▼This medicinal product is subject to additional monitoring in Australia due to provisional approval. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/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 has **provisional approval** in Australia 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.

The decision to approve this indication has been made on the basis of objective response rate (ORR) and duration of response from single arm clinical studies. The sponsor is required to submit further clinical data to confirm the clinical benefit of the medicine.

Basal Cell Carcinoma

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

LIBTAYO as monotherapy has **provisional approval** in Australia for the treatment of adult patients with metastatic BCC (mBCC) previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.

The decision to approve the mBCC indication has been made on the basis of objective response rate (ORR) and duration of response from a single arm clinical study. The sponsor is required to submit further clinical data to confirm the clinical benefit of the medicine.

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.

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 LIBTAYO 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-Related 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

Adverse Reaction[a]	Severity[b]	Dose modification	Additional intervention
Immune-Related Adverse Reactions			
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 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,	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper

Adverse Reaction[a]	Severity[b]	Dose modification	Additional intervention
Immune-Related Adverse Reactions			
	Grade 3 or 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	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Immune-related skin reaction or other immune-related 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-related 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-related 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

Adverse Reaction[a]	Severity[b]	Dose modification	Additional intervention
Immune-Related Adverse Reactions			
		Resume LIBTAYO if other immune-related adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	
	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-related adverse reaction Persistent Grade 2 or 3 immune-related 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
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	

Adverse Reaction[a]	Severity[b]	Dose modification	Additional intervention
Immune-Related Adverse Reactions			

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 the age of 18 years have not been established. No data are available.

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-related adverse reactions

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

Immune-related 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 closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions, as outlined in the sections below. Immune-related adverse reactions should be managed with cemiplimab treatment modifications, hormone replacement therapy (if clinically indicated), and corticosteroids. For suspected immune-related adverse reactions, patients should be evaluated to confirm an immune-related 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-related pneumonitis

Immune-related 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-related 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-related colitis

Immune-related 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-related hepatitis

Immune-related 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-related endocrinopathies

Immune-related 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-related skin adverse reactions

Immune-related 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-related nephritis

Immune-related nephritis, defined as requiring use of corticosteroids with no clear alternate aetiology, 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-related adverse reactions

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

Evaluate suspected immune-related adverse reactions to exclude other causes. Patients should be monitored for signs and symptoms of immune-related 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.

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-related 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).

The safety of cemiplimab has been evaluated in 1078 patients with advanced solid malignancies who received cemiplimab in 4 clinical studies. These studies included 219 patients with advanced CSCC, 132 patients with advanced BCC, 355 patients with advanced NSCLC and 372 patients with other solid tumours. A total of 810 patients received cemiplimab monotherapy and 268 received combination therapy. The median duration of exposure to cemiplimab was 25 weeks (range: 2 days to 144 weeks).

Immune-related adverse reactions occurred in 20.1% of patients treated with cemiplimab in clinical trials including Grade 5 (0.5%), Grade 4 (0.9%), Grade 3 (5.3%) and Grade 2 (10.5%). Immune-related adverse reactions led to permanent discontinuation of cemiplimab in 4.0% of patients. The most common immune-related adverse reactions were hypothyroidism (6.9%), pneumonitis (3.0%), hyperthyroidism (2.9%), hepatitis (1.9%), colitis (1.8%) and immune-related skin adverse reactions (1.8%) (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 30.0% of patients. Adverse events led to permanent discontinuation of cemiplimab in 7.5% 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 treated with cemiplimab

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	10.3	0.3	0
Urinary tract infection	Common	6.4	1.2	0
Blood and lymphatic system disorders				
Anaemia	Very Common	13.8	4.3	0
Immune system disorders				
Infusion-related reaction	Common	3.6	<0.1	0
Sjogren's syndrome	Uncommon	0.2	0	0
Immune thrombocytopenic purpura	Rare	<0.1	0	0
Vasculitis	Rare	<0.1	0	0
Endocrine disorders				
Hypothyroidism[b]	Common	6.9	<0.1	0
Hyperthyroidism	Common	2.9	<0.1	0
Adrenal insufficiency	Uncommon	0.5	0.3	0
Thyroiditis[c]	Uncommon	0.5	0	0
Type 1 diabetes mellitus[d]	Uncommon	0.4	0.4	0
Hypophysitis	Uncommon	0.3	0.2	0
Nervous system disorders				
Headache	Common	8.8	0.5	0
Peripheral neuropathy[e]	Common	1.6	<0.1	0

