ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

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.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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).

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 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

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

LIBTAYO in combination with platinum-based chemotherapy is indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

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

Cervical Cancer
LIBTAYO as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.

4.2 Posology and method of administration

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

PD-L1 testing for patients with NSCLC
Patients with NSCLC should be evaluated for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1).

Posology

Recommended dose
The recommended dose is 350 mg cemiplimab every 3 weeks (Q3W) administered as an intravenous infusion over 30 minutes.

Treatment may be continued until disease progression or unacceptable toxicity.

Dose modifications
No dose reductions are recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Recommended modifications to manage adverse reactions are provided in Table 1.

Detailed guidelines for the management of immune-mediated 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-mediated adverse reactions			
Pneumonitis	Grade 2	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if pneumonitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent	
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue	Initial dose of 2 to 4 mg/kg/day prednisone or equivalent followed by a taper
Colitis	Grade 2 or 3	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if colitis or diarrhoea improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent	
	Grade 4 or recurrent Grade 3	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper

Hepatitis	Grade 2 with AST or ALT > 3 and ≤ 5 × ULN or total bilirubin > 1.5 and ≤ 3 × ULN	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if hepatitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent or returns to baseline AST or ALT after completion of corticosteroid taper	
	Grade ≥ 3 with AST or ALT > 5 × ULN or total bilirubin > 3 × ULN	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Hypothyroidism	Grade 3 or 4	Withhold LIBTAYO	Initiate thyroid hormone replacement as clinically indicated
		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-mediated skin reaction or other immune-mediated adverse reactions in patients with prior treatment with idelalisib	Grade 2	Withhold LIBTAYO	Initiate management immediately, including initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if skin reaction or other immune-mediated adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent	
	Grade 3 or 4 (excluding endocrinopathies) or recurrent Grade 2	Permanently discontinue	Initiate management immediately, including initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Nephritis with renal dysfunction	Grade 2 creatinine increased	Withhold LIBTAYO	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
		Resume LIBTAYO if nephritis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent	
	Grade 3 or 4 creatinine increased	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper
Other immune-mediated adverse reactions (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 thrombocytopaenia, vasculitis, arthralgia,	Grade 2 or 3 based on type of reaction	Withhold LIBTAYO	Initiate symptomatic management including initial dose of 1 to 2 mg/kg/day prednisone or equivalent as clinically indicated followed by a taper
		Resume LIBTAYO if other immune-mediated adverse reaction improves and remains at Grade 0 to 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent	
	– 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	Permanently discontinue	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent as clinically indicated followed by a taper

arthritis, muscular weakness, myalgia, polymyalgia rheumatica, Sjogren's syndrome, pruritus, keratitis, immune-mediated gastritis, stomatitis and haemophagocytic lymphohistiocytosis)	– Confirmed haemophagocytic lymphohistiocytosis – Recurrent Grade 3 immune-mediated adverse reaction – Persistent Grade 2 or 3 immune-mediated adverse reactions lasting 12 weeks or longer (excluding endocrinopathies) – Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks		
Infusion-related reactions[a]			
Infusion-related reaction	Grade 1 or 2 Grade 3 or 4	Interrupt or slow rate of infusion Permanently discontinue	Initiate symptomatic management

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).

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-mediated 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.
Currently available data are described in sections 5.1 and 5.2 but no recommendation on posology can be made.

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, the name and the batch number of the administered product should be clearly recorded.

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

The guidance for immune-mediated adverse reactions applies to cemiplimab whether administered as monotherapy or in combination with chemotherapy.

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

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

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

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

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

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

Thyroid disorders (Hypothyroidism/Hyperthyroidism/Thyroiditis)
Immune-mediated 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-mediated 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-mediated type 1 diabetes mellitus, including diabetic ketoacidosis, has been observed in patients receiving cemiplimab (see section 4.8). Patients should be monitored for hyperglycaemia and signs and symptoms of diabetes as indicated based on clinical evaluation and managed with oral anti-hyperglycaemics or insulin and cemiplimab treatment modifications (see section 4.2).

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

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

Cases of SJS, fatal TEN and stomatitis occurred following 1 dose of cemiplimab in patients with prior exposure to idelalisib, who were participating in a clinical trial evaluating cemiplimab in Non-Hodgkin Lymphoma (NHL), and who had recent exposure to sulfa containing antibiotics (see section 4.8). Patients should be managed with cemiplimab treatment modifications and corticosteroids as described above (see section 4.2).

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

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

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

Evaluate suspected immune-mediated adverse reactions to exclude other causes. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions and managed with cemiplimab treatment modifications and corticosteroids as clinically indicated (see section 4.2 and section 4.8).

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 haematopoietic stem cell transplant.

Haemophagocytic lymphohistiocytosis (HLH) has been reported in patients receiving cemiplimab (see section 4.8). Patients should be monitored for clinical signs and symptoms of HLH. If HLH is confirmed, administration of cemiplimab should be discontinued and treatment for HLH initiated (see section 4.2).

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

Cemiplimab as monotherapy
The safety of cemiplimab as monotherapy has been evaluated in 1281 patients with advanced solid malignancies who received cemiplimab monotherapy in 5 clinical studies. The median duration of exposure to cemiplimab was 28 weeks (range: 2 days to 144 weeks).

Immune-mediated adverse reactions occurred in 21% of patients treated with cemiplimab in clinical trials including Grade 5 (0.3%), Grade 4 (0.6%), Grade 3 (5.7%), and Grade 2 (11.2%). Immune-mediated adverse reactions led to permanent discontinuation of cemiplimab in 4.6% of patients. The most common immune-mediated adverse reactions were hypothyroidism (6.8%), hyperthyroidism (3.0%), immune-mediated pneumonitis (2.6%), immune-mediated hepatitis (2.4%), immune-mediated colitis (2.0%), and immune-mediated skin adverse reactions (1.9%) (see “Description of selected adverse reactions” below, Special warnings and precautions for use in section 4.4 and Recommended treatment modifications in section 4.2).

Adverse events were serious in 32.4% of patients.

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

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

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

Immune-mediated adverse reactions occurred in 18.9% of patients including Grade 5 (0.3%), Grade 3 (2.6%), and Grade 2 (7.4%). Immune-mediated adverse reactions led to permanent discontinuation of cemiplimab in 1.0% of patients. The most common immune-mediated adverse reactions were hypothyroidism (7.7%), hyperthyroidism (5.1%), increased blood thyroid stimulating hormone (4.2%), immune-mediated skin reaction (1.9%), immune-mediated pneumonitis (1.9%), and decreased blood thyroid stimulating hormone (1.6%) (see "Description of selected adverse reactions" below, Special warnings and precautions for use in section 4.4 and Recommended treatment modifications in section 4.2).

Adverse events were serious in 25.3% of patients.

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

Tabulated list of adverse reactions
Table 2 lists the incidence of adverse reactions in the monotherapy safety dataset and in patients treated with cemiplimab in combination with chemotherapy. 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).

Adverse reactions known to occur with cemiplimab or combination therapy components given alone may occur during treatment with these medicinal products in combination.

Table 2: Tabulated list of adverse reactions in patients treated with cemiplimab monotherapy and cemiplimab in combination with chemotherapy

	Cemiplimab Monotherapy			**Cemiplimab in Combination with Chemotherapy**		
System organ class Preferred term	Any Grade %		Grade 3-5 (%)	Any Grade %		Grade 3-5 (%)
Infections and infestations						
Upper respiratory tract infection[a]	Very common	10.9	0.4			
Urinary tract infection[b]	Common	8.4	2.3			
Blood and lymphatic system disorders						
Anaemia	Very common	15.0	5.2	Very common	43.6	9.9
Neutropaenia				Very common	15.4	5.8
Thrombocytopaenia				Very common	13.1	2.6
Haemophagocytic lymphohistiocytosis[d]	Not Known	--	--			
Immune system disorders						
Infusion-related reaction	Common	3.3	< 0.1	Uncommon	0.3	0
Thrombocytopaenia[c]	Uncommon	0.9	0			
Sjogren's syndrome	Uncommon	0.2	0			
Solid organ transplant rejection[d]	Not known	--	--			

