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 of solution.

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

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Concentrate for solution for infusion (sterile concentrate).

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

4. **CLINICAL PARTICULARS**

4.1 Therapeutic indications

**Cutaneous Squamous Cell Carcinoma**

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

**Basal Cell Carcinoma**

LIBTAYO as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (lBCC 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.
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
For treatment with cemiplimab as monotherapy, patients should be selected based on PD-L1 tumour expression using 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-related adverse reactions are described in Table 1 (see also sections 4.4 and 4.8).

<table>
<thead>
<tr>
<th>Table 1: Recommended treatment modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction</td>
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<tr>
<td>------------------</td>
</tr>
<tr>
<td>Immune-related adverse reactions</td>
</tr>
<tr>
<td>Pneumonitis</td>
</tr>
<tr>
<td>Grade 2</td>
</tr>
<tr>
<td>Withhold LIBTAYO</td>
</tr>
<tr>
<td>Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper</td>
</tr>
<tr>
<td>Resume LIBTAYO if pneumonitis improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent</td>
</tr>
<tr>
<td>Grade 3 or 4 or recurrent Grade 2</td>
</tr>
<tr>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Initial dose of 2 to 4 mg/kg/day prednisone or equivalent followed by a taper</td>
</tr>
<tr>
<td>Colitis</td>
</tr>
<tr>
<td>Grade 2 or 3</td>
</tr>
<tr>
<td>Withhold LIBTAYO</td>
</tr>
<tr>
<td>Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper</td>
</tr>
<tr>
<td>Resume LIBTAYO if colitis or diarrhoea improves and remains at Grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent</td>
</tr>
<tr>
<td>Grade 4 or recurrent Grade 3</td>
</tr>
<tr>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper</td>
</tr>
<tr>
<td>Condition</td>
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<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Hepatitis</td>
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<tr>
<td>Hypothyroidism</td>
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<td>Hyperthyroidism</td>
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<td>Thyroiditis</td>
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<tr>
<td>Hypophysitis</td>
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<tr>
<td>Adrenal insufficiency</td>
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<td></td>
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<tr>
<td>Type 1 diabetes mellitus</td>
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<tr>
<td>Skin adverse reactions</td>
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<td>------------------------</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Immune-related skin reaction or other immune-related adverse reactions in patients with prior treatment with idelalisib</td>
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<tr>
<td></td>
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<tr>
<td>Nephritis with renal dysfunction</td>
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<tr>
<td>Other immune-related adverse reactions (including but not limited to paraneoplastic encephalomyelitis, meningitis, myositis, solid organ transplant rejection, graft-vs-host disease, Guillain-Barre syndrome, central nervous system inflammation, chronic inflammatory demyelinating polyradiculoneuropathy, encephalitis, myasthenia gravis, neuropathy peripheral, myocarditis, pericarditis, immune thrombocytopenic purpura, vasculitis, arthralgia,</td>
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</tbody>
</table>
Infusion-related reactions

<table>
<thead>
<tr>
<th>Infusion-related reaction</th>
<th>Grade 1 or 2</th>
<th>Grade 3 or 4</th>
<th>Interrupt or slow rate of infusion</th>
<th>Permanently discontinue</th>
<th>Initiate symptomatic management</th>
</tr>
</thead>
</table>

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-related adverse reactions and infusion-related reactions. The physician will provide the Patient Alert Card to each patient.

Special populations

Paediatric population

The safety and efficacy of LIBTAYO in children and adolescents below the age of 18 years have not been established. No data are available.

Elderly

No dose adjustment is recommended for elderly patients. Cemiplimab exposure is similar across all age groups (see 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-related adverse reactions
Severe and fatal immune-related adverse reactions have been observed with cemiplimab (see section 4.2 and section 4.8). These immune-related reactions may involve any organ system. Most immune-related reactions initially manifest during treatment with cemiplimab; however, immune-related adverse reactions can occur after discontinuation of cemiplimab.

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

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

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

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

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

**Immune-related endocrinopathies**

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

**Thyroid disorders (Hypothyroidism/Hyperthyroidism/Thyroiditis)**

Immune-related thyroid disorders have been observed in patients receiving cemiplimab. Thyroiditis can present with or without an alteration in thyroid function tests. Hypothyroidism can follow hyperthyroidism. Thyroid disorders can occur at any time during the treatment. Patients should be monitored for changes in thyroid function at the start of treatment and periodically during the treatment as indicated based on clinical evaluation (see section 4.8). Patients should be managed with hormone replacement therapy (if indicated) and cemiplimab treatment modifications. Hyperthyroidism should be managed according to standard medical practice (see section 4.2).