System organ class preferred term	Grades 1-5 (Frequency category)	Grades 1-5 (%)	Grades 3-4 (%)	Grade 5 (%)
Meningitis[f]	Uncommon	0.2	0.2	0
Encephalitis[g]	Uncommon	0.2	0.2	0
Myasthenia gravis	Uncommon	0.2	0	0
Paraneoplastic encephalomyelitis	Rare	<0.1	<0.1	<0.1
Guillain-Barre syndrome	Rare	<0.1	<0.1	0
Central nervous system inflammation	Rare	<0.1	0	0
Chronic inflammatory demyelinating polyradiculoneuropathy	Rare	<0.1	0	0
Eye disorders				
Keratitis	Rare	<0.1	0	0
Cardiac disorders				
Myocarditis[h]	Uncommon	0.5	0.4	<0.1
Pericarditis[i]	Uncommon	0.2	0.2	0
Vascular disorders				
Hypertension[j]	Common	4.8	1.9	0
Metabolism and nutrition disorders				
Decreased appetite	Very common	14.5	0.6	0
Respiratory, thoracic and mediastinal disorders				
Cough[k]	Very common	13.1	0.2	0
Dyspnoea[l]	Very common	10.9	1.5	<0.1
Pneumonitis[m]	Common	3.8	1.1	0.2
Gastrointestinal disorders				
Nausea	Very common	17.4	0.4	0
Diarrhoea	Very common	16.7	0.6	0
Constipation	Very common	13.7	0.4	0
Abdominal pain[n]	Very common	11.2	0.8	0
Vomiting	Common	9.5	0.5	0
Stomatitis	Common	2.1	0	0
Colitis[o]	Common	1.9	0.8	0
Hepatobiliary disorders				
Hepatitis[p]	Common	1.9	1.1	<0.1
Skin and subcutaneous skin disorders				
Rash[q]	Very common	21.9	1.8	0
Pruritus[r]	Very common	11.4	<0.1	0

System organ class preferred term	Grades 1-5 (Frequency category)	Grades 1-5 (%)	Grades 3-4 (%)	Grade 5 (%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[s]	Very Common	32.2	2.1	0
Arthritis[t]	Uncommon	0.8	<0.1	0
Muscular weakness	Uncommon	0.4	0	0
Myositis	Rare	<0.1	0	0
Polymyalgia rheumatica	Rare	< 0.1	0	0
Renal and urinary disorders				
Nephritis[u]	Common	1.1	0.2	<0.1
General disorders and administration site conditions				
Fatigue[v]	Very common	32.5	2.4	0
Investigations				
Aspartate aminotransferase increased	Common	4.0	0.8	0
Alanine aminotransferase increased	Common	4.0	0.6	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	0.6	0	0
Transaminases increased	Uncommon	0.5	0.2	0
Blood bilirubin increased	Uncommon	0.5	<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, respiratory tract infection, nasopharyngitis, sinusitis, pharyngitis, rhinitis, and viral upper respiratory tract infection. b. Hypothyroidism includes hypothyroidism and immune-mediated hypothyroidism. c. Thyroiditis includes autoimmune thyroiditis and thyroiditis. d. Type 1 diabetes mellitus includes diabetes mellitus, diabetic ketoacidosis and type 1 diabetes mellitus. e. Peripheral neuropathy includes peripheral neuropathy, peripheral sensory neuropathy, polyneuropathy, neuritis, paraesthesia, and peripheral motor neuropathy. f. Meningitis includes meningitis and aseptic meningitis. g. Encephalitis includes encephalitis and noninfective encephalitis. h. Myocarditis includes autoimmune myocarditis, immune-mediated myocarditis, and myocarditis. i. Pericarditis includes autoimmune pericarditis and pericarditis. j. Hypertension includes hypertension and hypertensive crisis. k. Cough includes cough, productive cough, and upper-airway cough syndrome. l. Dyspnoea includes dyspnoea and dyspnoea exertional. m. Pneumonitis includes pneumonitis, immune-mediated pneumonitis, interstitial lung disease. n. Abdominal pain includes abdominal pain, upper abdominal pain, abdominal discomfort, lower abdominal pain, and gastrointestinal pain. o. Colitis includes colitis, enterocolitis, immune-mediated enterocolitis, and autoimmune colitis. p. Hepatitis includes autoimmune hepatitis, hepatocellular injury, immune-mediated hepatitis, hepatic failure, hepatitis, and hepatotoxicity. q. Rash includes rash, dermatitis, urticaria, rash maculo-papular, erythema, rash erythematous, rash pruritic, psoriasis, autoimmune dermatitis, dermatitis acneiform, dermatitis allergic, atopic dermatitis, dermatitis bullous, drug eruption, dyshidrotic eczema, lichen planus, skin reaction, dermatitis exfoliative, erythema multiforme, parapsoriasis, pemphigoid, rash macular, and rash papular. r. Pruritus includes pruritus and allergic pruritus. s. Musculoskeletal pain includes back pain, arthralgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, bone pain, myalgia, neck pain, spinal pain, musculoskeletal stiffness, and musculoskeletal discomfort. t. Arthritis includes arthritis and polyarthritis. u. Nephritis includes nephritis, toxic nephropathy, acute kidney injury, and renal failure. v. Fatigue includes fatigue, asthenia, and malaise.				