Endocrine disorders						
Hypothyroidism[e]	Common	6.8	< 0.1	Common	7.7	0.3
Hyperthyroidism	Common	3.0	< 0.1	Common	5.1	0
Thyroiditis[f]	Uncommon	0.6	0	Uncommon	0.6	0
Hypophysitis[g]	Uncommon	0.5	0.2			
Adrenal insufficiency	Uncommon	0.5	0.5			
Type 1 diabetes mellitus[h]	Rare	< 0.1	< 0.1	Uncommon	0.3	0
Nervous system disorders						
Headache	Common	8.0	0.3			
Peripheral neuropathy[i]	Common	1.3	< 0.1	Very common	21.2	0
Meningitis[j]	Rare	< 0.1	< 0.1			
Encephalitis	Rare	< 0.1	< 0.1			
Myasthenia Gravis	Rare	< 0.1	0			
Paraneoplastic encephalomyelitis	Rare	< 0.1	< 0.1			
Chronic inflammatory demyelinating polyradiculoneuropathy	Rare	< 0.1	0			
Eye disorders						
Keratitis	Rare	< 0.1	0			
Uveitis	Rare	< 0.1	< 0.1			
Cardiac disorders						
Myocarditis[k]	Uncommon	0.5	0.3			
Pericarditis[l]	Uncommon	0.3	0.2			
Vascular disorders						
Hypertension[m]	Common	5.7	2.6			
Metabolism and nutrition disorders						
Decreased appetite	Very common	13.0	0.6	Very common	17.0	1.0
Hyperglycaemia				Very common	17.6	1.9
Hypoalbuminaemia				Very common	10.3	0.6
Respiratory, thoracic and mediastinal disorders						
Cough[n]	Very common	10.8	0.2			
Dyspnoea[o]	Common	9.7	1.2	Very common	12.8	2.2
Pneumonitis[p]	Common	3.3	1.1	Common	4.2	0.6
Gastrointestinal disorders						
Nausea	Very common	14.7	0.2	Very common	25.0	0
Diarrhoea	Very common	16.3	0.7	Very common	10.6	1.3
Constipation	Very common	12.3	0.2	Very common	13.8	0.3
Abdominal pain[q]	Very common	11.5	0.7			
Vomiting	Common	9.9	0.2	Very common	12.2	0
Colitis[r]	Common	2.0	0.8	Common	1.0	0.3
Stomatitis	Common	1.8	< 0.1			
Gastritis[s]	Uncommon	0.2	0			
Hepatobiliary disorders						
Hepatitis[t]	Common	2.7	1.8			
Psychiatric Disorders						
Insomnia				Very common	10.9	0
Skin and subcutaneous skin disorders						
Rash[u]	Very common	21.4	1.6	Very common	12.5	1.3
Pruritus[v]	Very common	12.7	0.2	Common	3.5	0
Actinic keratosis	Common	3.7	0			
Alopecia				Very common	36.9	0
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain[w]	Very common	28.3	1.8	Very common	26.9	1.3
Arthritis[x]	Uncommon	0.9	0.2	Common	1.0	0
Myositis[y]	Uncommon	0.3	< 0.1			
Muscular weakness	Uncommon	0.2	0			
Polymyalgia rheumatica	Uncommon	0.2	0			
Renal and urinary disorders						
Nephritis[z]	Common	1.2	0.2	Common	2.6	0

Noninfective cystitis	Not known	--	--			
General disorders and administration site conditions						
Fatigue[aa]	Very common	29.9	2.6	Very common	23.4	3.8
Pyrexia[bb]	Common	8.7	0.2			
Oedema[cc]	Common	7.9	0.4			
Investigations						
Alanine aminotransferase increased	Common	4.6	0.5	Very common	16.3	2.2
Aspartate aminotransferase increased	Common	4.4	0.7	Very common	14.7	0.3
Blood alkaline phosphatase increased	Common	1.9	0.2	Common	4.5	0
Blood creatinine increased	Common	1.6	0	Common	8.7	0
Blood thyroid stimulating hormone increased	Uncommon	0.8	0	Common	4.2	0
Transaminases increased	Uncommon	0.4	< 0.1			
Blood bilirubin increased	Uncommon	0.4	< 0.1	Common	1.6	0.3
Blood thyroid stimulating hormone decreased	Rare	< 0.1	0	Common	1.6	0
Weight decreased				Very common	11.2	1.3
Gamma-glutamyltransferase increased				Uncommon	0.6	0.3

Version 4.03 of NCI CTCAE was used to grade toxicity.

a. Upper respiratory tract infection includes upper respiratory tract infection, nasopharyngitis, sinusitis, respiratory tract infection, rhinitis, viral upper respiratory tract infection, viral respiratory tract infection, pharyngitis, laryngitis, viral rhinitis, acute sinusitis, tonsillitis, and tracheitis.

b. Urinary tract infection includes urinary tract infection, cystitis, pyelonephritis, kidney infection, pyelonephritis acute, urosepsis, bacterial cystitis, escherichia urinary tract infection, pyelocystitis, bacterial urinary tract infection, and urinary tract infection pseudomonal.

c. Thrombocytopaenia includes thrombocytopaenia and immune thrombocytopaenia.

d. Post-marketing event.

e. Hypothyroidism includes hypothyroidism and immune-mediated hypothyroidism.

f. Thyroiditis includes thyroiditis, autoimmune thyroiditis, and immune-mediated thyroiditis.

g. Hypophysitis includes hypophysitis and lymphocytic hypophysitis.

h. Type 1 diabetes mellitus includes diabetic ketoacidosis and Type 1 diabetes mellitus.

i. Peripheral neuropathy includes peripheral sensory neuropathy, peripheral neuropathy, paraesthesia, polyneuropathy, neuritis, and peripheral motor neuropathy.

j. Meningitis includes aseptic meningitis.

k. Myocarditis includes myocarditis, autoimmune myocarditis, and immune-mediated myocarditis.

l. Pericarditis includes autoimmune pericarditis and pericarditis.

m. Hypertension includes hypertension and hypertensive crisis.

n. Cough includes cough, productive cough, and upper-airway cough syndrome.

o. Dyspnea includes dyspnea and dyspnea exertional.

p. Pneumonitis includes pneumonitis, immune-mediated lung disease, interstitial lung disease, and pulmonary fibrosis.

q. Abdominal pain includes abdominal pain, abdominal pain upper, abdominal distension, abdominal pain lower, abdominal discomfort, and gastrointestinal pain.

r. Colitis includes colitis, autoimmune colitis, enterocolitis, and immune-mediated enterocolitis.

s. Gastritis includes gastritis and immune-mediated gastritis.

t. Hepatitis includes autoimmune hepatitis, immune-mediated hepatitis, hepatitis, hepatotoxicity, hyperbilirubinemia, hepatocellular injury, hepatic failure, and abnormal hepatic function.

u. Rash includes rash, rash maculo-papular, dermatitis, erythema, rash pruritic, urticaria, rash erythematous, dermatitis bullous, dermatitis acneiform, rash macular, psoriasis, rash papular, dyshidrotic eczema, pemphigoid, autoimmune dermatitis, dermatitis allergic, atopic dermatitis, drug eruption, erythema nodosum, skin reaction, skin toxicity, dermatitis exfoliative, dermatitis exfoliative generalised, dermatitis psoriasiform, erythema multiforme, exfoliative rash, immune-mediated dermatitis, lichen planus, and parapsoriasis.

v. Pruritus includes pruritus and allergic pruritus.

w. Musculoskeletal pain includes arthralgia, back pain, pain in extremity, myalgia, neck pain, musculoskeletal chest pain, bone pain, musculoskeletal pain, spinal pain, musculoskeletal stiffness, and musculoskeletal discomfort.

x. Arthritis includes arthritis, polyarthritis, autoimmune arthritis, and immune-mediated arthritis.

y. Myositis includes myositis and dermatomyositis.
z. Nephritis includes acute kidney injury, renal impairment, immune-mediated nephritis, nephritis, renal failure, tubulointerstitial nephritis, and nephropathy toxic.
aa. Fatigue includes fatigue, asthenia, and malaise.
bb. Pyrexia includes pyrexia, hyperthermia, and hyperpyrexia.
cc. Edema includes peripheral edema, face edema, peripheral swelling, face swelling, localised edema, generalised edema, and swelling.

Description of selected adverse reactions
The selected adverse reactions described below are based on safety of cemiplimab in 1281 patients in clinical studies in monotherapy.

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

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

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

Immune-mediated colitis
Immune-mediated diarrhoea or colitis occurred in 25 (2.0%) of 1281 patients receiving cemiplimab, including 10 (0.8%) with Grade 3 immune-mediated diarrhoea or colitis. Immune-mediated diarrhoea or colitis led to permanent discontinuation of cemiplimab in 5 (0.4%) of 1281 patients. Among the 25 patients with immune-mediated diarrhoea or colitis, the median time to onset was 3.8 months (range: 1 day to 16.6 months) and the median duration of immune-mediated diarrhoea or colitis was 2.1 months (range: 4 days to 26.8 months). Nineteen of the 25 patients (76.0%) with immune-mediated diarrhoea or colitis received high-dose corticosteroids for a median of 22 days (range: 2 days to 5.2 months). Resolution of immune-mediated diarrhoea or colitis had occurred in 14 (56.0%) of the 25 patients at the time of data cutoff.

Immune-mediated hepatitis
Immune-mediated hepatitis occurred in 31 (2.4%) of 1281 patients receiving cemiplimab, including 1 (< 0.1%) patient with Grade 5, 4 (0.3%) patients with Grade 4, and 21 (1.6%) patients with Grade 3 immune-mediated hepatitis. Immune-mediated hepatitis led to permanent discontinuation of cemiplimab in 18 (1.4%) of 1281 patients. Among the 31 patients with immune-mediated hepatitis, the median time to onset was 2.8 months (range: 7 days to 22.5 months) and the median duration of hepatitis was 2.3 months (range: 5 days to 8.7 months). Twenty-seven of the 31 patients (87.1%) with immune-mediated hepatitis received high-dose corticosteroids for a median of 24 days (range: 2 days to 3.8 months). Resolution of hepatitis had occurred in 12 (38.7%) of the 31 patients at the time of data cutoff.

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

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

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

Adrenal insufficiency occurred in 6 (0.5%) of 1281 patients receiving cemiplimab, including 6 (0.5%) patients with Grade 3 adrenal insufficiency. One (< 0.1%) of 1281 patients discontinued cemiplimab due to adrenal insufficiency. Among the 6 patients with adrenal insufficiency, the median time to onset was 7.5 months (range: 4.2 months to 18.3 months) and the median duration was 2.9 months (range: 22 days to 6.1 months). Two of the 6 patients (33.3%) received high-dose corticosteroids. Resolution of adrenal insufficiency had occurred in 1 (16.7%) of 6 patients at the time of data cutoff.

