LIBTAYO

1. NAME OF THE MEDICINAL PRODUCT

LIBTAYO

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. The solution may contain trace amounts of translucent to white particles in a single-use vial.

Patient safety information card
The marketing of Libtayo is subject to a risk management plan (RMP) including a 'Patient safety information card'. The Patient safety information card' emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

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.

Basal Cell Carcinoma
LIBTAYO as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI).

4.2 Posology and method of administration

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

Posology

Recommended dose
Cutaneous Squamous Cell Carcinoma
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.

Alternatively, a dose of 3 mg/kg every 2 weeks administered as an intravenous infusion over 30 minutes may be considered according to the treating physician's discretion.

Basal Cell Carcinoma

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 sections 4.4 and 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

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, 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	
	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(including but not limited to paraneoplastic encephalomyelitis, meningitis, myositis, solid organ transplant rejection, graft-vs-host disease, Guillain-Barre syndrome, central nervous system inflammation, chronic inflammatory demyelinating polyradiculoneuropathy, encephalitis, myasthenia gravis, neuropathy peripheral, myocarditis, pericarditis, immune thrombocytopenic purpura, vasculitis, arthralgia, arthritis, muscular weakness, myalgia, polymyalgia rheumatica, Sjogren's syndrome, keratitis, stomatitis, thyroiditis)	Grade 3 clinical signs or symptoms of an immune-related adverse reaction not described above	Withhold LIBTAYO	Initiate symptomatic management
		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 4 adverse reaction (excluding endocrinopathies) – Recurrent severe 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 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	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

[a] See also sections 4.4 and 4.8

[b] Toxicity should be graded with the current version of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

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 sections 5.1 and 5.2). Data are limited in patients ≥75 years on cemiplimab monotherapy.

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 CLcr 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, it is recommended that the name and the batch number of the administered product 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 patients for signs and symptoms of immune-related adverse reactions. 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)
Immune-related 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
Immune-related 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
Immune-related 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).

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).

Noninfective cystitis has been reported with other PD-1/PD-L1 inhibitors.

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).

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with cemiplimab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with cemiplimab versus the risk of possible organ rejection should be considered in these patients. 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, were immunocompromised, had a history of autoimmune diseases, ECOG PS ≥2 or a history of interstitial lung disease were not included. For a full list of patients excluded from clinical studies, 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 Interaction with other medicinal products and other forms of interaction

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.

Pregnancy
Animal reproduction studies have not been conducted with cemiplimab. There are no available data on the use of cemiplimab in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing foetus resulting in foetal death (see section 5.3).

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.

Breast-feeding
It is unknown whether cemiplimab is secreted in human milk. It is known that antibodies (including IgG4) are secreted in human milk; a risk to the 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.

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

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 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 816 patients with advanced solid malignancies who received cemiplimab monotherapy in 4 clinical studies. The median duration of exposure to cemiplimab was 30.8 weeks (range: 2 days to 144 weeks).

Immune-related adverse reactions occurred in 22.1% of patients treated with cemiplimab in clinical trials including Grade 5 (0.4%), Grade 4 (0.7%), Grade 3 (5.4%), and Grade 2 (11.8%). Immune-related adverse reactions led to permanent discontinuation of cemiplimab in 4.0% of patients. The most common immune-related adverse reactions were hypothyroidism (7.5%), hyperthyroidism (3.3%), pneumonitis (3.2%), hepatitis (2.0%), colitis (2.2%) and immune-related skin adverse reactions (1.6%) (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 30.1% of patients. Adverse events led to permanent discontinuation of cemiplimab in 8.1% 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
Adverse reactions observed in clinical studies of cemiplimab as monotherapy (N=816) or reported from post-marketing use of cemiplimab are listed in Table 2. Adverse reactions are presented 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).

Table 2: **Tabulated list of adverse reactions in patients treated with cemiplimab monotherapy**