Description of selected adverse reactions

The selected adverse reactions described below are based on safety of cemiplimab in 1078 patients with advanced solid malignancies in four clinical studies.

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

Immune-related pneumonitis

Immune-related pneumonitis occurred in 32 (3.0%) of 1078 patients receiving cemiplimab, including 2 (0.2%) patients with Grade 5, 4 (0.4%) patients with Grade 4, 6 (0.6%) patients with Grade 3 pneumonitis. Immune-related pneumonitis led to permanent discontinuation of cemiplimab in 15 (1.4%) of 1078 patients. Among the 32 patients with immune-related pneumonitis, the median time to onset was 3.1 months (range: 7 days to 18 months) and the median duration of pneumonitis was 25.5 days (range: 5 days to 6.5 months). Twenty-eight of the 32 patients (87.5%) received high-dose corticosteroids for a median of 9 days (range: 1 day to 5.9 months). Resolution of pneumonitis had occurred in 17 (53.1%) of the 32 patients at the time of data cut-off.

Immune-related colitis

Immune-related diarrhoea or colitis occurred in 19~~7~~ (1.8%) of 1078 patients receiving cemiplimab including 8 (0.7%) with Grade 3 immune-related diarrhoea or colitis. Immune-related diarrhoea or colitis led to permanent discontinuation of cemiplimab in 4 (0.4%) of 1078 patients. Among the 19 patients with immune-related diarrhoea or colitis, the median time to onset was 3.7 months (range: 15 days to 15.5 months) and the median duration of immune-related diarrhoea or colitis was 2.0 months (range: 4 days to 10.0 months). Fourteen patients (73.7%) with immune-related diarrhoea or colitis received high-dose corticosteroids for a median of 29 days (range: 5 days to 5.2 months). Resolution of immune-related diarrhoea or colitis had occurred in 8 (42.1%) of the 19 patients at the time of data cut-off.

Immune-related hepatitis

Immune-related hepatitis occurred in 20 (1.9%) of 1078 patients receiving cemiplimab including 1 (<0.1%) patient with Grade 5, 2 (0.2%) patients with Grade 4, and 14 (1.3%) patients with Grade 3 immune-related hepatitis. Immune-related hepatitis led to permanent discontinuation of cemiplimab in 11 (1.0%) of 1078 patients. Among the 20 patients with immune-related hepatitis, the median time to onset was 2.5 months (range: 7 days to 22.5 months) and the median duration of hepatitis was 22.5 days (range: 8 days to 7.6 months). Eighteen (90.0%) patients with immune-related hepatitis received high-dose corticosteroids for a median of 24 days (range: 2 days to 3.1months). Resolution of hepatitis had occurred in 10 (50.0%) of the 20 patients at the time of data cut-off.

Immune-related endocrinopathies

Hypothyroidism occurred in 74 (6.9%) of 1078 patients receiving cemiplimab including 1 (<0.1%) patient with Grade 3 hypothyroidism. One patient discontinued cemiplimab due to hypothyroidism. Among the 74 patients with hypothyroidism, the median time to onset was 4.0 months (range: 15 days to 18.9 months) with a median duration of 6.9 months (range: 1 day to 23.3 months). Resolution of hypothyroidism had occurred in 6 (8.1%) of the 74 patients at the time of data cutoff.

Hyperthyroidism occurred in 31 (2.9%) of 1078 patients receiving cemiplimab including 1 (<0.1%) patient with Grade 3 and 8 (0.7%) patients with Grade 2 hyperthyroidism. No patient discontinued cemiplimab due to hyperthyroidism. Among the 31 patients with hyperthyroidism, the median time to onset was 2.1 months (range: 20 days to 23.8 months) and the median duration was 1.9 months (range: 9 days to 24.5 months). Resolution of hyperthyroidism had occurred in 16 (51.6%) of the 31 patients at the time of data cutoff.

Thyroiditis occurred in 5 (0.5%) of 1078 patients receiving cemiplimab including 2 (0.2%) patients with Grade 2 thyroiditis. No patient discontinued cemiplimab due to thyroiditis. Thyroiditis had not resolved in any patient at the time of data cutoff.