Immune-mediated hypophysitis occurred in 7 (0.5%) of 1281 patients receiving cemiplimab, including 3 (0.2%) patients with Grade 3 immune-mediated hypophysitis. One (< 0.1%) of 1281 patients discontinued cemiplimab due to hypophysitis. Among the 7 patients with hypophysitis, the median time to onset was 7.4 months (range: 2.5 months to 10.4 months) with a median duration of 2.7 months (range: 9 days to 34.9 months). Three of the 7 patients (42.9%) received high-dose corticosteroids. Resolution of hypophysitis had occurred in 1 (14.3%) of 7 patients at the time of data cutoff.

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

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

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

Other immune-mediated adverse reactions
The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% (unless otherwise noted) of 1281 patients treated with cemiplimab monotherapy. The events were Grade 3 or less unless stated otherwise:

Nervous system disorders: Aseptic meningitis, paraneoplastic encephalomyelitis (Grade 5), chronic inflammatory demyelinating polyradiculoneuropathy, encephalitis, myasthenia gravis, peripheral neuropathy[a]
Cardiac Disorders: Myocarditis[b] (Grade 5), pericarditis[c]
Immune system disorders: Immune thrombocytopaenia
Musculoskeletal and connective tissue disorders: Arthralgia (1.2%), arthritis[d], muscular weakness, myalgia, myositis[e] (Grade 4), polymyalgia rheumatica, Sjogren's syndrome
Skin and Subcutaneous Tissue Disorders: Pruritus
Eye disorders: Keratitis, Uveitis[f] (Grade 4)
Gastrointestinal disorders: Stomatitis, immune-mediated gastritis

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

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

Immune checkpoint inhibitor class effects

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

Infusion-related reactions
Infusion-related reactions occurred in 94 (7.3%) of 1281 patients treated with cemiplimab monotherapy including 2 (0.2%) patients with Grade 3 or 4 infusion-related reactions. Infusion-related reaction led to permanent discontinuation of cemiplimab in 1 (< 0.1%) patient. Common symptoms of infusion-related reaction include nausea, pyrexia, and vomiting. Ninety-three of 94 (98.9%) patients recovered from the infusion-related reaction at the time of data cutoff.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity with cemiplimab. In clinical studies with 1029 patients treated with cemiplimab, 2.1% of patients developed treatment-emergent antibodies, with approximately 0.3% exhibiting persistent antibody responses. No neutralising antibodies have been observed. There was no evidence of an altered pharmacokinetic 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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

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

Clinical efficacy 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 in Groups 1 to 3 with a combined median follow-up time of 15.7 months total. Median duration of follow-up was 18.5 months for the mCSCC 3 mg/kg every 2 weeks (Q2W) group (Group 1), 15.5 months for the laCSCC 3 mg/kg Q2W group (Group 2), 17.3 months for the mCSCC 350 mg Q3W group (Group 3). In an additional cohort of 165 advanced CSCC patients (mCSCC and laCSCC) dosed at 350 mg Q3W, the median duration of follow-up was 8.7 months (Group 6).

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 (Groups 1 and 2) or 350 mg Q3W for 54 weeks (Group 3)]. If patients with locally advanced disease showed sufficient response to treatment, surgery with curative intent was permitted. Tumour response assessments were performed every 8 or 9 weeks (for patients receiving 3 mg/kg Q2W or 350 mg Q3W, respectively). The primary 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).

In the efficacy analysis of 193 patients with advanced CSCC from Study 1540 Groups 1 to 3, 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 percent (33.7%) of patients had received at least 1 prior anti-cancer systemic therapy, 81.3% 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 based on the final analysis of Study 1540 Groups 1 to 3 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 every 2 weeks (Group 1) (N=59)** ICR	**laCSCC cemiplimab: 3 mg/kg every 2 weeks (Group 2) (N=78)** ICR	**mCSCC cemiplimab: 350 mg every 3 weeks (Group 3) (N=56)** ICR
Confirmed objective response rate (ORR)[a]			
ORR	50.8%	44.9%	46.4%
95% CI for ORR	(37.5, 64.1)	(33.6, 56.6)	(33.0, 60.3)
Complete response (CR)[b]	20.3%	12.8%	19.6%
Partial response (PR)	30.5%	32.1%	26.8%
Stable disease (SD)	15.3%	34.6%	14.3%
Progressive disease (PD)	16.9%	12.8%	25.0%
Duration of response (DOR)			
Median[c] (months) (95% CI)	NR (20.7, NE)	41.9 (20.5, 54.6)	41.3 (40.8, 46.3)
Range (months)	2.8-38.9	1.9-54.6	4.2-46.3
Patients with DOR ≥ 6 months, %	93.3%	88.6%	96.2%
Time to response (TTR)			
Median (months) range (min:max)	1.9 (1.7: 21.8)	2.1 (1.8: 8.8)	2.1 (2.0: 22.8)
Progression-free survival (PFS)[a, c]			
6 months (95% CI)	66.4% (52.5, 77.1)	72.4% (60.1, 81.5)	60.7% (46.7, 72.1)
12 months (95% CI)	53.8% (40.0, 65.8)	60.8% (47.8, 71.5)	53.4% (39.5, 65.4)
Overall survival (OS)[a, c]			
12 months (95% CI)	81.3% (68.7, 89.2)	91.8% (82.6, 96.2)	72.5% (58.6, 82.5)

CI: Confidence interval; ICR: Independent Central Review; NR: Not reached; NE: Not evaluable.

a. In Groups 1, 2, and 3, median durations of follow-up were 18.5, 15.5, and 17.3 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.

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 138 patients with advanced BCC were included in the efficacy analysis of Study 1620, 84 patients with laBCC and 54 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 63.5 years (range: 38 to 90): 27 (50%) patients were < 65 years old and 27 (50%) were 65 years or older. A total of 38 (70%) were male and 47 (87%) were White; the ECOG PS was 0 (67%) and 1 (33%); Eighty-five per cent (85%) of patients had received at least 1 prior cancer-related surgery and 28% of patients had > 3 prior cancer-related surgeries (median: 2.0 surgeries, range: 1 to 8); 59% of patients had received at least 1 prior anti-cancer radiotherapy (RT) (median: 1.0 RT, range: 1 to 4).

All 138 patients were previously treated with a HHI, and 12% (16/138) 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 54 mBCC patients, 76% (41/54) of patients discontinued HHI therapy due to disease progression, 33% (18/54) of patients discontinued HHI therapy due to intolerance, and 6% (3/54) 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 in locally advanced and metastatic basal cell carcinoma

Efficacy endpoints	**laBCC** **cemiplimab 350 mg every 3 weeks**	**mBCC** **cemiplimab 350 mg every 3 weeks**
	N=84	N=54
	ICR	**ICR**
Best overall response (BOR)[a, b, c]		
Objective response rate (ORR: CR+ PR) (95% CI)	27 (32.1%) (22.4, 43.2)	12 (22.2%) (12.0, 35.6)
Complete response (CR) rate[d] (95 % CI)	6 (7.1%) (2.7, 14.9)	1 (1.9%) (0.0, 9.9)
Partial response (PR) rate	21 (25.0%)	11 (20.4%)
Progressive disease (PD) rate	9 (10.7%)	16 (29.6%)
Duration of response (DOR)	N=27 responders	N=12 responders
Median[e] (months) (95% CI)	NR (15.5, NE)	16.7 (9.8, NE)
Range (observed) (months)	2.1 - 36.8+	9.0 - 25.8+
Patients with DOR ≥ 6 months, %[e] (95% CI)	88.5% (68.4, 96.1)	100.0% (100, 100)
Time to response (TTR)	N=27 responders	N=12 responders
Median (months) (Range)	4.3 (2.1 - 21.4)	3.1 (2.0 - 10.5)

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

a. Median duration of follow-up: laBCC: 15.9 months, mBCC: 8.4 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 ICR were PR for 1 patient and SD 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.

NSCLC

First-line treatment of NSCLC with cemiplimab as monotherapy

The efficacy and safety of cemiplimab compared with platinum-doublet chemotherapy in patients with locally advanced NSCLC who were not candidates for 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, ECOG performance score (PS) ≥ 2, medical conditions that required systemic immunosuppression, uncontrolled infection with hepatitis B (HBV) or hepatitis C (HCV) or human immunodeficiency virus (HIV), history of interstitial lung disease, who were never smokers or who had an autoimmune disease that required systemic therapy within 2 years of treatment. 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) and geographic region (Europe, Asia, or Rest of World). 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; or 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 independent review committee (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) as assessed by blinded IRC using RECIST 1.1. A key secondary endpoint was objective response rate (ORR).

Among the 710 patients, baseline characteristics were: median age 63 years (45% were 65 or older), 85% male, 86% White, an ECOG performance score 0 and 1 in 27% and 73% respectively, and 12% with history of brain metastasis. Disease characteristics were locally advanced (16%), metastatic (84%), squamous (44%) and non-squamous (56%).

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

Efficacy results are presented in Table 5, Figure 1 and Figure 2.