System organ class preferred term	**Grades 1–5 (Frequency category)**	**Grades 1–5 (%)**	**Grades 3-5 (%)**
Infections and infestations			
Upper respiratory tract infection[a]	Very Common	10.8	0.4
Urinary tract infection	Common	5.4	1.0
Blood and lymphatic system disorders			
Anaemia	Very Common	13.0	3.3
Immune system disorders			
Infusion-related reaction	Common	3.2	0
Sjogren's syndrome	Uncommon	0.2	0
Immune thrombocytopenic purpura	Uncommon	0.1	0
Solid organ transplant rejection[b]	Not known	--	--
Endocrine disorders			
Hypothyroidism[c]	Common	7.5	0
Hyperthyroidism	Common	3.3	0
Adrenal insufficiency	Uncommon	0.4	0.4
Thyroiditis[d]	Uncommon	0.6	0
Type 1 diabetes mellitus[e]	Uncommon	0.1	0.1
Hypophysitis	Uncommon	0.4	0.2
Nervous system disorders			
Headache	Common	7.7	0.4
Peripheral neuropathy[f]	Common	1.5	0.1
Meningitis[g]	Uncommon	0.1	0.1
Encephalitis	Uncommon	0.1	0.1
Myasthenia gravis	Uncommon	0.1	0
Paraneoplastic encephalomyelitis	Uncommon	0.1	0.1
Eye disorders			
Keratitis	Uncommon	0.1	0
Cardiac disorders			
Myocarditis[h]	Uncommon	0.6	0.5
Pericarditis[i]	Uncommon	0.2	0.2

Vascular disorders			
Hypertension[j]	Common	6.1	2.5
Metabolism and nutrition disorders			
Decreased appetite	Very common	12.5	0.6
Respiratory, thoracic and mediastinal disorders			
Cough[k]	Very common	12.5	0.1
Dyspnoea[l]	Common	9.9	1.3
Pneumonitis[m]	Common	4.2	1.2
Gastrointestinal disorders			
Nausea	Very common	12.3	0.1
Diarrhoea	Very common	16.7	0.5
Constipation	Very common	10.8	0.2
Abdominal pain[n]	Common	9.7	0.6
Vomiting	Common	7.4	0.1
Stomatitis	Common	1.5	0
Colitis[o]	Common	2.2	1.0
Hepatobiliary disorders			
Hepatitis[p]	Common	2.2	1.3
Skin and subcutaneous skin disorders			
Rash[q]	Very common	22.7	1.6
Pruritus[r]	Very common	13.1	0.1
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[s]	Very Common	29.8	1.6
Arthritis[t]	Common	1.0	0.1
Muscular weakness	Uncommon	0.4	0
Myositis	Uncommon	0.1	0
Polymyalgia rheumatica	Uncommon	0.1	0
Renal and urinary disorders			
Nephritis[u]	Common	1.3	0.2
Noninfective cystitis	Not known	-	-
General disorders and administration site conditions			
Fatigue[v]	Very common	28.1	2.3
Investigations			
Aspartate aminotransferase increased	Common	4.8	0.9
Alanine aminotransferase increased	Common	4.7	0.6
Blood alkaline phosphatase increased	Common	2.3	0.2
Blood creatinine increased	Common	2.0	0
Blood thyroid stimulating hormone increased	Uncommon	0.7	0
Transaminases increased	Uncommon	0.6	0.1

Blood bilirubin increased	Uncommon	0.5	0.1
Blood thyroid stimulating hormone decreased	Uncommon	0.1	0

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.] Post marketing event

[c.] Hypothyroidism includes hypothyroidism and immune-related hypothyroidism.

[d.] Thyroiditis includes autoimmune thyroiditis and thyroiditis.

[e.] Type 1 diabetes mellitus includes diabetic ketoacidosis and type 1 diabetes mellitus.

[f.] Peripheral neuropathy includes peripheral neuropathy, peripheral sensory neuropathy, polyneuropathy, neuritis, paraesthesia, and peripheral motor neuropathy.

[g.] Meningitis includes aseptic meningitis.

[h.] Myocarditis includes autoimmune myocarditis immune-related 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-related 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-related enterocolitis, and autoimmune colitis.

[p] Hepatitis includes autoimmune hepatitis, hepatocellular injury, immune-related 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, 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 816 patients in clinical studies in monotherapy.

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

Immune-related pneumonitis

Immune-related pneumonitis occurred in 26 (3.2%) of 816 patients receiving cemiplimab, including 4(0.5%) patients with Grade 4, 4 (0.5%) patients with Grade 3 pneumonitis. Immune-related pneumonitis led to permanent discontinuation of cemiplimab in 11 (1.3%) of 816 patients. Among the 26 patients with immune-related pneumonitis, the median time to onset was 2.5 months (range: 7 days to 18 months) and the median duration of pneumonitis was 22 days (range: 5 days to 16.9 months). Twenty two of the 26 patients (84.6%) received high-dose corticosteroids for a median of 11 days (range: 1 day to 5.9 months). Resolution of pneumonitis had occurred in 15 (57.7%) of the 26 patients at the time of data cutoff.