Adrenal insufficiency occurred in 5 (0.5%) of 1078 patients receiving cemiplimab including 3 (0.3%) patients with Grade 3, and 2 (0.2%) patients with Grade 2 adrenal insufficiency. One (<0.1%) of 1078 patients discontinued cemiplimab due to adrenal insufficiency. Among the 5 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: 4.6 months to

6.4 months). Three of the 5 patients (60%) 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 1078 patients receiving cemiplimab, including 2 (0.2%) patients with Grade 3 hypophysitis. One (<0.1%) of 1078 patients discontinued cemiplimab 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) with a median duration of 23 days (range: 9 days to 1.5 months). Two of the 3 patients (66.7%) were treated with corticosteroids. Hypophysitis had not resolved in any patient at the time of data cutoff.

Type 1 diabetes mellitus without an alternative aetiology occurred in 4 (0.4%) of 1078 patients including 3 (0.3%) patients with Grade 4 and 1 (<0.1%) patient with Grade 3 type 1 diabetes mellitus. Type 1 diabetes mellitus led to permanent discontinuation of cemiplimab in 1 (<0.1%) of 1078 patients. Among the 4 patients with type 1 diabetes mellitus, the median time to onset was 2.3 months (range: 28 days to 6.2 months). Type 1 diabetes had not resolved in any patient at the time of data cutoff.

Immune-related skin adverse reactions

Immune-related skin adverse reactions occurred in 19 (1.8%) of 1078 patients receiving cemiplimab including 10 (0.9%) patients with Grade 3 immune-related skin adverse reactions. Immune-related skin adverse reactions led to permanent discontinuation of cemiplimab in 2 (0.2%) of 1078 patients. Among the 19 patients with immune-related skin adverse reactions, the median time to onset was 1.2 months (range: 2 days to 17.0 months) and the median duration was 2.7 months (range: 13 days to 12.5 months). Thirteen patients (68.4%) with immune-related skin adverse reactions received high-dose corticosteroids for a median of 16 days (range: 4 days to 2.6 months). Resolution had occurred in 11 (57.9%) of 19 patients at the time of data cut-off.

Immune-related nephritis

Immune-related nephritis occurred in 6 (0.6%) of 1078 patients receiving cemiplimab including 1 (<0.1%) patient with Grade 5, and 2 (0.2%) patients with Grade 3 immune-related nephritis. Immune-related nephritis led to permanent discontinuation of cemiplimab in 2 (0.2%) of 1078 patients. Among the 6 patients with immune-related nephritis, the median time to onset was 2.2 months (range: 14 days to 5.6 months) and the median duration of nephritis was 22 days (range: 9 days to 1.6 months). Five (83.3%) patients with immune-related nephritis received high-dose corticosteroids for a median of 16 days (range: 3 days to 2.6 months). Resolution of nephritis had occurred in 5 (83.3%) of the 6 patients at the time of data cut-off.

Other immune-related adverse reactions

The following clinically significant, immune-related adverse reactions occurred at an incidence of less than 1% of 1078 patients treated with cemiplimab. The events were Grade 3 or less unless stated otherwise:

Nervous system disorders: Meningitis[a] (Grade 4), paraneoplastic encephalomyelitis (Grade 5), Guillain-Barre syndrome, central nervous system inflammation, chronic

inflammatory demyelinating polyradiculoneuropathy, encephalitis[b], myasthenia gravis, peripheral neuropathy[c]

Cardiac Disorders: Myocarditis[d], pericarditis[e]

Immune system disorders: Immune thrombocytopenic purpura

Vascular disorders: Vasculitis

Musculoskeletal and connective tissue disorders: Arthralgia, arthritis[f], muscular weakness, myalgia, myositis, polymyalgia rheumatica, Sjogren's syndrome

Eye disorders: Keratitis

Gastrointestinal disorders: Stomatitis

[a] includes meningitis and aseptic meningitis
[b] includes encephalitis and noninfective encephalitis
[c] includes neuritis and peripheral neuropathy
[d] includes autoimmune myocarditis and myocarditis
[e] includes autoimmune pericarditis and pericarditis
[f] includes arthritis and polyarthritis

Infusion-related reactions

Infusion-related reactions occurred in 89 (9.1%) of 1078 patients treated with cemiplimab including 2 (0.2%) patients with Grade 3 infusion-related reaction. Infusion-related reaction led to permanent discontinuation of cemiplimab in 3 (0.3%) patients. The most common symptoms of infusion-related reaction were nausea, pyrexia, vomiting, and rash. All patients recovered from the infusion-related reaction.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with cemiplimab. Approximately 2.2% of patients developed treatment-emergent antibodies to cemiplimab, with approximately 0.4% 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

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, monoclonal antibodies. ATC code: L01XC33.