Table 5: Efficacy results for Study 1624 in non-small cell lung cancer

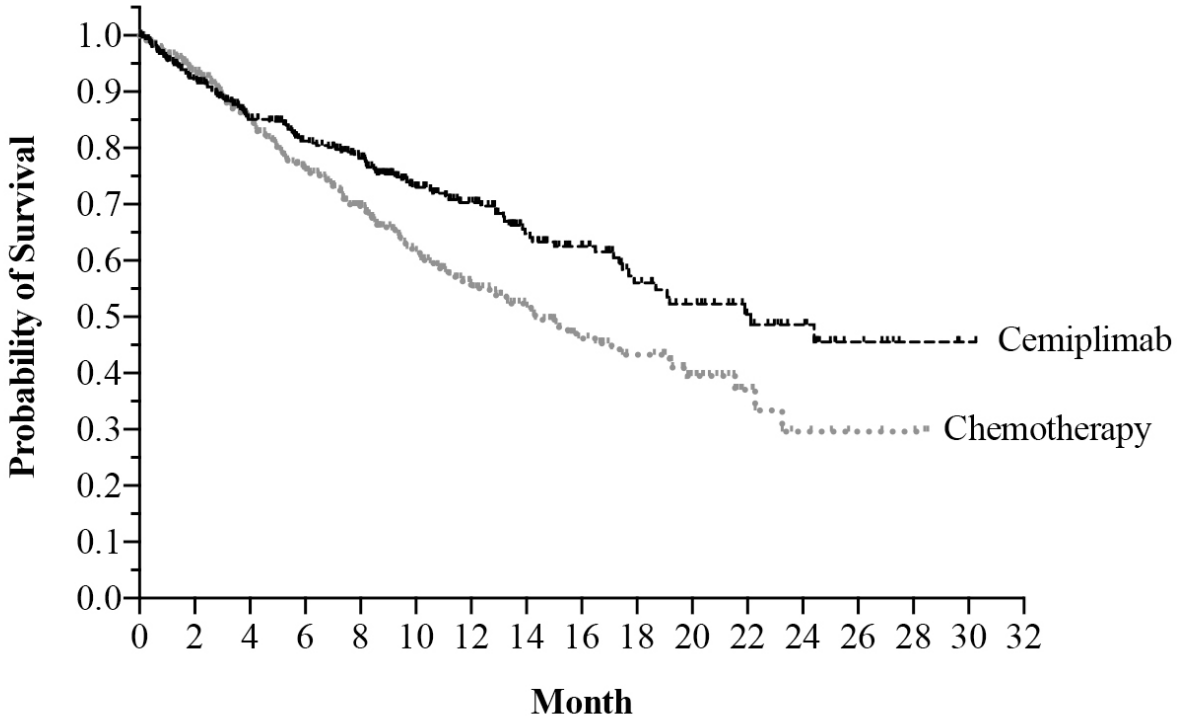
Efficacy endpoints[a]	Cemiplimab 350 mg every 3 weeks N=356	Chemotherapy N=354
Overall survival (OS)		
Deaths n(%)	108 (30.3)	141 (39.8)
Median in months (95% CI)[b]	22.1 (17.7, NE)	14.3 (11.7, 19.2)
Hazard ratio (95% CI)[c]	0.68 (0.53, 0.87)	
p-Value[d]	0.0022	
OS rate at 12 months (95% CI)[b]	70% (64, 75)	56% (49, 62)
Progression-free survival (PFS)		
Events n(%)	201 (56.5)	262 (74.0)
Median in months (95% CI)[b]	6.2 (4.5, 8.3)	5.6 (4.5, 6.1)
Hazard ratio (95% CI)[c]	0.59 (0.49, 0.72)	
PFS rate at 12 months (95% CI)[b]	38% (32, 44)	7% (4, 11)
Objective response rate (%)[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
Duration of response	N=130 responders	N=73 responders
Median (months)[b]	21.0	6.0
Range (months)	(1.9 +, 23.3+)	(1.3+, 16.5+)
Patients with observed DOR ≥ 6 months, %	69%	41%

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

a. Median duration of follow-up: cemiplimab: 13.1 months; chemotherapy: 13.1 months
b. Based on Kaplan-Meier estimates
c. Based on stratified proportional hazards model
d. Based on a two-sided p-value

e. Based on Clopper-Pearson exact confidence interval

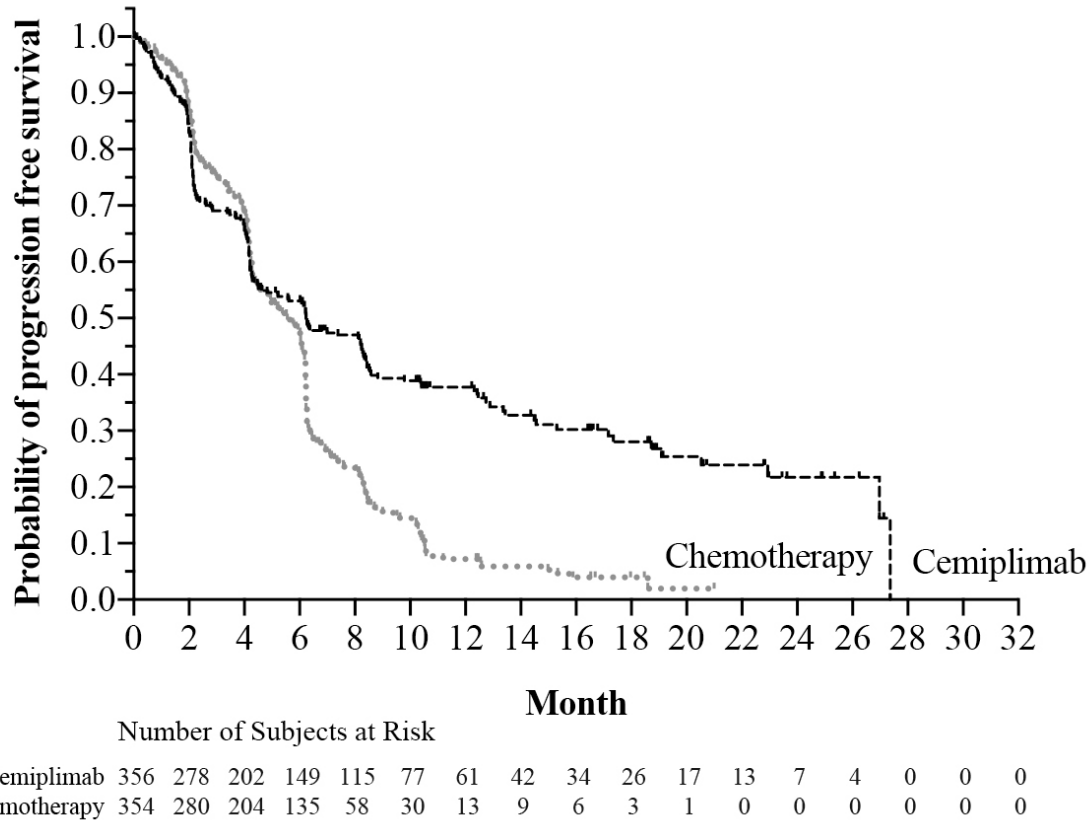
Figure 1: OS in Study 1624 in NSCLC



Number of Subjects at Risk

Cemiplimab	356	304	254	223	198	147	120	87	71	48	37	27	18	8	3	1	0
Chemotherapy	354	303	254	205	172	126	93	73	52	41	27	12	7	4	3	0	0

Figure 2: PFS in Study 1624 in NSCLC



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

The efficacy and safety of cemiplimab in combination with platinum-based chemotherapy were evaluated in Study 16113, a randomised, multi-centre, double-blind, active-controlled trial in 466 patients with locally advanced NSCLC who were not candidates for definitive chemoradiation, or with metastatic NSCLC, regardless of tumour PD-L1 expression status and who had not previously received systemic treatment for metastatic NSCLC. Testing for genomic tumour aberrations other than EGFR, ALK or ROS1 was not mandatory for enrolment in Study 16113.

Patients with EGFR, ALK or ROS1 genomic tumour aberrations; a medical condition that required systemic immunosuppression; active infection with hepatitis B (HBV) or hepatitis C (HCV), uncontrolled human immunodeficiency disease (HIV), or ongoing or recent autoimmune disease that required systemic therapy were ineligible. Patients with a history of brain metastases were eligible if they had been adequately treated and had neurologically returned to baseline for at least 2 weeks prior to randomisation. Radiological confirmation of stability or response was not required.

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

Treatment with cemiplimab or placebo was continued until RECIST 1.1-defined progressive disease, unacceptable toxicity, or up to 108 weeks. Treatment with chemotherapy was given for 4 cycles followed by maintenance of pemetrexed as clinically indicated or until RECIST 1.1-defined progressive disease or unacceptable toxicity. Chemotherapy in Study 16113 consisted of carboplatin or cisplatin combined with paclitaxel or pemetrexed with mandatory maintenance for pemetrexed regimens. Assessment of tumour status was performed every 9 weeks beginning at week 9 during year

1 and every 12 weeks beginning at week 55 during year 2. The primary efficacy endpoint was overall survival (OS). Key secondary endpoints as assessed by blinded IRC using RECIST 1.1, were progression-free survival (PFS), and objective response rate (ORR).

Among the 466 patients, 327 (70%) had tumours expressing PD-L1 (in ≥ 1% of tumour cells). Of these, 217 patients were in the cemiplimab and chemotherapy group and 110 patients were in the placebo and chemotherapy group. The baseline characteristics of the 327 patients with tumours expressing PD-L1 in ≥ 1% of tumour cells were: median age 62 years (38% were 65 or older), 83% male, 87% White, an ECOG performance score 0 and 1 in 16% and 83% respectively, and 6% with history of brain metastasis; 51% of patients were current smokers, 34% were past smokers and 15% had never smoked (less than 100 cigarettes a lifetime). Disease characteristics were locally advanced (14%), metastatic (86%), squamous histology (45%), and non-squamous histology (55%).