**Hypophysitis**

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

**Adrenal insufficiency**

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

**Type 1 Diabetes mellitus**

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

**Immune-related skin adverse reactions**

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

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

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

**Immune-related nephritis**

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

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

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

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

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with cemiplimab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with cemiplimab versus the risk of possible organ rejection should be considered in these patients. Cases of graft-versus-host disease have been reported in the post-marketing setting in patients treated with other PD-1/PD-L1 inhibitors in association with allogeneic hematopoietic stem cell transplant.

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

Patients excluded from clinical studies
Patients that had active infections, were immunocompromised, had a history of autoimmune diseases, ECOG PS ≥2 or a history of interstitial lung disease were not included. For a full list of patients excluded from clinical studies, see section 5.1.

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

4.5 Interaction with other medicinal products and other forms of interaction
No pharmacokinetic (PK) drug-drug interaction studies have been conducted with cemiplimab. The use of systemic corticosteroids or immunosuppressants before starting cemiplimab, except for physiological doses of systemic corticosteroid (≤10 mg/day prednisone or equivalent), should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of cemiplimab. However, systemic corticosteroids or other immunosuppressants can be used after starting cemiplimab to treat immune-related adverse reactions (see section 4.2).

4.6 Fertility, pregnancy and lactation

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

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

Human IgG4 is known to cross the placental barrier and cemiplimab is an IgG4; therefore, cemiplimab has the potential to be transmitted from the mother to the developing foetus. Cemiplimab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk.

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

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

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

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

4.8 Undesirable effects

Summary of the safety profile
Immune-related adverse reactions can occur with cemiplimab. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of cemiplimab (see “Description of selected adverse reactions” below).

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

Immune-related adverse reactions occurred in 22.1% of patients treated with cemiplimab in clinical trials including Grade 5 (0.4%), Grade 4 (0.7%), Grade 3 (5.4%), and Grade 2 (11.8%). Immune-related adverse reactions led to permanent discontinuation of cemiplimab in 4.0% of patients. The most common immune-related adverse reactions were hypothyroidism (7.5%), hyperthyroidism (3.3%), pneumonitis (3.2%), hepatitis (2.0%), colitis (2.2%) and immune-related skin adverse reactions (1.6%) (see “Description of selected adverse reactions” below, Special warnings and precautions for use in section 4.4 and Recommended treatment modifications in section 4.2).

Adverse events were serious in 30.1% of patients. Adverse events led to permanent discontinuation of cemiplimab in 8.1% of patients.

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

Tabulated list of adverse reactions
Adverse reactions observed in clinical studies of cemiplimab as monotherapy (N=816) or reported from post-marketing use of cemiplimab are listed in Table 2. Adverse reactions are presented by
system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available data).