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 trials

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 patients with mCSCC or laCSCC with a combined median duration of follow up time of 9.4 months total. Median duration of follow up was 16.5 months for the mCSCC 3 mg/kg every 2 weeks (Q2W) group, 9.3 months for the laCSCC 3 mg/kg Q2W group and 8.1 months for the mCSCC 350 mg every 3 weeks (Q3W) group.

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 or 350 mg Q3W for 54 weeks]. 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).

Results are presented from 193 patients in Study 1540. Of these 193 patients, 115 had mCSCC 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 (44.6%) and 1 (55.4%). Thirty-three and 7/10 per cent (33.7%) of patients had received at least 1 prior anti-cancer systemic therapy, 90.2% of patients had received prior cancer related surgery, and 67.9% of patients had received prior radiotherapy. Among patients with mCSCC, 76.5% had distant metastases, and 22.6% had only nodal metastases.

Efficacy results for Study 1540 are presented in Table 3.

Table 3 - Efficacy results: Study 1540 - metastatic CSCC by dosing group, locally advanced CSCC

Efficacy endpoints	mCSCC cemiplimab: 3 mg/kg Q2W (Group 1) (N = 59)	laCSCC cemiplimab: 3 mg/kg Q2W (Group 2) (N = 78)	mCSCC cemiplimab: 350 mg Q3W (Group 3) (N = 56)
	ICR	ICR	ICR
Confirmed objective response rate (ORR) [a]			
ORR	49.2%	43.6%	41.1%
95% CI for ORR	(35.9, 62.5)	(32.4, 55.3)	(28.1, 55.0)
Complete response (CR) [b]	16.9%	12.8%	5.4%
Partial response (PR)	32.2%	30.8%	35.7%
Stable disease (SD)	15.3%	35.9%	14.3%
Progressive disease (PD)	16.9%	11.5%	25.0%
Duration of response (DOR)			
Median[c] (months)	NR	NR	NR
Range (months)	(2.8-21.6+)	(1.9 – 24.2+)	(2.1-11.1+)
Patients with DOR ≥ 6 months	93.1%	67.6%	65.2%
Time to response (TTR)			
Median (months) range (min:max)	1.9 (1.7: 9.1)	1.9 (1.8: 8.8)	2.1 (2.0: 8.3)
Progression free survival (PFS) [a, c]			
6 months (95% CI)	65.8% (51.8, 76.7)	71.5% (58.9, 80.9)	59.3% (45.0, 71.0)
12 months (95% CI)	52.9% (39.0, 65.0)	58.1% (43.7, 70.0)	47.4% (29.6, 63.3)
Overall survival (OS)[a, c]			
12 months (95% CI)	81.3% (68.7, 89.2)	93.2% (84.4, 97.1)	76.1% (56.9, 87.6)

Efficacy endpoints	mCSCC cemiplimab: 3 mg/kg Q2W (Group 1) (N = 59)	laCSCC cemiplimab: 3 mg/kg Q2W (Group 2) (N = 78)	mCSCC cemiplimab: 350 mg Q3W (Group 3) (N = 56)
	ICR	ICR	ICR

Data cut-off was Sep 20, 2018 for Groups 1 and 3 patients, and Oct 10, 2018 for Group 2 patients.

CI: confidence interval; ICR: Independent Central Review; NR: Not Reached; +: Denotes ongoing at last assessment; Q2W: every 2 weeks; Q3W: every 3 weeks

a. In Groups 1, 2, and 3, median durations of follow-up were 16.5, 9.3, and 8.1 months, respectively.
b. Only includes patients with complete healing of prior cutaneous involvement; laCSCC patients in Study 1540 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. The relationship between PD-L1 status and efficacy was analysed post-hoc in patients with available tissue samples. Overall in Studies 1423 and 1540, PD-L1 IHC results were available for 75 advanced CSCC patients. Among 22 advanced CSCC patients with PD-L1 <1%, ORR per ICR was 40.9% (9/22). Among 53 advanced CSCC patients with PD-L1 ≥1%, ORR was 54.7% (29/53). Among 21 mCSCC patients, ORR was 60% (3/5) in patients with PD-L1 <1% and 56.3% (9/16) among patients with PD-L1 ≥1%. Among 54 patients with laCSCC, ORR was 35.3% (6/17) in patients with PD-L1 <1% and 54.1% (20/37) among patients with PD-L1 ≥1%.