At the primary analysis in the overall population with a median follow-up time of 16.4 months, the study showed a statistically significant improvement in OS for patients randomised to cemiplimab in combination with chemotherapy compared with placebo in combination with chemotherapy.

Efficacy results in patients whose tumours expressed PD-L1 ≥ 1% are presented in Table 6, Figure 3, and Figure 4.

Table 6: Efficacy results for Study 16113 in non-small cell lung cancer (patients with PD-L1 expression ≥ 1%)[a]

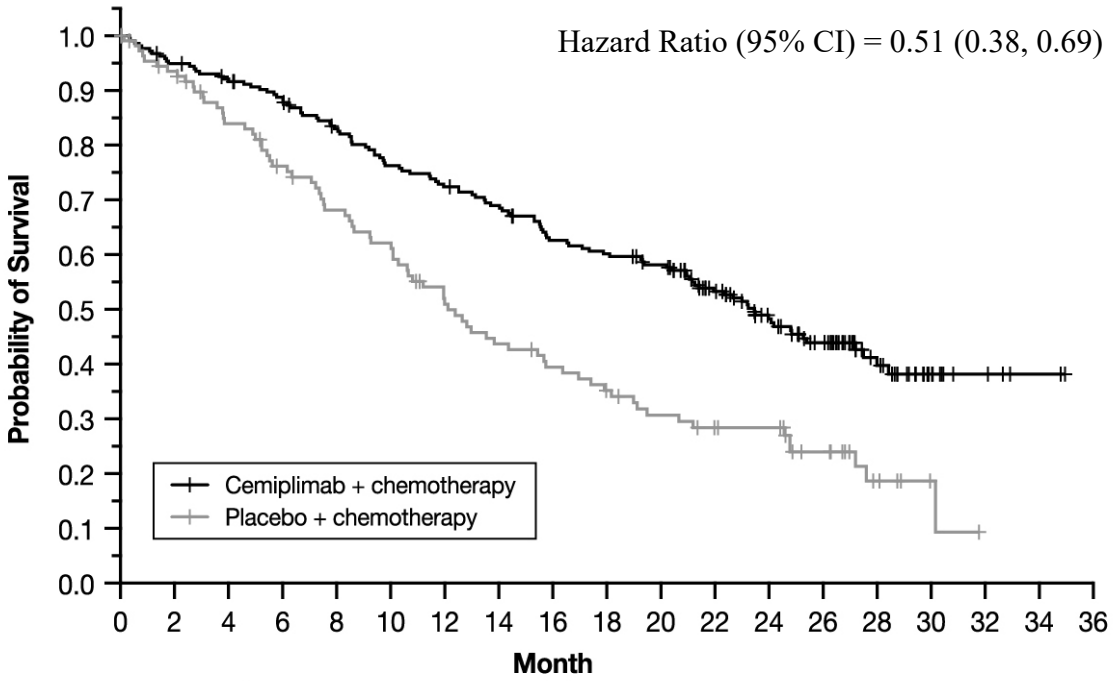
Endpoints[a]	**cemiplimab and chemotherapy N=217**	**placebo and chemotherapy N=110**
Overall Survival (OS)		
Deaths, n (%)	78 (35.9)	55 (50.0)
Median in months (95% CI)[b]	21.9 (17.3, NE)	12.6 (10.3, 16.4)
Hazard ratio (95% CI)[c]	0.55 (0.39, 0.78)	
Progression-free Survival (PFS)		
Events, n (%)	134 (61.8)	86 (78.2)
Median in months (95% CI)[b]	8.5 (6.7, 10.7)	5.5 (4.3, 6.2)
Hazard ratio (95% CI)[c]	0.48 (0.36, 0.63)	
Objective Response Rate (ORR) (%)		
ORR (95% CI)[d]	47.9 (41.1, 54.8)	22.7 (15.3, 31.7)
Complete response (CR) rate	2.8	0
Partial response (PR) rate	45.2	22.7
Duration of Response (DOR)		
Median in months[b] (range)	15.6 (1.7, 18.7+)	4.9 (1.9, 18.8+)

CI: confidence interval; NE: Not evaluable; +: Ongoing response (Data cutoff – Jun 14, 2021)

a. Median duration of follow up: cemiplimab and chemotherapy: 15.9 months, placebo and chemotherapy: 16.1 months
b. Based on Kaplan-Meier method
c. Based on stratified proportional hazards model
d. Clopper-Pearson exact confidence interval

At the time of the pre-specified final analysis, patients whose tumours expressed PD-L1 ≥ 1% randomised to cemiplimab in combination with chemotherapy, at a median duration of follow-up of 27.9 months, continued to show a clinically meaningful survival and progression free survival benefit compared to chemotherapy alone.

Figure 3: OS in Study 16113 in NSCLC (patients with PD-L1 expression ≥ 1%) – (Final analysis)[a]

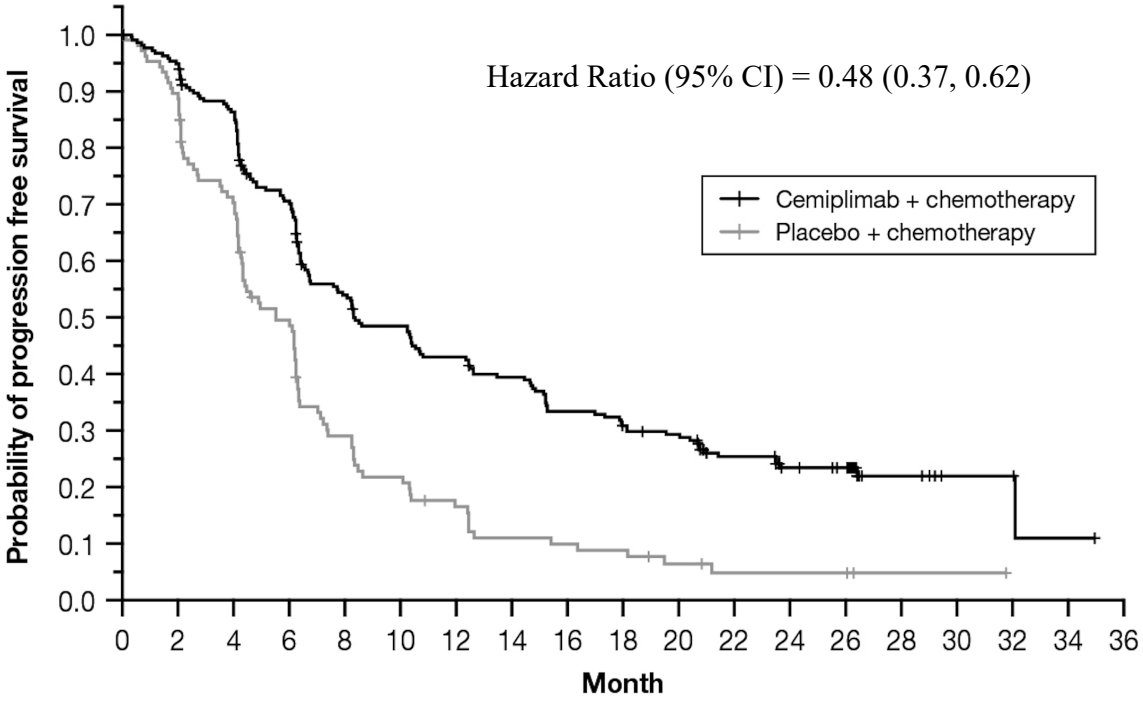


Number of Subjects at Risk

Cemiplimab + chemotherapy	217	204	196	187	172	158	150	142	127	122	115	92	70	54	27	11	5	2	0
Placebo + chemotherapy	110	100	87	77	68	62	49	42	37	32	27	23	22	14	6	2	0	0	0

[a] Based on final OS analysis (Data cutoff Jun 14, 2022)

Figure 4: PFS in Study 16113 in NSCLC (patients with PD-L1 expression ≥ 1%) – (Final analysis)[a]



Number of Subjects at Risk

Cemiplimab + chemotherapy	217	203	182	146	109	97	86	78	66	60	56	41	32	29	10	3	3	1	0
Placebo + chemotherapy	110	95	72	49	28	21	15	10	9	8	5	3	3	3	1	1	0	0	0

[a] Based on final PFS analysis (Data cutoff Jun 14, 2022)

Cervical Cancer

The efficacy and safety of cemiplimab were evaluated in patients with recurrent or metastatic cervical cancer whose tumours progressed on or after platinum-based chemotherapy, with or without bevacizumab in Study 1676, a randomised, open-label, multi-centre study. Patients were enrolled regardless of PD-L1 tumour expression status. The study excluded patients with autoimmune disease that required systemic therapy with immunosuppressant agents within 5 years and prior treatment with anti-PD-1/PD-L1 therapy.

The stratification factors for the efficacy analysis were geographic region (North America, Asia, Rest of World) and histology [squamous histology (SCC), adenocarcinoma / adenosquamous histologies (AC)]. Randomisation was also stratified by whether or not patients had received prior bevacizumab treatment and their ECOG performance status. Patients were randomised (1:1) to receive cemiplimab 350 mg intravenously every 3 weeks or investigator's choice of intravenous chemotherapy among pemetrexed, topotecan, irinotecan, gemcitabine, or vinorelbine, for up to 96 weeks.