<table>
<thead>
<tr>
<th>System organ class preferred term</th>
<th>Grades 1-5 (Frequency category)</th>
<th>Grades 1-5 (%)</th>
<th>Grades 3-5 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infectiona</td>
<td>Very Common</td>
<td>10.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Common</td>
<td>5.4</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>Very Common</td>
<td>13.0</td>
<td>3.3</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>Common</td>
<td>3.2</td>
<td>0</td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td>Uncommon</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Immune thrombocytopenic purpura</td>
<td>Uncommon</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Solid organ transplant rejectionb</td>
<td>Not known</td>
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<tr>
<td><strong>Endocrine disorders</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Hypothyroidismc</td>
<td>Common</td>
<td>7.5</td>
<td>0</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Common</td>
<td>3.3</td>
<td>0</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Uncommon</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Thyroiditisd</td>
<td>Uncommon</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>Type 1 diabetes mellitusc</td>
<td>Uncommon</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>Uncommon</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Headache</td>
<td>Common</td>
<td>7.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Peripheral neuropathyf</td>
<td>Common</td>
<td>1.5</td>
<td>0.1</td>
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<tr>
<td>Meningitisg</td>
<td>Uncommon</td>
<td>0.1</td>
<td>0.1</td>
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<tr>
<td>Encephalitis</td>
<td>Uncommon</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Uncommon</td>
<td>0.1</td>
<td>0</td>
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<tr>
<td>Paraneoplastic encephalomyelitis</td>
<td>Uncommon</td>
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<td>0.1</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyradiculoneuropathy</td>
<td>Uncommon</td>
<td>0.1</td>
<td>0</td>
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<tr>
<td><strong>Eye disorders</strong></td>
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<td></td>
</tr>
<tr>
<td>Keratitis</td>
<td>Uncommon</td>
<td>0.1</td>
<td>0</td>
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<tr>
<td><strong>Cardiac disorders</strong></td>
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<td></td>
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<tr>
<td>Myocarditisb</td>
<td>Uncommon</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Pericarditisl</td>
<td>Uncommon</td>
<td>0.2</td>
<td>0.2</td>
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<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hypertensionj</td>
<td>Common</td>
<td>6.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
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<td>--------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>Very common</td>
<td>12.5</td>
<td>0.6</td>
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<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Cough</td>
<td>Very common</td>
<td>12.5</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Common</td>
<td>9.9</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Common</td>
<td>4.2</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Gastrointestinal disorders</th>
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</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Very common</td>
<td>12.3</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Very common</td>
<td>16.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>Very common</td>
<td>10.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Common</td>
<td>9.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Common</td>
<td>7.4</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>Common</td>
<td>1.5</td>
</tr>
<tr>
<td>Colitis</td>
<td>Common</td>
<td>2.2</td>
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<thead>
<tr>
<th>Hepatobiliary disorders</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td>Common</td>
<td>2.2</td>
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</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous skin disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>Very common</td>
<td>22.7</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Very common</td>
<td>13.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal and connective tissue disorders</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal pain</td>
<td>Very Common</td>
<td>29.8</td>
</tr>
<tr>
<td>Arthritis</td>
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</tr>
<tr>
<td>Muscular weakness</td>
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<tr>
<td>Myositis</td>
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<tr>
<td>Polymyalgia rheumatica</td>
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<table>
<thead>
<tr>
<th>Renal and urinary disorders</th>
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<tr>
<td>Nephritis</td>
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<tr>
<td>Noninfective cystitis</td>
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<tr>
<th>General disorders and administration site conditions</th>
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<tbody>
<tr>
<td>Fatigue</td>
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</table>

<table>
<thead>
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<th>Investigations</th>
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<tr>
<td>Aspartate aminotransferase increased</td>
<td>Common</td>
<td>4.8</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>Common</td>
<td>4.7</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>Common</td>
<td>2.3</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>Common</td>
<td>2.0</td>
</tr>
<tr>
<td>Blood thyroid stimulating hormone increased</td>
<td>Uncommon</td>
<td>0.7</td>
</tr>
<tr>
<td>Transaminases increased</td>
<td>Uncommon</td>
<td>0.6</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>Uncommon</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Blood thyroid stimulating hormone decreased

| Uncommon | 0.1 | 0 |

Version 4.03 of NCI CTCAE was used to grade toxicity.

- Upper respiratory tract infection includes upper respiratory tract infection, respiratory tract infection, nasopharyngitis, sinusitis, pharyngitis, rhinitis, and viral upper respiratory tract infection.
- Post-marketing event.
- Hypothyroidism includes hypothyroidism and immune-related hypothyroidism.
- Thyroiditis includes autoimmune thyroiditis and thyroiditis.
- Type 1 diabetes mellitus includes diabetic ketoacidosis and type 1 diabetes mellitus.
- Peripheral neuropathy includes peripheral neuropathy, peripheral sensory neuropathy, polyneuropathy, neuritis, paraesthesia, and peripheral motor neuropathy.
- Meningitis includes aseptic meningitis.
- Myocarditis includes autoimmune myocarditis, immune-related myocarditis, and myocarditis.
- Pericarditis includes autoimmune pericarditis and pericarditis.
- Hypertension includes hypertension and hypertensive crisis.
- Cough includes cough, productive cough, and upper-airway cough syndrome.
- Dyspnoea includes dyspnoea and dyspnoea exertional.
- Pneumonitis includes pneumonitis, immune-related pneumonitis, interstitial lung disease.
- Abdominal pain includes abdominal pain, upper abdominal pain, abdominal discomfort, lower abdominal pain, and gastrointestinal pain.
- Colitis includes colitis, enterocolitis, immune-related enterocolitis, and autoimmune colitis.
- Hepatitis includes autoimmune hepatitis, hepatocellular injury, immune-related hepatitis, hepatic failure, hepatitis, and hepatotoxicity.
- Rash includes rash, dermatitis, urticaria, rash maculo-papular, erythema, rash erythematous, rash pruritic, psoriasis, autoimmune dermatitis, dermatitis acniform, dermatitis allergic, atopic dermatitis, dermatitis bullous, drug eruption, dyshidrotic eczema, lichen planus, skin reaction, dermatitis exfoliative, parapsoriasis, pemphigoid, rash macular, and rash papular.
- Pruritus includes pruritus and allergic pruritus.
- Musculoskeletal pain includes back pain, arthralgia, pain in extremity, musculoskeletal pain, musculoskeletal chest pain, bone pain, myalgia, neck pain, spinal pain, musculoskeletal stiffness, and musculoskeletal discomfort.
- Arthritis includes arthritis and polyarthritis.
- Nephritis includes nephritis, toxic nephropathy, acute kidney injury, and renal failure.
- Fatigue includes fatigue, asthenia, and malaise.