NSCLC

The efficacy and safety of cemiplimab compared with platinum-doublet chemotherapy in patients with locally advanced NSCLC who were not candidates for surgical resection or definitive chemoradiation, or with metastatic NSCLC who had tumour PD-L1 expression ≥ 50% using the PD-L1 IHC 22C3 pharmDx assay were evaluated in Study 1624, a randomised, open-label, multi-centre study. A total of 710 patients were enrolled.

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).

Among the 710 patients, baseline characteristics were: median age of 63 years (range: 31 to 84 years), 45% age 65 or older; 85% male, 86% white. Twenty-seven percent had ECOG PS 0 and 73% had ECOG PS 1; 84% had metastatic disease and 16% had stage IIIB or IIIC disease. 56% had non-squamous and 44% had squamous histology; and 12% had history of treated brain metastases at baseline.

The study demonstrated statistically significant improvement in OS and PFS for patients randomised to cemiplimab as compared with chemotherapy.

Efficacy results are presented in Table 4, and Figure 1 and Figure 2.

Table 4 - Efficacy results from study 1624 in non-small cell lung cancer

Efficacy endpoints	Cemiplimab 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)		
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)	

Efficacy endpoints	Cemiplimab 350 mg every 3 weeks N=356	Chemotherapy N=354
p-Value[c]	<0.0001	
Objective response rate (%)[d,e]		
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

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 1 - Kaplan-Meier curve for OS

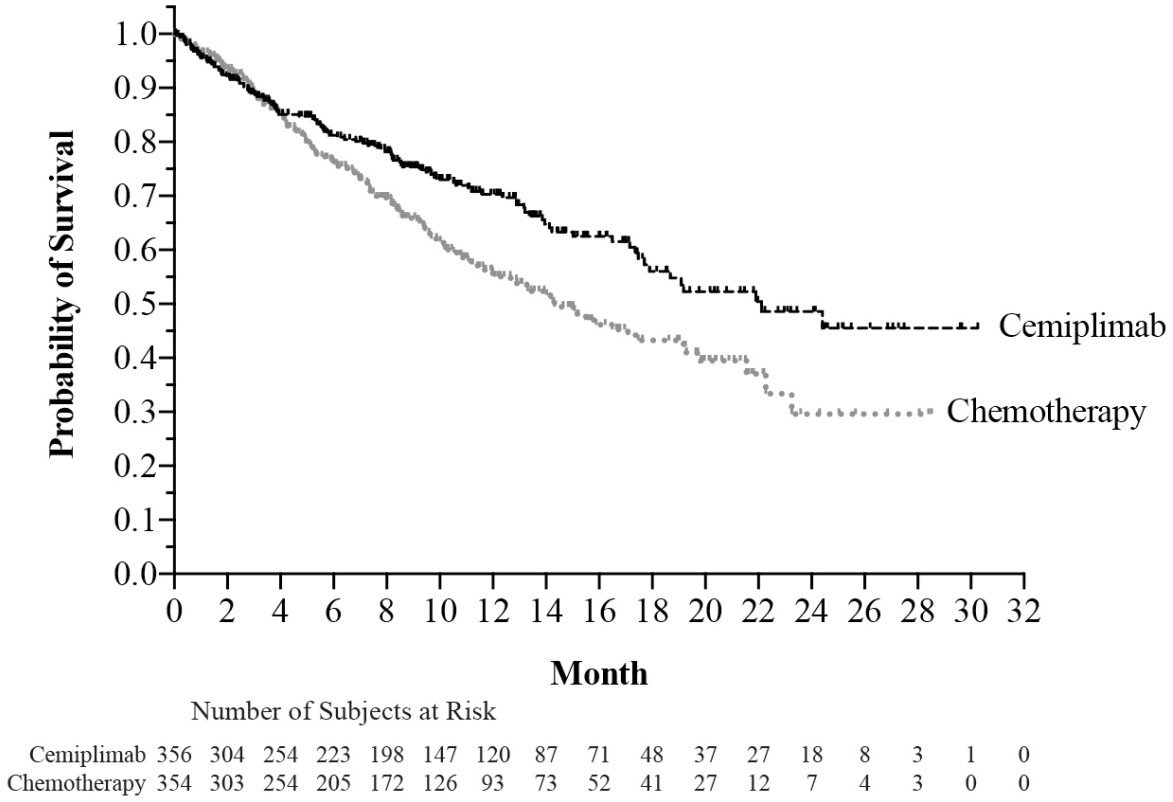
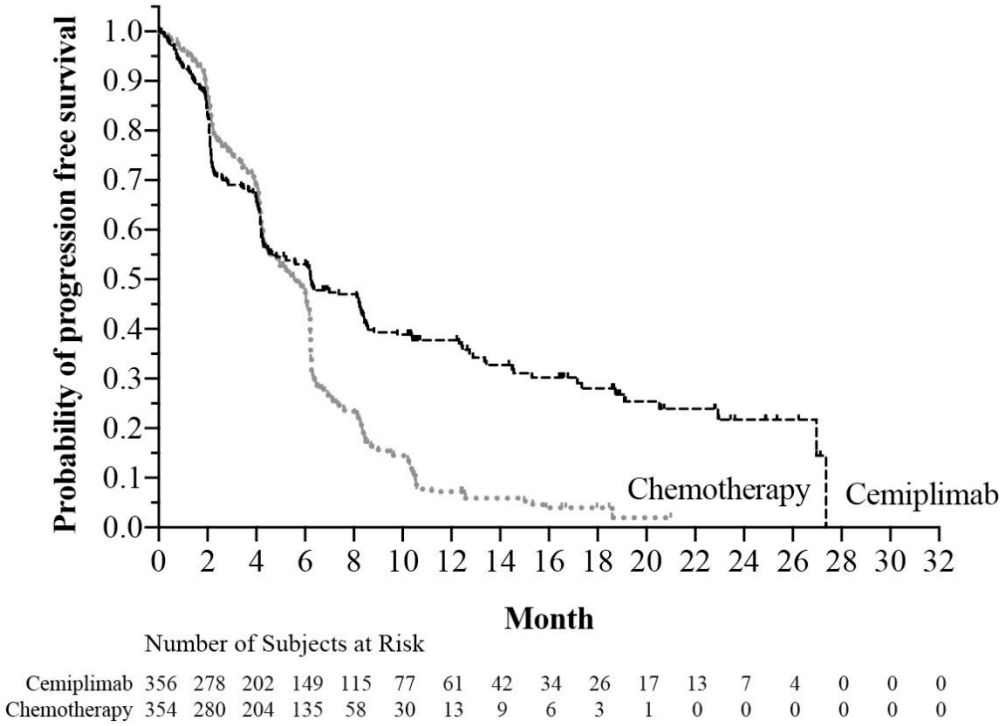