Immune-related colitis

Immune-related diarrhoea or colitis occurred in 18 (2.2%) of 816 patients receiving cemiplimab including 7 (0.9%) with Grade 3 immune-related diarrhoea or colitis. Immune-related diarrhoea or colitis led to permanent discontinuation of cemiplimab in 3 (0.4%) of 816 patients. Among the 18 patients with immune-related diarrhoea or colitis, the median time to onset was 3.8 months (range: 21 days to 15.5 months) and the median duration of immune-related diarrhoea or colitis was 2.3 months (range: 6 days to 10.0 months). Thirteen of the 18 patients (72.2%) with immune-related diarrhoea or colitis received high-dose corticosteroids for a median of 20 days (range: 5 days to 5.2 months). Resolution of immune-related diarrhoea or colitis had occurred in 8 (44.4%) of the 18 patients at the time of data cutoff.

Immune-related hepatitis

Immune-related hepatitis occurred in 16 (2.0%) of 816 patients receiving cemiplimab including 1 (0.1%) patient with Grade 5, 1 (0.1%) patient with Grade 4, and 11 (1.3%) patients with Grade

3 immune-related hepatitis. Immune-related hepatitis led to permanent discontinuation of cemiplimab in 10 (1.2%) of 816 patients. Among the 16 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 27.5 days (range: 10 days to 7.6 months). Fourteen (87.5%) patients with immune-related hepatitis received high-dose corticosteroids for a median of 30 days (range: 6 days to 3.1 months). Resolution of hepatitis had occurred in 8 (50.0%) of the 16 patients at the time of data cutoff.

*Immune-related endocrinopathies*Hypothyroidism occurred in 61 (7.5%) of 816 patients receiving cemiplimab. One (0.1%) of 816 patients discontinued cemiplimab due to hypothyroidism. Among the 61 patients with hypothyroidism, the median time to onset was 4.1 months (range: 15 days to 18.9 months) with a median duration of 7.9 months (range: 1 day to 23.3 months). Resolution of hypothyroidism had occurred in 5 (8.2%) of the 61 patients at the time of data cutoff. Hyperthyroidism occurred in 27 (3.3%) of 816 patients receiving cemiplimab including 7 (0.9%) patients with Grade 2 hyperthyroidism. No patient discontinued cemiplimab due to hyperthyroidism. Among the 27 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: 1 day to 24.5 months). Resolution of hyperthyroidism had occurred in 13 (48.1%) of the 27 patients at the time of data cutoff.

Thyroiditis occurred in 5 (0.6%) of 816 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 3 (0.4%) of 816 patients receiving cemiplimab including 3 (0.4%) patients with Grade 3 adrenal insufficiency. One (0.1%) of 816 patients discontinued cemiplimab due to adrenal insufficiency. Among the 3 patients with adrenal insufficiency, the median time to onset was 11.5 months (range: 4.2 months to 18.3 months) and the median duration was 5.1 months (range: 4.9 months to 6.1 months). One of the 3 patients (33.3%) received high-dose corticosteroids. Adrenal insufficiency had not resolved in any patient at the time of data cutoff.

Immune-related hypophysitis occurred in 3 (0.4%) of 816 patients receiving cemiplimab, including 2 (0.2%) patients with Grade 3 hypophysitis. One (0.1%) of 816 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). One of the 3 patients (33.3%) received high-dose corticosteroids. Hypophysitis had not resolved in any patient at the time of data cutoff.

Type 1 diabetes mellitus without an alternative aetiology occurred in 1 (0.1%) of 816 patients including 1 (0.1%) patient with Grade 4 type 1 diabetes mellitus.

Immune-related skin adverse reactions
Immune-related skin adverse reactions occurred in 13 (1.6%) of 816 patients receiving cemiplimab including 7 (0.9%) patients with Grade 3 immune-related skin adverse reactions. Immune-related skin adverse reactions led to permanent discontinuation of cemiplimab in 1 (0.1%) of 816 patients. Among the 13 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). Eight patients (61.5%) with immune-related skin adverse reactions received high-dose corticosteroids for a median of 15 days (range: 4 days to 2.6 months). Resolution of skin reaction had occurred in 9 (69.2%) of 13 patients at the time of data cutoff.