Description of selected adverse reactions

The selected adverse reactions described below are based on safety of cemiplimab in 816 patients in clinical studies in monotherapy.

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

Immune-related pneumonitis

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

Immune-related colitis

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

**Immune-related hepatitis**

Immune-related hepatitis occurred in 16 (2.0%) of 816 patients receiving cemiplimab including 1 (0.1%) patient with Grade 5, 1 (0.1%) patient with Grade 4, and 11 (1.3%) patients with Grade 3 immune-related hepatitis. Immune-related hepatitis led to permanent discontinuation of cemiplimab in 10 (1.2%) of 816 patients. Among the 16 patients with immune-related hepatitis, the median time to onset was 2.5 months (range: 7 days to 22.5 months) and the median duration of hepatitis was 27.5 days (range: 10 days to 7.6 months). Fourteen (87.5%) patients with immune-related hepatitis received high-dose corticosteroids for a median of 30 days (range: 6 days to 3.1 months). Resolution of hepatitis had occurred in 8 (50.0%) of the 16 patients at the time of data cutoff.

**Immune-related endocrinopathies**

Hypothyroidism occurred in 61 (7.5%) of 816 patients receiving cemiplimab. One (0.1%) of 816 patients discontinued cemiplimab due to hypothyroidism. Among the 61 patients with hypothyroidism, the median time to onset was 4.1 months (range: 15 days to 18.9 months) with a median duration of 7.9 months (range: 1 day to 23.3 months). Resolution of hypothyroidism had occurred in 5 (8.2%) of the 61 patients at the time of data cutoff.

Hyperthyroidism occurred in 27 (3.3%) of 816 patients receiving cemiplimab including 7 (0.9%) patients with Grade 2 hyperthyroidism. No patient discontinued cemiplimab due to hyperthyroidism. Among the 27 patients with hyperthyroidism, the median time to onset was 2.1 months (range: 20 days to 23.8 months) and the median duration was 1.9 months (range: 1 day to 24.5 months). Resolution of hyperthyroidism had occurred in 13 (48.1%) of the 27 patients at the time of data cutoff.

Thyroiditis occurred in 5 (0.6%) of 816 patients receiving cemiplimab including 2 (0.2%) patients with Grade 2 thyroiditis. No patient discontinued cemiplimab due to thyroiditis. Thyroiditis had not resolved in any patient at the time of data cutoff.

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

Immune-related hypophysitis occurred in 3 (0.4%) of 816 patients receiving cemiplimab, including 2 (0.2%) patients with Grade 3 hypophysitis. One (0.1%) of 816 patients discontinued cemiplimab due to hypophysitis. Among the 3 patients with hypophysitis, the median time to onset was 4.6 months (range: 2.6 months to 7.4 months) with a median duration of 23 days (range: 9 days to 1.5 months). One of the 3 patients (33.3%) received high-dose corticosteroids. Hypophysitis had not resolved in any patient at the time of data cutoff.

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

**Immune-related skin adverse reactions**

Immune-related skin adverse reactions occurred in 13 (1.6%) of 816 patients receiving cemiplimab including 7 (0.9%) patients with Grade 3 immune-related skin adverse reactions. Immune-related skin adverse reactions led to permanent discontinuation of cemiplimab in 1 (0.1%) of 816 patients. Among the 13 patients with immune-related skin adverse reactions, the median time to onset was 1.2 months (range: 2 days to 17.0 months) and the median duration was 2.7 months (range: 13 days to 12.5 months). Eight patients (61.5%) with immune-related skin adverse reactions received high-dose corticosteroids for a median of 15 days (range: 4 days to 2.6 months). Resolution of skin reaction had occurred in 9 (69.2%) of 13 patients at the time of data cutoff.
Immune-related nephritis
Immune-related nephritis occurred in 5 (0.6%) of 816 patients receiving cemiplimab including 1 (0.1%) patient with Grade 5, and 1 (0.1%) patients with Grade 3 immune-related nephritis. Immune-related nephritis led to permanent discontinuation of cemiplimab in 1 (0.1%) of 816 patients. Among the 5 patients with immune-related nephritis, the median time to onset was 1.8 months (range: 14 days to 5.6 months) and the median duration of nephritis was 26 days (range: 9 days to 1.6 months). Four (80%) patients with immune-related nephritis received high-dose corticosteroids for a median of 16 days (range: 3 days to 1.0 months). Resolution of nephritis had occurred in 4 (80%) of the 5 patients at the time of data cutoff.