Figure 2 - Kaplan-Meier curve for PFS



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 112 patients with advanced BCC were included in the efficacy analysis of Study 1620. Of these, 25% had mBCC and 75% had laBCC. See Table 5 for a summary of baseline patient and disease characteristics.

Table 5 - Summary of baseline patient characteristics and prior treatments in Study 1620

	mBCC N=28	**laBCC N=84**
Patient characteristics		
Median age years (Range)	65.5 (38 – 90)	70.0 (42 – 89)
<65	13 (46%)	31 (37%)
≥65	15 (54%)	53 (63%)
Gender: Male	23 (82%)	56 (67%)
Race: White	22 (79%)	57 (68%)
ECOG performance status		
0	16 (57%)	51 (61%)
1	12 (43%)	33 (39%)
Prior treatments		
Prior cancer-related surgery		
Patients with at least 1 prior cancer-related surgery, n (%)	23 (82%)	70 (83%)
Patients with >3 prior cancer-related surgeries, n (%)	11 (39%)	29 (35%)
Median number of prior cancer-related surgeries (Range)	3.0 (1 - 7)	3.0 (1 - 43)
Prior anti-cancer radiotherapy		
Patients with at least 1 prior anti-cancer radiotherapy, n (%)	17 (61%)	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]	28 (100%)	84 (100%)
Prior treatment with both vismodegib and sonidegib (as separate lines of therapy), n (%)	3 (11%)	9 (11%)
Reason for discontinuation of HHI		
Disease progression/lack of response[b], n (%)	26 (93%)	63 (75%)
Intolerance to HHI therapy, n (%)	2 (7%)	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 time to response was 3.2 months (range 2.1 to 10.5 months) for the mBCC group, 4.2 months (range: 2.1 to 13.4 months) for the laBCC and 4.2 months overall (range: 2.1 to 13.4 months).

Thirty-two patients (28.6%) 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 6.