Treatment continued until disease progression, unacceptable toxicity, or completion of planned treatment. Tumour assessments were performed every 6 weeks for the first 24 weeks and every 12 weeks thereafter. The primary efficacy endpoint was OS in SCC followed by the total population. Secondary endpoints included PFS, ORR according to RECIST 1.1, and DOR by investigator assessment.

The median age was 51 years (22 to 87 years); 63% were White, 29% Asian, 3.5% Black; 49% received prior bevacizumab treatment, 47% had ECOG PS 0 and 53% had ECOG PS 1; 78% had SCC and 22% had AC, 94% had metastatic disease; 57% had 1 prior line of treatment in the recurrent or

metastatic setting and 43% had > 1 prior line of treatment in the recurrent or metastatic setting. The median duration of follow-up for the primary analysis in the total population was 18.2 months.

Cemiplimab showed a statistically significant improvement in OS in both SCC and total population compared to chemotherapy.

Efficacy results are presented in Table 7, Figure 5, and Figure 6.

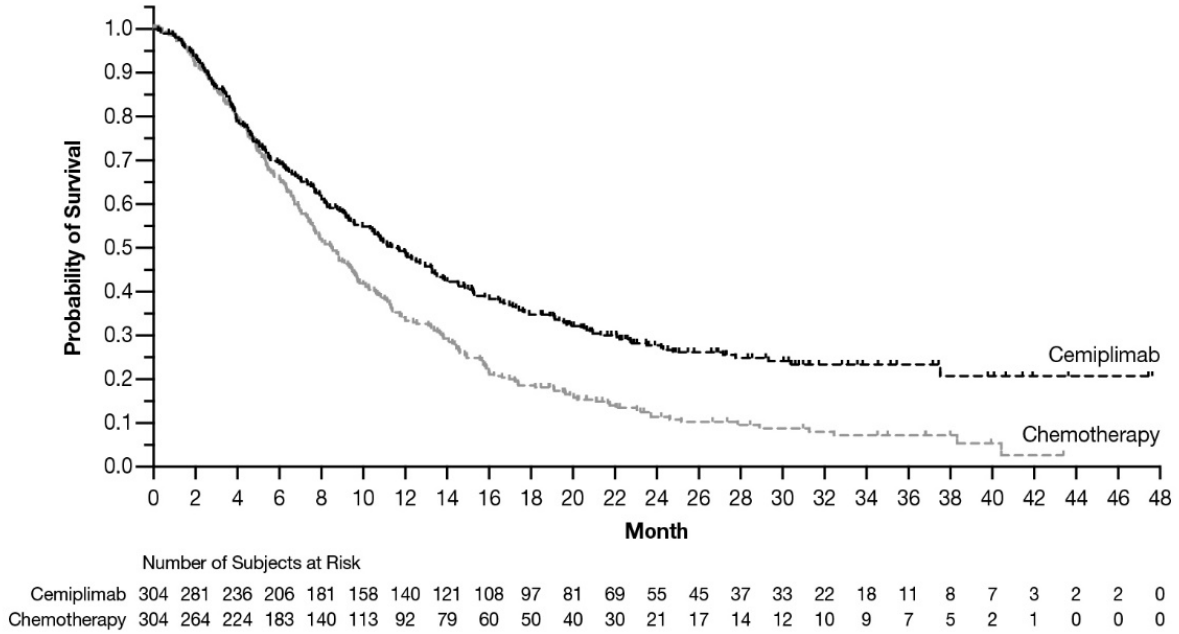
Table 7: Efficacy results for Study 1676 in cervical cancer

	Squamous histology (SCC) (N=477)		**Total population (N=608)**	
Efficacy endpoints	**cemiplimab 350 mg every 3 weeks (n=239)**	**chemotherapy (n=238)**	**cemiplimab 350 mg every 3 weeks (n=304)**	**chemotherapy (n=304)**
Overall survival (OS)[a]				
Deaths, n (%)	143 (59.8%)	161 (67.6%)	184 (60.5%)	211 (69.4%)
Median in months (95% CI)[b]	11.1 (9.2, 13.4)	8.8 (7.6, 9.8)	12.0 (10.3, 13.5)	8.5 (7.5, 9.6)
Hazard ratio (95% CI)[c]	0.73 (0.58, 0.91)		0.69 (0.56, 0.84)	
p-value[d]	0.00306		0.00011	
Progression-free survival (PFS) [a]				
Events, n (%)	197 (82.4%)	214 (89.9%)	253 (83.2%)	269 (88.5%)
Median in months (95% CI)[b]	2.8 (2.6, 4.0)	2.9 (2.7, 3.9)	2.8 (2.6, 3.9)	2.9 (2.7, 3.4)
Hazard ratio (95% CI)[c]	0.71 (0.58, 0.86)		0.75 (0.62, 0.89)	
p-value[d]	0.00026		0.00048	
Objective response rate (%)[a]				
ORR (95% CI)[e]	17.6 (13.0, 23.0)	6.7 (3.9, 10.7)	16.4 (12.5,21.1)	6.3 (3.8, 9.6)
Duration of Response (DOR)[a]	N=42	N=16	N=50	N=19
Median (months)[b] (95% CI)	16.4 (12.4, NE)	6.9 (4.2, 7.7)	16.4 (12.4, NE)	6.9 (5.1, 7.7)

a. Median follow-up: 18.2 months. (Data cutoff - Jan 04, 2021)
b. Based on Kaplan-Meier estimates.
c. Based on stratified proportional hazards model stratified by histology and geographic region.
d. One-sided p-value based on stratified proportional hazards model (cemiplimab vs. chemotherapy).
e. Based on Clopper-Pearson exact confidence interval.

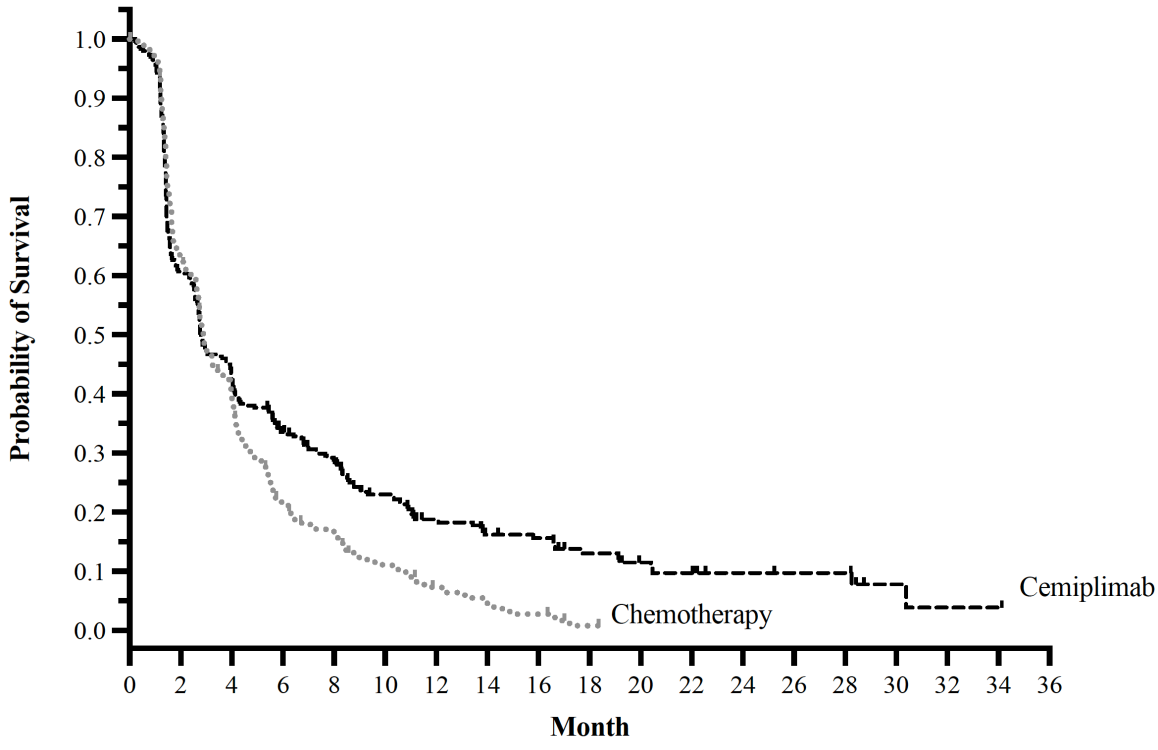
In an updated OS analysis (data cutoff Jan 04, 2022), at a median duration of follow-up of 30.2 months, cemiplimab showed a continued survival benefit compared to chemotherapy (Hazard Ratio (HR): 0.66, 95% CI [0.55, 0.79]) (see Figure 5).

Figure 5: OS in Study 1676 in cervical cancer – Total population (Updated analysis)[a]



a. Based on results from an updated OS analysis which was conducted one year after the primary analysis.

Figure 6: PFS in Study 1676 in cervical cancer – Total population (Primary Analysis)



Subgroup analyses:

In a subgroup analysis of overall survival by histology based on the updated exploratory OS analysis. the HR for the SCC group was 0.69 (95% CI: 0.56, 0.85) and the HR for the AC group was 0.55 (95% CI: 0.36, 0.81).

An exploratory subgroup analysis was conducted on survival by tumour PD-L1 Tumour Cell (TC) expression status using a clinical trial assay (VENTANA PD-L1 SP263 Assay). Of the 608 enrolled patients, 42% of patients had samples that were tested for PD-L1. Among these samples, 64% were PD-L1 ≥ 1% and 36% were PD-L1 < 1%. At the updated exploratory OS analysis, with median duration of follow-up of 30.2 months, the HR for the PD-L1 ≥ 1% group was 0.70 (95% CI: 0.48, 1.01) and the HR for the PD-L1 < 1% group was 0.85 (95% CI: 0.53, 1.36).