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

Nervous system disorders: Meningitisa (Grade 4), paraneoplastic encephalomyelitis (Grade 5), chronic inflammatory demyelinating polyradiculoneuropathy, encephalitisb, myasthenia gravis, peripheral neuropathyc
Cardiac Disorders: Myocarditisd, pericarditise
Immune system disorders: Immune thrombocytopenic purpura
Musculoskeletal and connective tissue disorders: Arthralgia, arthritisf, muscular weakness, myalgia, myositis, polymyalgia rheumatica, Sjogren’s syndrome
Eye disorders: Keratitis
Gastrointestinal disorders: Stomatitis
c includes meningitis and aseptic meningitis
b includes encephalitis and noninfective encephalitis
c includes neuritis and peripheral neuropathy
d includes autoimmune myocarditis and myocarditis
e includes autoimmune pericarditis and pericarditis
f includes arthritis and polyarthritis

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

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. 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, monoclonal antibodies. ATC code: L01XC33

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

Clinical efficacy and safety

CSCC
The efficacy and safety of cemiplimab in patients with mCSCC (nodal or distant) or laCSCC who were not candidates for curative surgery or curative radiation were studied in clinical trial R2810-ONC-1540 (Study 1540). Study 1540 was a phase 2, open-label, multi-centre study that enrolled 193 patients with mCSCC or laCSCC with a combined median follow-up time of 9.4 months total. Median duration of follow-up was 16.5 months for the mCSCC 3 mg/kg every 2 weeks (Q2W) group, 9.3 months for the laCSCC 3 mg/kg Q2W group and 8.1 months for the mCSCC 350 mg Q3W group.

Patients with any of the following were excluded: autoimmune disease that required systemic therapy with immunosuppressant agents within 5 years; history of solid organ transplant; history of pneumonitis within the last 5 years; prior treatment with anti-PD-1/PD-L1 or other immune checkpoint inhibitor therapy; active infection requiring therapy, including known infection with human immunodeficiency virus, or active infection with hepatitis B or hepatitis C virus; chronic lymphocytic leukaemia (CLL); brain metastases or Eastern Cooperative Oncology Group (ECOG) performance score (PS) ≥ 2.

In Study 1540, patients received cemiplimab intravenously (IV) until progression of disease, unacceptable toxicity or completion of planned treatment [3 mg/kg Q2W for 96 weeks or 350 mg Q3W for 54 weeks]. If patients with locally advanced disease showed sufficient response to treatment, surgery with curative intent was permitted. Tumour response assessments were performed every 8 or 9 weeks (for patients receiving 3 mg/kg Q2W or 350 mg Q3W, respectively). The primary efficacy endpoint of Study 1540 was confirmed objective response rate (ORR), as assessed by independent central review (ICR). For patients with mCSCC without externally visible target lesions, ORR was determined by Response Evaluation Criteria in Solid Tumours (RECIST 1.1). For patients with externally visible target lesions (laCSCC and mCSCC), ORR was determined by a composite endpoint that integrated ICR assessments of radiologic data (RECIST 1.1) and digital medical photography (WHO criteria). The key secondary endpoint was duration of response (DOR) by ICR. Other secondary endpoints included ORR and DOR by investigator assessment (IA), progression-free survival (PFS) by ICR and IA, overall survival (OS), complete response rate (CR) by ICR, and change in scores in patient reported outcomes on the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30).

Results are presented from 193 patients in Study 1540. Of these 193 patients, 115 had mCSCC and 78 had laCSCC. The median age was 72 years (range: 38 to 96): Seventy-eight (40.4%) patients were 75 years or older, 66 patients (34.2%) were 65 to less than 75 years, and 49 patients (25.4%) were less than 65 years. A total of 161 (83.4%) patients were male, and 187 (96.9%) patients were White; the ECOG PS was 0 (44.6%) and 1 (55.4%). Thirty-three and 7/10 per cent (33.7%) of patients had received at least 1 prior anti-cancer systemic therapy, 90.2% of patients had received prior cancer
related surgery, and 67.9% of patients had received prior radiotherapy. Among patients with mCSCC, 76.5% had distant metastases, and 22.6% had only nodal metastases.

Efficacy results for Study 1540 are presented in Table 3.

