients less than 65 years, 6.2 months (4.2, 8.2) in the cemiplimab group and 6.2 months (4.4, 6.2) in the chemotherapy group in patients 65 to less than 75 years, and 8.4 months (4.3, 19.1) in the cemiplimab group and 4.9 months (3.4, 6.2) in the chemotherapy group in patients 75 years or older.

In the 138 advanced BCC patients in the efficacy analysis, the objective response rate (ORR) by Independent Central Review (ICR) (95% CI) was 29.3% (18.1, 42.7) in 58 of 138 patients less than 65 years, 27.0% (13.8, 44.1) in 37 of 138 patients 65 to less than 75 years, and 30.2% (17.2, 46.1) in 43 of 138 patients 75 years or older.

LIBTAYO in combination with platinum-based chemotherapy

Among 466 advanced NSCLC patients in the efficacy analysis, 312 were treated with LIBTAYO and chemotherapy and 154 were treated with chemotherapy. Of the 312 patients receiving LIBTAYO and 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 40% (44/110) of patients 65 to less than 75 years and 55.6% (10/18) of patients 75 years or older.

The median OS (95% CI) was 21.9 months (15.6, NE) in the LIBTAYO and chemotherapy group and 12.6 months (9.3, 14.9) in the chemotherapy group in patients less than 65 years, 15.5 months (13.7, NE) in the LIBTAYO and chemotherapy group and 18 months (10.3, NE) in the chemotherapy group in patients 65 to less than 75 years, and was not reached (6, NE) in the LIBTAYO and chemotherapy group and 10.3 months (3.6, NE) in the chemotherapy group in patients 75 years or older.

5.2 PHARMACOKINETIC PROPERTIES

Concentration data from 1063 patients with various solid tumours who received cemiplimab were combined in a population PK analysis.

At 350 mg Q3W, the mean cemiplimab concentrations at steady-state ranged between a C_{trough} of 59 mg/L and a concentration at end of infusion (C_{max}) of 171 mg/L. 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.

Absorption

Cemiplimab is administered via the intravenous route and hence is completely bioavailable.

Distribution

Cemiplimab is primarily distributed in the vascular system with a volume of distribution at steady state (VSS) of 5.9 litres.

Metabolism

Specific metabolism studies were not conducted because cemiplimab is a protein. Cemiplimab is expected to degrade to small peptides and individual amino acids.

Excretion

Clearance of cemiplimab is linear at doses of 1 mg/kg to 10 mg/kg Q2W. Cemiplimab clearance after the first dose is approximately 0.25 l/day. The total clearance appears to decrease by approximately 11% over time, resulting in a steady state clearance (CL_{ss}) of 0.22 l/day; the decrease in CL is not considered clinically relevant. The within dosing interval half-life at steady state is 22 days.

Linearity/non-linearity

At the dosing regimens of 1 mg/kg to 10 mg/kg every two weeks, pharmacokinetics of cemiplimab were linear and dose proportional, suggesting saturation of the systemic target-mediated pathway.

Special populations

A population PK analysis suggests that the following factors have no clinically significant effect on the exposure of cemiplimab: age, gender, body weight, race, cancer type, albumin level, renal impairment, and mild to moderate hepatic impairment.

Paediatric Population

Pharmacokinetics in paediatric patients were estimated based on an updated population PK model containing PK data from 1227 adults with various solid tumours who received intravenous cemiplimab monotherapy pooled with PK data from 55 paediatric to young adult patients aged 1 to 24 years who received cemiplimab intravenously at 3 mg/kg or 4.5 mg/kg every 2 weeks, with or without radiotherapy. The exposure in paediatric patients was comparable to that in adults receiving cemiplimab intravenously 350 mg every 3 weeks, with slightly higher exposure seen for paediatric patients 0 to less than 12 years old receiving 4.5 mg/kg every 2 weeks. Overall, the lowest predicted median $C_{trough,ss}$ and highest $C_{max,ss}$ for all paediatric patients was within the observed range for adult patients receiving 350 mg intravenously every 3 weeks.

Renal impairment

The effect of renal impairment on the exposure of cemiplimab was evaluated by a population PK analysis in patients with mild (CL_{cr} 60 to 89 mL/min; n= 396), moderate (CL_{cr} 30 to 59 mL/min; n= 166), or severe (CL_{cr} 15 to 29 mL/min; n= 7) renal impairment. No clinically important differences in the exposure of cemiplimab were found between patients with renal impairment and patients with normal renal function. Cemiplimab has not been studied in patients with CL_{cr} <21 mL/min (see Section 4.2).

Hepatic impairment

The effect of hepatic impairment on the exposure of cemiplimab was evaluated by population PK analysis in patients with mild hepatic impairment (n=22) (total bilirubin greater than 1.0

to 1.5 times the upper limit of normal [ULN] and any aspartate aminotransferase [AST]) and patients with moderate hepatic impairment (n=3) (total bilirubin >1.5 times ULN up to 3.0 times ULN) and any AST; no clinically important differences in the exposure of cemiplimab were found between patients with mild to moderate hepatic impairment and patients with normal hepatic function. Cemiplimab has not been studied in patients with severe hepatic impairment. There are insufficient data in patients with severe hepatic impairment for dosing recommendations (see Section 4.2).

5.3 PRECLINICAL SAFETY DATA

No studies have been performed to test the potential of cemiplimab for carcinogenicity or genotoxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine

Histidine monohydrochloride monohydrate

Sucrose

Proline

Polysorbate 80

Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 SHELF LIFE

Unopened vial

48 months

After opening

Once opened, the medicinal product should be diluted and infused immediately (see Section 6.6 for instructions on dilution of the medicinal product before administration).

After preparation of infusion

Libtayo does not contain a preservative.

Once prepared, to reduce microbiological hazard 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 10 days from the time of infusion preparation to the end of infusion. Do not freeze. Allow the diluted solution to come to room temperature prior to administration.

If diluted solution is not administered immediately, in use storage conditions prior to use are the responsibility of the user.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vial

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original carton in order to protect from light.

For storage conditions after first opening or dilution of the medicinal product, see Section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

LIBTAYO is provided in a 10 mL clear Type 1 glass vial, with a grey chlorobutyl stopper with FluroTec coating and seal cap with a flip-off button.

Each carton contains 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Preparation and administration

- Visually inspect medicinal product for particulate matter and discoloration prior to administration. LIBTAYO is a 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 a few translucent to white particles.
- Do not shake the vial.

- Withdraw 7 mL (350 mg) from the vial of LIBTAYO and transfer into an intravenous infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection. Mix the diluted solution by gentle inversion. Do not shake the solution. The final concentration of the diluted solution should be between 1 mg/mL to 20 mg/mL.
- LIBTAYO is administered by intravenous infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding, in-line or add-on filter (0.2 micron to 5 micron pore size).
- Do not co-administer other medicinal products through the same infusion line.

LIBTAYO is for single use only. In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

17 July 2020

10 DATE OF REVISION

26 September 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of pancreatitis as Other Immune-mediated adverse reaction.
4.8	Addition of pancreatitis as Gastrointestinal disorder in Table 2 and description of Other Immune-mediated adverse reactions.