Elderly population

Monotherapy
Of the 1281 patients treated with cemiplimab monotherapy in clinical studies, 52.2% (669/1281) were less than 65 years, 25.9% (332/1281) were 65 to less than 75 years, and 21.9% (280/1281) were 75 years or older.

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 treated with cemiplimab monotherapy.

Combination therapy
Of the 312 patients treated with cemiplimab in combination with chemotherapy, 59% (184/312) were less than 65 years, 35.3% (110/312) were 65 to less than 75 years, and 5.8% (18/312) were 75 years or older.

No overall differences in safety or efficacy were observed between elderly patients and younger patients treated with cemiplimab in combination with platinum-based chemotherapy.

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

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

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

No new risks or safety signals were identified.

5.2 Pharmacokinetic properties

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

At 350 mg Q3W, the mean cemiplimab concentrations at steady-state ranged between a C_{trough} of 59 mg/l and a concentration at end of infusion (C_{max}) of 171 mg/l. Steady-state exposure is achieved after approximately 4 months of treatment.

Cemiplimab exposure at steady-state in patients with solid tumours is similar at 350 mg Q3W and at 3 mg/kg Q2W.

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

Distribution
Cemiplimab is primarily distributed in the vascular system with a volume of distribution at steady-state (V_{ss}) of 5.9 l. Median T_{max} 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 0.25 l/day. The total clearance appears to decrease by approximately 11% over time, resulting in a steady-state clearance (CLss) of 0.22 l/day; the decrease in CL is not considered clinically relevant. The within dosing interval half-life at steady-state is 22 days.

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

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

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

Renal impairment
The effect of renal impairment on the exposure of cemiplimab was evaluated by a population PK analysis in patients with mild (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

L-histidine
L-histidine monohydrochloride monohydrate
Sucrose
L-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
4 years.

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
From a microbiological point of view the prepared solution for infusion should be used immediately. If diluted solution is not administered immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Chemical and physical in-use stability has been demonstrated as follows:

- at room temperature up to 25°C for no more than 8 hours from the time of infusion preparation to the end of infusion.
  Or
- under refrigeration at 2°C to 8°C for no more than 10 days from the time of infusion preparation to the end of infusion. Allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

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

Regeneron Ireland Designated Activity Company (DAC)
One Warrington Place
Dublin 2, D02 HH27
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1376/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 June 2019
Date of latest renewal: 01 July 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike
Rensselaer, NY 12144
United States

Regeneron Ireland DAC
Raheen Business Park
Limerick
Ireland

Name and address of the manufacturer(s) responsible for batch release

Regeneron Ireland DAC
Raheen Business Park
Limerick
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of LIBTAYO in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where LIBTAYO is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use LIBTAYO have access to/are provided with the following educational package:

- A patient guide
- A patient alert card

- **The patient guide** shall contain the following key messages
  - Description of the main signs or symptoms of the immune-mediated adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated skin adverse reactions, nephritis and other imARs) and infusion-related reactions, and the importance of notifying their treating physician immediately if symptoms occur.
  - The importance of not attempting to self-treat any symptoms without consulting their healthcare professional first.
  - The importance of carrying the Patient Alert Card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals).
  - A reminder that all known or suspected adverse drug reactions (ADRs) can also be reported to local regulatory authorities.

- **The patient alert card** shall contain the following key messages:

  - A warning message for health care professionals treating the patient at any time, including in conditions of emergency, that the patient is treated with LIBTAYO.
  - Description of the main signs or symptoms of the immune-mediated adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, immune-mediated skin adverse reactions, nephritis and other imARs) and infusion-related reactions, and the importance of notifying their treating physician immediately if symptoms occur.
  - The contact details of their LIBTAYO prescriber.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

LIBTAYO 350 mg concentrate for solution for infusion
cemiplimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 50 mg of cemiplimab.
Each vial contains 350 mg of cemiplimab in 7 ml.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine monohydrochloride monohydrate, L-proline, polysorbate 80, sucrose, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

concentrate for solution for infusion
350 mg/7 ml

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Regeneron Ireland DAC
One Warrington Place
Dublin 2, D02 HH27, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1376/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

LIBTAYO 350 mg sterile concentrate
cemiplimab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

350 mg/7 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

LIBTAYO 350 mg concentrate for solution for infusion

cemiplimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- It is important that you keep the Patient Alert Card with you during treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What LIBTAYO is and what it is used for
2. What you need to know before you are given LIBTAYO
3. How you are given LIBTAYO
4. Possible side effects
5. How to store LIBTAYO
6. Contents of the pack and other information

1. What LIBTAYO is and what it is used for

LIBTAYO is an anti-cancer medicine that contains the active substance cemiplimab, which is a monoclonal antibody.

LIBTAYO is used in adults to treat:

- a type of skin cancer called advanced cutaneous squamous cell carcinoma (CSCC).
- a type of skin cancer called advanced basal cell carcinoma (BCC) for which you have received treatment with a hedgehog pathway inhibitor and this treatment did not work well or was not well tolerated.
- a type of lung cancer called advanced non-small cell lung cancer (NSCLC).
- a type of cancer called cervical cancer that has worsened on or after chemotherapy.

LIBTAYO may be given in combination with chemotherapy for NSCLC. It is important that you also read the package leaflets for the specific chemotherapy you may be receiving. If you have any questions about these medicines, ask your doctor.

LIBTAYO works by helping your immune system fight your cancer.

2. What you need to know before you are given LIBTAYO

You should not be given LIBTAYO if:
- you are allergic to cemiplimab or any of the other ingredients of this medicine (listed in section 6).

If you think you may be allergic, or you are not sure, talk to your doctor before you are given LIBTAYO.

Warnings and precautions
Talk to your doctor or nurse before you are given LIBTAYO if:

- you have an autoimmune disease (a condition where the body attacks its own cells)
- you have had an organ transplant, or you have received or plan to receive a bone marrow transplant using bone marrow from another person (allogeneic haematopoietic stem cell transplant)
- you have lung or breathing problems
- you have liver problems
- you have kidney problems
- you have diabetes
- you have any other medical conditions.

If any of the above apply to you, or you are not sure, talk to your doctor or nurse before you are given LIBTAYO.

Look out for side effects
LIBTAYO can cause some serious side effects that you need to tell your doctor about immediately. These problems may happen anytime during treatment or even after your treatment has ended. You may have more than one side effect at the same time.

These serious side effects include:

- Skin problems
- Lung problems (pneumonitis)
- Gut problems (colitis)
- Liver problems (hepatitis)
- Hormone gland problems - especially thyroid, pituitary, adrenal glands and the pancreas
- Type 1 diabetes, including diabetic ketoacidosis (acid in the blood produced from diabetes)
- Kidney problems (nephritis and kidney failure)
- Central nervous system problems (such as meningitis)
- Infusion-related reactions
- Muscle problems (inflammation of the muscles called myositis)
- Inflammation of the heart muscle (myocarditis)
- A disease where the immune system makes too many of otherwise normal infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (haemophagocytic lymphohistiocytosis) (see 'Possible side effects' for the list of signs and symptoms)
- Problems in other parts of the body (see 'Possible side effects')

Look out for these side effects while you are receiving LIBTAYO. See 'Possible side effects' section in section 4. If you have any of these effects, talk to your doctor immediately.
Your doctor may give you other medicines in order to stop more severe reactions and reduce your symptoms. Your doctor also may delay your next dose of LIBTAYO or stop your treatment.

Children and adolescents
LIBTAYO should not be used in children and adolescents below 18 years of age.

Other medicines and LIBTAYO
Tell your doctor if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor if you are taking or have ever taken any of the following medicines:

- a cancer medicine called idelalisib

- medicines that make your immune system weak – examples include corticosteroids, such as prednisone. These medicines may interfere with the effect of LIBTAYO. However, once you are treated with LIBTAYO, your doctor may give you corticosteroids to reduce the side effects that you may have with LIBTAYO.

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

- LIBTAYO can harm your unborn baby.
- Tell your doctor immediately if you become pregnant while you are being treated with LIBTAYO.
- If you are able to become pregnant, you must use an effective method of contraception to avoid becoming pregnant:
  – while you are being treated with LIBTAYO and
  – for at least 4 months after the last dose.
- Talk to your doctor about the contraception methods that you must use during this time.

Breast-feeding

- If you are breast-feeding or plan to breast-feed, ask your doctor for advice before you are given this medicine.
- Do not breast-feed while you are being treated with LIBTAYO and for at least 4 months after the last dose.
- It is not known if LIBTAYO passes into your breast milk.

Driving and using machines
LIBTAYO has no or minor influence on your ability to drive and use machines. If you feel tired, do not drive or use machines until you feel better.

3. How you are given LIBTAYO

- LIBTAYO will be given to you in a hospital or clinic - supervised by a doctor experienced in cancer treatment.
- LIBTAYO is given as a drip into a vein (intravenous infusion).
- The infusion will last about 30 minutes.
- LIBTAYO is usually given every 3 weeks.

How much you will receive

The recommended dose of LIBTAYO is 350 mg.

Your doctor will decide how much LIBTAYO you will receive and how many treatments you will need.

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

If you miss an appointment
Call your doctor as soon as possible to make another appointment. It is very important that you do not miss a dose of this medicine.