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

Data cutoff was Sep 20, 2018 for Groups 1 and 3 patients, and Oct 10, 2018 for Group 2 patients. CI: confidence interval; ICR: Independent Central Review; NR: Not Reached; +: Denotes ongoing at last assessment; Q2W: every 2 weeks; Q3W: every 3 weeks

a. In Groups 1, 2, and 3, median durations of follow-up were 16.5, 9.3, and 8.1 months, respectively.
b. Only includes patients with complete healing of prior cutaneous involvement; laCSCC patients in Study 1540 required biopsy to confirm CR.
c. Based on Kaplan Meier estimates

**Efficacy and PD-L1 status**

Clinical activity was observed regardless of tumour PD-L1 expression status. The relationship between PD-L1 status and efficacy was analysed post-hoc in patients with available tissue samples. Overall in Studies 1423 and 1540, PD-L1 IHC results were available for 75 advanced CSCC patients. Among 22 advanced CSCC patients with PD-L1 < 1%, ORR per ICR was 40.9% (9/22). Among 53 advanced CSCC patients with PD-L1 ≥ 1%, ORR was 54.7% (29/53). Among 21 mCSCC patients, ORR was 60% (3/5) in patients with PD-L1 < 1% and 56.3% (9/16) among patients with PD-L1 ≥ 1%. Among
54 patients with laCSCC, ORR was 35.3% (6/17) in patients with PD-L1 < 1% and 54.1% (20/37) among patients with PD-L1 ≥ 1%.

**BCC**

The efficacy and safety of cemiplimab in patients with laBCC or mBCC who had progressed on HHI therapy, were intolerant of prior HHI therapy, or had no better than SD after 9 months on HHI therapy (exclusive of treatment breaks), were evaluated in Study 1620, an open-label, multi-centre, non-randomised study. The study excluded patients with autoimmune disease that required systemic therapy with immunosuppressant agents within 5 years; history of solid organ transplant; prior treatment with anti-PD-1/PD-L1 therapy or other immune checkpoint inhibitor therapy; infection with HIV, hepatitis B or hepatitis C; or ECOG performance score (PS) ≥ 2.

Patients received cemiplimab 350 mg intravenously (IV) every 3 weeks for 5 cycles of 9 weeks followed by 4 cycles of 12 weeks up to 93 weeks of treatment. Treatment continued until disease progression, unacceptable toxicity or completion of planned treatment. Tumour assessments were performed every 9 weeks during cycles 1 to 5 and every 12 weeks during cycles 6 to 9. The major efficacy endpoints were confirmed ORR and DOR as assessed by ICR. Secondary efficacy outcomes included ORR and DOR by IA, PFS, OS, CR by ICR, and time to response. For patients with mBCC without externally visible target lesions, ORR was determined by RECIST 1.1. For patients with externally visible target lesions (laBCC and mBCC), ORR was determined by a composite endpoint that integrated ICR assessments of radiologic data (RECIST 1.1) and digital medical photography (WHO criteria).

A total of 119 patients with advanced BCC were included in the efficacy analysis of Study 1620, 84 patients with laBCC and 35 patients with mBCC.

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

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

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

Efficacy results are presented in Table 4.

**Table 4: Efficacy results for Study 1620**

<table>
<thead>
<tr>
<th>Efficacy endpoints</th>
<th>laBCC</th>
<th>mBCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cemiplimab 350 mg Q3W</td>
<td>cemiplimab 350 mg Q3W</td>
</tr>
<tr>
<td>N</td>
<td>84</td>
<td>35</td>
</tr>
</tbody>
</table>

18
<table>
<thead>
<tr>
<th>Best overall response (BOR)(^{a,b,c})</th>
<th>ICR</th>
<th>IA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response rate</strong>&lt;br&gt;(ORR: CR + PR) (95% CI)</td>
<td>27 (32.1%)&lt;br&gt;(22.4, 43.2)</td>
<td>10 (28.6%)&lt;br&gt;(14.6, 46.3)</td>
</tr>
<tr>
<td><strong>Complete response (CR) rate(^d)</strong>&lt;br&gt;(95% CI)</td>
<td>6 (7.1%)&lt;br&gt;(2.7, 14.9)</td>
<td>1 (2.9%)&lt;br&gt;(0.1, 14.9)</td>
</tr>
<tr>
<td><strong>Partial response (PR) rate</strong></td>
<td>21 (25.0%)</td>
<td>9 (25.7%)</td>
</tr>
<tr>
<td><strong>Progressive disease (PD) rate</strong></td>
<td>9 (10.7%)</td>
<td>9 (25.7%)</td>
</tr>
</tbody>
</table>