Immune-related nephritis
Immune-related nephritis occurred in 5 (0.6%) of 816 patients receiving cemiplimab including 1 (0.1%) patient with Grade 5, and 1 (0.1%) patients with Grade 3 immune-related nephritis. Immune-related nephritis led to permanent discontinuation of cemiplimab in 1 (0.1%) of 816 patients. Among the 5 patients with immune-related nephritis, the median time to onset was 1.8 months (range: 14 days to 5.6 months) and the median duration of nephritis was 26 days (range: 9 days to 1.6 months). Four (80%) patients with immune-related nephritis received high-dose corticosteroids for a median of 16

days (range: 3 days to 1.0 months). Resolution of nephritis had occurred in 4 (80%) of the 5 patients at the time of data cutoff.

Other immune-related adverse reactions
The following clinically significant, immune-related adverse reactions occurred at an incidence of less than 1% of 816 patients treated with cemiplimab monotherapy. The events were Grade 3 or less unless stated otherwise:

Nervous system disorders: Meningitis[a] (Grade 4), paraneoplastic encephalomyelitis (Grade 5), chronic inflammatory demyelinating polyradiculoneuropathy, encephalitis[b], myasthenia gravis, peripheral neuropathy[c]
Cardiac Disorders: Myocarditis[d], pericarditis[e]
Immune system disorders: Immune thrombocytopenic purpura
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

The following additional immune-related adverse reactions were observed in patients receiving combination therapy in clinical trials: vasculitis, Guillain-Barre syndrome and central nervous system inflammation, each with the frequency of rare.

Infusion-related reactions
Infusion-related reactions occurred in 63 (7.7%) of 816 patients treated with cemiplimab including 1 (0.1%) patient with Grade 3 infusion-related reaction. Infusion-related reaction led to permanent discontinuation of cemiplimab in 1 (0.1%) patient. The most common symptoms of infusion-related reaction were pyrexia, nausea, and rash. All patients recovered from the infusion-related reaction.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity with cemiplimab. In clinical studies with patients treated with cemiplimab, 2.2% of patients developed treatment-emergent antibodies, with approximately 0.4%exhibiting persistent antibody responses. No neutralizing antibodies have been observed. There was no evidence of an altered PK or safety profile with anti-cemiplimab antibody development.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

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

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 efficacy and safety

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 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 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 intravenously (IV) 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 efficacy 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) ICR	laCSCC cemiplimab: 3 mg/kg Q2W (Group 2) (N = 78) ICR	mCSCC cemiplimab: 350 mg Q3W (Group 3) (N = 56) 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)

Data cutoff 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 CR.

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%.

BCC

The efficacy and safety of cemiplimab in patients with laBCC or mBCC who had progressed on HHI therapy, were intolerant of prior HHI therapy, or had no better than 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 ORR and DOR as assessed by ICR. Secondary efficacy outcomes included ORR and DOR by IA, PFS, OS, CR by ICR, and time to response. For patients with mBCC without externally visible target lesions, ORR was determined by 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 119 patients with advanced BCC were included in the efficacy analysis of Study 1620, 84 patients with laBCC and 35 patients with mBCC.

In the laBCC group, the median age was 70.0 years (range: 42 to 89): 31 (37%) patients were <65 years old and 53 (63%) were 65 years or older. A total of 56 (67%) were male and 57 (68%) were White; the ECOG PS was 0 (61%) and 1 (39%); Eighty-three per cent (83%) of patients had received at least 1 prior cancer-related surgery and 35% of patients had >3 prior cancer-related surgeries (median: 3.0 surgeries, range: 1 to 43); 50% of patients had received at least 1 prior anti-cancer radiotherapy (RT) (median: 1.0 RT, range: 1 to 6).

In the mBCC group, the median age was 65.0 years (range: 38 to 90: 17 (49%) patients were <65 years old and 18 (51%) were 65 years or older. A total of 25 (71%) were male and 28 (80%) were White; the ECOG PS was 0 (57%) and 1 (43%); Eighty per cent (80%) of patients had received at least 1 prior cancer-related surgery and 37% of patients had >3 prior cancer-related surgeries (median: 3.0 surgeries, range: 1 to 7); 63% of patients had received at least 1 prior anti-cancer radiotherapy (RT) (median: 1.0 RT, range: 1 to 4).

All 119 patients were previously treated with a HHI, and 11% (13/119) of patients were previously treated with both vismodegib and sonidegib (as separate lines of therapy). Of the 84 laBCC patients, 71% (60/84) of patients discontinued HHI therapy due to disease progression, 38% (32/84) of patients discontinued HHI therapy due to intolerance and 2% (2/84) discontinued solely due to lack of response. Of the 35 mBCC patients, 77% (27/35) of patients discontinued HHI therapy due to disease progression, 31% (11/35) of patients discontinued HHI therapy due to intolerance, and 9% (3/35) discontinued solely due to lack of response. Investigators could select more than one reason for discontinuation of prior HHI therapy for an individual patient.