Table 6 - Efficacy results for Study 1620 in basal cell carcinoma

Efficacy endpoints	Metastatic BCC Cemiplimab 350 mg every 3 weeks	Locally Advanced BCC Cemiplimab 350 mg every 3 weeks
	N=28	N=84
	ICR	ICR
Best overall response (BOR)[a]		
Objective response rate (ORR: CR+ PR) (95% CI)	6 (21.4%) (8.3, 41.0)	26 (31.0%)[b] (21.3, 42.0)
Complete response (CR) rate[c] (95 % CI)	0% (0.0, 12.3)	5 (6.0%) (2.0, 13.3)
Partial response (PR) rate	6 (21.4%)	21 (25.0%)
Stable disease (SD) rate	10 (35.7%)	41 (48.8%)
Progressive disease (PD) rate	7 (25.0%)	9 (10.7%)
Duration of response (DOR)		
Median[d] (months) (95% CI)	NR (9.0, NE)	NR (15.0, NE)
Range (observed) (months)	9.0 - 23.0+	2.1 - 21.4+
Patients with DOR ≥ 6 months, % (95% CI)[d]	100% (NE, NE)	90.9% (68.3, 97.6)
Patients with DOR ≥12 months, % (95% CI)[d]	66.7% (19.5, 90.4)	85.2% (60.5, 95.0)
Time to response (TTR)		
Median (months) (Range)	3.2 (2.1 - 10.5)	4.2 (2.1 - 13.4)
Progression free survival[d]		
6 months (95% CI)	58.1% (37.1, 74.3)	76.3% (65.1, 84.4)
Overall survival[d, e]		

Efficacy endpoints	Metastatic BCC Cemiplimab 350 mg every 3 weeks	Locally Advanced BCC Cemiplimab 350 mg every 3 weeks
	N=28	N=84
	ICR	ICR
12 months (95% CI)	92.6% (73.4, 98.1)	92.3% (83.6, 96.5)
Disease control rate (DCR) and Durable DCR		
DCR[f] n, % (95% CI)	19 (67.9%) (47.6, 84.1)	67 (79.8%) (69.6, 87.7)
Durable DCR[g] n, % (95% CI)	13 (46.4%) (27.5, 66.1)	50 (59.5%) (48.3, 70.1)
Median duration of follow-Up (months) (Range)	9.5 (1.5 - 27.2)	15.1 (0.5 - 25.1)

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. Includes 2 patients who achieved PR prior to data cutoff; confirmatory assessments were obtained after data cutoff point.
c. Locally advanced BCC patients in Study 1620 required biopsy to confirm complete response.
d. Based on Kaplan Meier estimates.
e. OS does not require central review.
f. DCR: proportion of patients with CR, PR, SD or Non-CR/Non-PD at the first evaluable tumour assessment occurring no sooner than Day 56.
g. Durable DCR: proportion of patients with CR, PR, SD or Non-PR/Non-PD for at least 182 days without PD.

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.

Of the 1078 patients treated with cemiplimab in clinical studies, 48.7% (525/1078) were less than 65 years, 32.3% (348/1078) were 65 to less than 75 years, and 19.0% (205/1078) were 75 years or older. Grade ≥3 adverse events occurred in 44.5% (155/348) of patients 65 to less than 75 years and 51.2% (105/205) of patients 75 years or older.

In the 193 advanced CSCC patients in the efficacy analysis, the ORR by ICR (95% CI) was 40.8% (27.0%, 55.8%) in patients less than 65 years, 48.5% (36.0%, 61.1%) in patients 65 to less than 75 years, and 43.6% (32.4%, 55.3%) in 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 112 advanced BCC patients in the efficacy analysis, the objective response rate (ORR) by Independent Central Review (ICR) (95% CI) was 29.5% (16.8, 45.2) in 44 of 112 patients less than 65 years, 21.4% (8.3, 41.0) in 28 of 112 patients 65 to less than 75 years, and 27.5% (14.6, 43.9) in 40 of 112 patients 75 years or older.

5.2 PHARMACOKINETIC PROPERTIES

Concentration data were combined in a population PK analysis in 1062 patients with various solid tumours who received cemiplimab.

At 350 mg Q3W, the mean cemiplimab concentrations at steady-state ranged between a C_{trough} of 61 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.

In patients with CSCC, cemiplimab exposure at steady-state at 350 mg Q3W (N=53) and at 3 mg/kg Q2W (N=135) is similar.

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 5.3 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 0.29 l/day. The total clearance appears to decrease by approximately 29% over time, resulting in a steady state clearance (CL_{ss}) of 0.20 l/day; the decrease in CL is not considered clinically relevant. The within dosing interval half-life at steady state is 20.3 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.

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

30 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 24 hours 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.

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

sanofi-aventis australia pty ltd

12-24 Talavera Road
Macquarie Park NSW 2113
Tel: 1800 818 806

9 DATE OF FIRST APPROVAL

17 July 2020

10 DATE OF REVISION

09 December 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.1	Addition of NSCLC and BBC indications
4.2	Addition of NSCLC patient selection information Treatment modification recommendation for thyroiditis
4.4	Addition of thyroiditis to immune-related endocrinopathies section
4.8	Additional AE data from NSCLC and BCC clinical trials
5.1	Additional efficacy and safety information for Study 1624 and Study 1620
5.2	Additional data added