**Duration of response (DOR)**<br>\(N=27\) responders<br>\(N=10\) responders

| Median\(^e\) (months) (95% CI) | NR (15.5, NE) | NR (4.3, NE) |
| Range (observed) (months) | 1.9 – 25.8+<br>(70.6, 97.8) | 4.3 – 25.1+<br>(47.3, 98.5) |
| Patients with DOR \(\geq\) 6 months, %\(^f\)<br>(95% CI) | 91.7%<br>(4.3, NE) | 90.0%<br>(4.3, NE) |

**Time to response (TTR)**<br>\(N=27\) responders<br>\(N=10\) responders

| Median (months) (Range) | 4.3 (2.1 - 21.4) | 4.1 (2.1 – 8.2) |

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

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

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

**NSCLC**
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 \(\geq\) 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) \(\geq\) 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 from study 1624 in non-small cell lung cancer

<table>
<thead>
<tr>
<th>Efficacy endpointsa</th>
<th>Cemiplimab 350 mg every 3 weeks</th>
<th>Chemotherapy N=354</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall survival (OS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths (%)</td>
<td>108 (30.3)</td>
<td>141 (39.8)</td>
</tr>
<tr>
<td>Median in months (95% CI)b</td>
<td>22.1 (17.7, NE)</td>
<td>14.3 (11.7, 19.2)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)c</td>
<td>0.68 (0.53, 0.87)</td>
<td></td>
</tr>
<tr>
<td>p-Valuec</td>
<td>0.0022</td>
<td></td>
</tr>
<tr>
<td>OS rate at 12 months (95% CI)b</td>
<td>70% (64, 75)</td>
<td>56% (49, 62)</td>
</tr>
<tr>
<td><strong>Progression-free survival (PFS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>201 (56.5)</td>
<td>262 (74.0)</td>
</tr>
<tr>
<td>Median in months (95% CI)b</td>
<td>6.2 (4.5, 8.3)</td>
<td>5.6 (4.5, 6.1)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)c</td>
<td>0.59 (0.49, 0.72)</td>
<td></td>
</tr>
<tr>
<td>PFS rate at 12 months (95% CI)b</td>
<td>38% (32,44)</td>
<td>7% (4,11)</td>
</tr>
<tr>
<td><strong>Objective response rate (%)e</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>36.5 (31.5, 41.8)</td>
<td>20.6 (16.5, 25.2)</td>
</tr>
<tr>
<td>Complete response (CR) rate</td>
<td>3.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Partial response (PR) rate</td>
<td>33.4</td>
<td>19.8</td>
</tr>
<tr>
<td>Duration of response N=130 responders</td>
<td></td>
<td>N=73 responders</td>
</tr>
<tr>
<td>Median (months)b</td>
<td>21.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Range (months)</td>
<td>(1.9 +, 23.3+)</td>
<td>6.0 (1.3+, 16.5+)</td>
</tr>
<tr>
<td>Patients with observed DOR ≥ 6 months, %</td>
<td>69%</td>
<td>41%</td>
</tr>
</tbody>
</table>

+: 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: Kaplan-Meier curve for OS

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

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

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with cemiplimab in all subsets of the paediatric population in the treatment of all conditions included in the category of malignant neoplasms, except haematopoietic and lymphoid tissue (see section 4.2 for information on paediatric use).

Conditional approval
This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.
5.2 Pharmacokinetic properties

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

At 350 mg Q3W, the mean cemiplimab concentrations at steady-state ranged between a C_{trough} of 61 mg/l and a concentration at end of infusion (C_{max}) of 171 mg/l. Steady-state exposure is achieved after approximately 4 months of treatment.

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

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

**Distribution**
Cemiplimab is primarily distributed in the vascular system with a volume of distribution at steady-state (V_{ss}) of 5.3 l. Median 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 0.29 l/day. The total clearance appears to decrease by approximately 29% over time, resulting in a steady state clearance (CL_{ss}) of 0.20 l/day; the decrease in CL is not considered clinically relevant. The within dosing interval half-life at steady state is 20.3 days.

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

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

**Renal impairment**
The effect of renal impairment on the exposure of cemiplimab was evaluated by a population PK analysis in patients with mild (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
3 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
Once prepared, administer the diluted solution immediately. If diluted solution is not administered immediately, it may be stored temporarily either:

- at room temperature up to 25°C for no more than 8 hours from the time of infusion preparation to the end of infusion.
  Or
- under refrigeration at 2°C to 8°C for no more than 24 hours from the time of infusion preparation to the end of infusion. Do not freeze. Allow the diluted solution to come to room temperature prior to administration.