If you stop receiving LIBTAYO
Do not stop treatment of LIBTAYO unless you have discussed this with your doctor. This is because stopping your treatment may stop the effect of the medicine.

Patient Alert Card

The information in this Package Leaflet can be found in the Patient Alert Card you have been given by your doctor. It is important that you keep this Patient Alert Card and show it to your partner or caregivers.

If you have any questions about your treatment, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the risks and benefits of your treatment.

LIBTAYO acts on your immune system and may cause inflammation in parts of your body (see the conditions listed in 'Look out for side effects' in section 2). Inflammation may cause serious damage to your body and may need treatment or require you to stop treatment with LIBTAYO. Some inflammatory conditions may also lead to death.

Seek urgent medical attention if you have any of the following signs or symptoms, or if they get worse:

- **Skin problems** such as rash or itching, skin blistering or ulcers in mouth or other mucous membrane.
- **Lung problems (pneumonitis)** such as new or worsening cough, being short of breath or chest pain.
- **Gut problems (colitis)** such as frequent diarrhoea often with blood or mucus, more bowel movements than usual, stools that are black or tarry, and severe stomach (abdomen) pain or tenderness.
- **Liver problems (hepatitis)** such as yellowing of your skin or the whites of your eyes, severe nausea or vomiting, pain on right side of your stomach (abdomen), feeling sleepy, dark urine (the colour of tea), bleeding or bruising more easily than normal and feeling less hungry than usual.
- **Hormone gland problems** such as headache that will not go away or unusual headaches, fast heartbeat, increased sweating, feeling more cold or hot than usual, very tired, dizzy or fainting, weight gain or weight loss, feeling more hungry or thirsty than usual, hair loss, constipation, your voice gets deeper, very low blood pressure, passing water more often than usual, nausea or vomiting, stomach (abdomen) pain, changes in mood or behaviour (such as decreased sex drive, being irritable or forgetful).
- **Symptoms of type 1 diabetes or diabetic ketoacidosis** such as feeling more hungry or thirsty than usual, needing to urinate more often, weight loss, feeling tired or feeling sick, stomach pain, fast and deep breathing, confusion, unusual sleepiness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat.
- **Kidney problems (nephritis and kidney failure)** such as passing water less often than usual, passing blood, swollen ankles and feeling less hungry than normal.
- **Infusion-related reactions (sometimes can be severe or life-threatening)** such as chills, shaking or fever, itching or rash, flushing or swollen face, being short of breath or wheezing, feeling dizzy or feel like passing out and back or neck pain, nausea, vomiting or abdominal pain.
- **Problems in other parts of the body** such as:
  - **Nervous system problems** such as headache or stiff neck, fever, feeling tired or weak, chills, vomiting, confusion, memory problems or feeling sleepy, fits (seizures), seeing or hearing things that are not really there (hallucinations), severe muscle weakness, tingling, numbness, weakness or burning pain in arms or legs, paralysis in the extremities
  - **Muscle and joint problems** such as joint pain or swelling, muscle pain, weakness or stiffness
  - **Eye problems** such as changes in eyesight, eye pain or redness, sensitivity to light

- **Heart and circulatory problems** such as changes in heartbeat, heart beating fast, seeming to skip a beat or pounding sensation, chest pain, shortness of breath
- **Other:** dryness in many parts of the body from mouth to eyes, nose, throat and the top layers of skin, bruises on the skin or bleeding, enlarged liver and/or spleen, lymph node enlargement

The following side effects have been reported in clinical trials of patients treated with cemiplimab alone:

Very common (may affect more than 1 in 10 people):
- feeling tired
- muscle pain or bone pain
- rash
- diarrhoea (loose stools)
- decreased number of red blood cells
- nausea
- feeling less hungry
- itching
- constipation
- cough
- stomach pain (abdominal pain)
- upper respiratory tract infection.

Common (may affect up to 1 in 10 people):
- vomiting
- shortness of breath
- fever
- urinary tract infection
- headache
- swelling (oedema)
- thyroid gland problems (hyperthyroidism and hypothyroidism)
- high blood pressure
- increased liver enzymes in blood
- patches of thick, scaly, or crusty skin (actinic keratosis)
- cough, inflammation of the lungs
- infusion-related reactions
- inflammation of the liver
- inflammation of the intestines (diarrhoea, more bowel movements than usual, stools that are black or tarry, severe stomach (abdomen) pain or tenderness)
- inflammation of the mouth
- abnormal kidney function test
- inflammation of the nerves causing tingling, numbness, weakness or burning pain of the arms or legs
- inflammation of the kidneys.

Uncommon (may affect up to 1 in 100 people):
- joint pain, swelling, polyarthritis and joint effusion
- bruises on the skin or bleeding
- inflammation of the thyroid
- inflammation of the heart muscle, which may present as shortness of breath, irregular heartbeat, feeling tired or chest pain
- decreased secretion of hormones produced by the adrenal glands

- muscle weakness
- inflammation of the pituitary gland situated at the base of the brain
- inflammation of the covering of the heart
- dryness in many parts of the body, from mouth to eyes, nose, throat and the top layers of skin
- inflammation of the muscles which may include muscle pain or weakness (myositis) and could be associated with a rash (dermatomyositis)
- inflammation of the stomach lining
- muscle pain or stiffness (polymyalgia rheumatica).

Rare (may affect up to 1 in 1000 people):
- inflammation of brain and spinal cord membranes, which can be caused by infection
- type 1 diabetes that may include feeling more hungry or thirsty than usual, needing to urinate more often, weight loss, and feeling tired, or diabetic ketoacidosis
- eye pain, irritation, itchiness or redness, inflammation, blurred vision, uncomfortable sensitivity to light (uveitis and keratitis)
- a temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities
- a condition in which the muscles become weak and tire easily, muscle pain.

Other side effects that have been reported (frequency not known):
- organ transplant rejection
- inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in the lower abdomen
- haemophagocytic lymphohistiocytosis. A disease in which your immune system makes too many of otherwise normal infection fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney and heart problems
- coeliac disease (characterized by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)
- lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency).

The following side effects have been reported in clinical trials of patients treated with cemiplimab in combination with chemotherapy:

Very common (may affect more than 1 in 10 people):
- decreased number of red blood cells
- hair loss
- muscle pain or bone pain
- nausea
- feeling tired
- inflammation of the nerves causing tingling, numbness, weakness or burning pain of the arms or legs
- high blood sugar
- feeling less hungry
- increased liver enzymes in blood
- decrease in the number of white blood cell (neutrophils)
- constipation
- decrease in the number of platelets
- shortness of breath
- rash
- vomiting

- weight loss
- trouble sleeping
- diarrhoea (loose stools)
- low levels in the blood of a protein called ‘albumin’.

Common (may affect up to 1 in 10 people):
- abnormal kidney function test
- thyroid gland problems (hyperthyroidism and hypothyroidism)
- cough, inflammation of the lungs
- itching
- inflammation of the kidneys
- inflammation of the intestines (diarrhoea, more bowel movements than usual, stools that are black or tarry, severe stomach (abdomen) pain or tenderness)
- joint pain, swelling, polyarthritis and joint effusion.

Uncommon (may affect up to 1 in 100 people):
- inflammation of the thyroid
- infusion-related reactions
- type 1 diabetes that may include feeling more hungry or thirsty than usual, needing to urinate more often, weight loss, and feeling tired.

Other side effects that have been reported (frequency not known):
- coeliac disease (characterized by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)
- lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency).

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store LIBTAYO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

Do not freeze.

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

From a microbiological point of view the prepared solution for infusion should be used immediately. If diluted solution is not administered immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Chemical and physical in-use stability has been demonstrated as follows:
- at room temperature up to 25°C for no more than 8 hours from the time of infusion preparation to the end of infusion.
  Or

- under refrigeration at 2°C to 8°C for no more than 10 days from the time of infusion preparation to the end of infusion. Allow the diluted solution to come to room temperature prior to administration.

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

6. Contents of the pack and other information

What LIBTAYO contains

The active substance is cemiplimab:

- One ml of concentrate contains 50 mg of cemiplimab.
- Each vial contains 350 mg cemiplimab in 7 ml of concentrate.

The other ingredients are L-Histidine, L-Histidine monohydrochloride monohydrate, L-proline, sucrose, polysorbate 80 and water for injections.

What LIBTAYO looks like and contents of the pack

LIBTAYO concentrate for solution for infusion (sterile concentrate) is supplied as a clear to slightly opalescent, colourless to pale yellow sterile solution that may contain trace amounts of translucent to white particles.

Each carton contains 1 glass vial with 7 ml of concentrate.

Marketing Authorisation Holder
Regeneron Ireland Designated Activity Company (DAC)
One Warrington Place,
Dublin 2, D02 HH27
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Manufacturer
Regeneron Ireland DAC
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Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Regeneron Ireland DAC
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Slovenija
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu----------

The following information is intended for healthcare professionals only:

Instructions for use

Preparation

- Visually inspect the 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 trace amounts of 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 for single use only. Dispose of any unused medicinal product or waste material in accordance with local requirements.

Storage of diluted solution

LIBTAYO does not contain a preservative.

From a microbiological point of view the prepared solution for infusion should be used immediately. If diluted solution is not administered immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Chemical and physical in-use stability has been demonstrated as follows:

- at room temperature up to 25°C for no more than 8 hours from the time of infusion preparation to the end of infusion.
  Or
- under refrigeration at 2°C to 8°C for no more than 10 days from the time of infusion preparation to the end of infusion. Allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

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).
- Do not co-administer other medicines through the same infusion line.