Efficacy results are presented in Table 4.

Table 4: Efficacy results for Study 1620

Efficacy endpoints	**laBCC** **cemiplimab 350 mg Q3W**	**mBCC** **cemiplimab 350 mg Q3W**
	N=84	N=35
	ICR	**IA**
Best overall response (BOR)[a, b, c]		
Objective response rate (ORR: CR+ PR) (95% CI)	27 (32.1%) (22.4, 43.2)	10 (28.6%) (14.6, 46.3)
Complete response (CR) rate[d] (95 % CI)	6 (7.1%) (2.7, 14.9)	1 (2.9%) (0.1, 14.9)
Partial response (PR) rate	21 (25.0%)	9 (25.7%)
Progressive disease (PD) rate	9 (10.7%)	9 (25.7%)
Duration of response (DOR)	N=27 responders	N=10 responders
Median[e] (months) (95% CI)	NR (15.5, NE)	NR (4.3, NE)

Range (observed) (months)	1.9 – 25.8+	4.3 – 25.1+
Patients with DOR ≥ 6 months, %[e] (95% CI)	91.7% (70.6, 97.8)	90.0% (47.3, 98.5)
Time to response (TTR)	N=27 responders	N=10 responders
Median (months) (Range)	4.3 (2.1 - 21.4)	4.1 (2.1 – 8.2)

CI: confidence interval; +: Denotes ongoing at last assessment; Q3W: every 3 weeks; ICR: Independent Central Review; IA: Investigator Assessed; NR: Not reached; NE: Not evaluable

a. Median duration of follow-up: laBCC: 15.9 months, mBCC: 8.5 months
b. Includes 2 laBCC patients who met the inclusion criteria solely on the basis of "No better than stable disease (SD) after 9 months on HHI therapy". BOR results by ICR were SD for 1 patient and NE for 1 patient.
c. Includes 3 mBCC patients who met the inclusion criteria solely on the basis of "No better than SD after 9 months on HHI therapy". BOR results by IA were PR for 1 patient and PD for 2 patients.
d. Locally advanced BCC patients in Study 1620 required biopsy to confirm complete response.
e. Based on Kaplan Meier estimates.

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

Elderly population
Of the 816 patients treated with cemiplimab in clinical studies,
45.8% (374/816) were less than 65 years,
31.9% (260/816) were 65 to less than 75 years, and
22.3% (182/816) were 75 years or older.

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

5.2 Pharmacokinetic properties

Concentration data from 1062 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 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 (V_{ss}) of 5.3 l. Median Tmax occurs at the end of the 30-minute infusion.

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

Elimination
Clearance of cemiplimab is linear at doses of 1 mg/kg to 10 mg/kg every two weeks. 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 (CLss) 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 (CLcr 60 to 89 ml/min; n= 396), moderate (CLcr 30 to 59 ml/min; n= 166), or severe (CLcr 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 CLcr <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 [TB] 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 compared to 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. Animal reproduction studies have not been conducted with cemiplimab (see section 4.6). As reported in the literature, PD-1/PD-L1 signalling pathway plays a role in sustaining pregnancy by maintaining immunological tolerance and studies have shown that PD-1 receptor blockade results in early termination of pregnancy. The increase of spontaneous abortion and/or resorption in animals with restricted PD-L1 expression (knock-out or anti-PD-1/PD-L1 monoclonal antibodies) has been shown in both mice and monkeys. These animal species have similar maternal-foetal interface to that in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
L-proline
Polysorbate 80
L-histidine monohydrochloride monohydrate
L-histidine
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

The expiry date of the product is indicated on the packaging materials.

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

- at room temperature up to 25°C for no more than 8 hours from the time of infusion preparation to the end of infusion.
  Or
- under refrigeration at 2°C to 8°C for no more than 24 hours from the time of infusion preparation to the end of infusion. 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 and other handling

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. Dispose of any unused medicinal product or waste material in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-aventis Israel Ltd. 10 Beni Gaon, POB 8090, Netanya

8. MANUFACTURER
Sanofi-Aventis Deutschland GmbH, Germany

9. LICENSE NUMBER

36023

The leaflet has been revised on 11/2021 according to MOHs guidelines.

LIBT350V-6.0