6.4 Special precautions for storage

Unopened vial
Store in a refrigerator (2°C to 8°C).

Do not freeze.

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

For storage conditions after first opening or dilution of the medicinal product, see section 6.3.
6.5 Nature and contents of container

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

Each carton contains 1 vial.

6.6 Special precautions for disposal and other handling

Preparation and administration

- Visually inspect medicinal product for particulate matter and discoloration prior to administration. LIBTAYO is a clear to slightly opalescent, colourless to pale yellow solution that may contain trace amounts of translucent to white particles.
- Discard the vial if the solution is cloudy, discoloured or contains extraneous particulate matter other than a few translucent to white particles.
- Do not shake the vial.
- Withdraw 7 ml (350 mg) from the vial of LIBTAYO and transfer into an intravenous infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection. Mix the diluted solution by gentle inversion. Do not shake the solution. The final concentration of the diluted solution should be between 1 mg/ml to 20 mg/ml.
- LIBTAYO is administered by intravenous infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding, in-line or add-on filter (0.2 micron to 5 micron pore size).
- Do not co-administer other medicinal products through the same infusion line.

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

7. MARKETING AUTHORISATION HOLDER

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: 10 May 2021

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 AUTHORIZATION

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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORIZATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORIZATION
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 AUTHORIZATION

- 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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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-related adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other irARs) 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-related adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other irARs) and infusion-related reactions, and the importance of notifying their treating physician immediately if symptoms occur.
  - The contact details of their LIBTAYO prescriber.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post authorisation efficacy study (PAES): in order to further characterise the efficacy and safety of cemiplimab in mBCC, the MAH should submit the primary analysis for mBCC and the final study report from clinical study 1620 evaluating objective response rate and duration of response of cemiplimab in patients with mBCC who experienced progression of disease on hedgehog pathway inhibitor therapy or were intolerant of prior hedgehog pathway inhibitor therapy.</td>
<td>30th June 2024</td>
</tr>
<tr>
<td>Submission of final clinical study report</td>
<td>30th June 2024</td>
</tr>
</tbody>
</table>
E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>In order to confirm the efficacy and safety of cemiplimab for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation, the MAH should provide interim data of a single-arm trial in the same population [study 1540 group 6]. The MAH should investigate biomarkers in order to confirm that PD-L1 expression is not predictive of efficacy. The study should be conducted according to an agreed protocol.</td>
<td>31st March 2023</td>
</tr>
<tr>
<td>In order to confirm the efficacy and safety of cemiplimab for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation, the MAH should submit the final study report for Groups 1-3 in the phase 2 pivotal study 1540.</td>
<td>31st October 2022</td>
</tr>
</tbody>
</table>
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:
<table>
<thead>
<tr>
<th><strong>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS LABEL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></td>
</tr>
</tbody>
</table>
| LIBTAYO 350 mg sterile concentrate  
cepiplimab  
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 use 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).

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 hematopoietic 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
- Kidney problems (nephritis and kidney failure)
- Central nervous system problems (such as meningitis)
- Infusion-related reactions
- Problems in other parts of the body (see ‘Possible side effects’)
- Muscle problems (inflammation of the muscles called myositis)

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** such as feeling more hungry or thirsty than usual, needing to urinate more often, weight loss, and feeling tired.
- **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.

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

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

Common (may affect up to 1 in 10 people):
• shortness of breath
• stomach pain (abdominal pain)
• headache
• thyroid gland problems (hyperthyroidism and hypothyroidism)
• vomiting
• high blood pressure
• urinary tract infection
• increased liver enzymes in blood
• 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)
• abnormal kidney function test
• inflammation of the mouth
• inflammation of the nerves causing tingling, numbness, weakness or burning pain of the arms or legs
• inflammation of the kidneys
• joint pain, swelling, polyarthritis and joint effusion.

Uncommon (may affect up to 1 in 100 people):
• inflammation of the heart muscle, which may present as shortness of breath, irregular heartbeat, feeling tired or chest pain
• inflammation of the thyroid
• 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 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
• eye pain, irritation, itchiness or redness; uncomfortable sensitivity to light
• muscle pain or stiffness (polymyalgia rheumatica)
• inflammation of the muscles which may include muscle pain or weakness (myositis)
• bruises on the skin or bleeding
- 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.

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

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

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
Ireland

**Manufacturer**
Regeneron Ireland DAC
Raheen Business Park
Limerick
Ireland

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

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This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

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.

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

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

  Or

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

Do not freeze.

**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.