PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for LIBTAYO® (cemiplimab)

This is a summary of the RMP for cemiplimab. The RMP details important risks of cemiplimab, how these risks can be minimised, and how more information will be obtained about cemiplimab risks and uncertainties (missing information).

Cemiplimab summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how cemiplimab should be used.

This summary of the RMP for cemiplimab should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of cemiplimab RMP.

I. The Medicine and What it is Used For

Cemiplimab is authorised as monotherapy indicated for the treatment of adult patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation (see the SmPC for further details). It contains cemiplimab as the active substance and it is given by IV infusion.

Two new indications are being proposed:

(1) -Basal Cell Carcinoma

Treatment of adult patients with locally advanced BCC previously treated with a hedgehog pathway inhibitor.

(2) - Non-small Cell Lung Cancer

First-line treatment of patients with NSCLC expressing PD-L1 in ≥50% tumor cells, with no EGFR, ALK, or ROS1 aberrations, who have:

- locally advanced NSCLC and who are not candidates for surgical resection or definitive chemoradiation, or who have progressed after treatment with definitive chemoradiation, or
- metastatic NSCLC

Further information about the evaluation of cemiplimab benefits can be found in cemiplimab EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage with the product's EPAR summary.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of cemiplimab, together with measures to minimise such risks and the proposed studies for learning more about cemiplimab's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

In the case of cemiplimab, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of cemiplimab is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of cemiplimab are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of cemiplimab. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information:

Important Identified Risks:

- irARs **(**such as immune-related pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis, and other irARs
- IRRs

Important Potential Risks:

Lack of effect due to ADAs

Missing Information:

Long-term safety data

II.B Summary of Important Risks

Important Identified Risk: Immune-related Adverse Reactions	
Evidence for Linking the Risk to the Medicine	A total of 217 (20.1%) patients exposed to cemiplimab in clinical trials included in the RMP experienced at least 1 irAR including 5 patients (0.5%) with grade 5, and 67 patients (6.2%) with grade 3/4 irARs. Forty-three (4.0%) patients discontinued treatment due to irARs.
Risk Factors and Risk Groups	Patients with a history of or ongoing autoimmune disease may be at higher risk of developing irAEs and were excluded from the development programme for cemiplimab. Patients who were previously exposed to idelalisib may be at increased risk of experiencing severe immune related mucocutaneous adverse reactions.
Risk Minimisation Measures	Routine risk communication messages: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.2 and 4.4 PL sections 2 and 3 Other routine risk minimisation measures beyond the Product Information: Legal status: Cemiplimab is subject to restricted medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of cancer. Additional risk minimisation measures: Patient Guide and Alert Card

Important Identified Risk: Infusion-related Reactions	
Evidence for Linking the Risk to the Medicine	In Study 1423, Study 1540, Study 1620, and Study 1624 IRRs occurred in patients receiving cemiplimab. These have also been observed in patients exposed to other PD-1 inhibitors.

Important Identified Risk: Infusion-related Reactions	
	Infusion-related reaction occurred in 8.3% (89/1078) of patients receiving cemiplimab including 2 (0.2%) patients with grade 3/4 IRRs. Infusion-related reaction led to permanent discontinuation of cemiplimab in 3 (0.3%) patients. The most common symptoms of infusion-related reaction were nausea, pyrexia, vomiting, abdominal pain, chills, flushing, and dyspnoea. All patients recovered from infusion-related reaction.
Risk Factors and Risk Groups	Even though all patients are potentially at risk of IRRs, patients with documented allergic reactions or acute hypersensitivity reactions attributed to antibody treatments may be at higher risk of developing severe IRRs and were excluded from the development programme for cemiplimab.
Risk Minimisation Measures	Routine communication messages: SmPC section 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.2, 4.3, and 4.4. PL sections 2 and 3 Other routine risk minimisation measures beyond the Product Information: Legal status: Cemiplimab is subject to restricted medical prescription and treatment must be initiated and supervised by physicians experienced in the treatment of cancer. Additional risk minimisation measures: Patient Guide and Alert Card
Additional pharmacovigilance activities	Use of specific follow-up questionnaire for spontaneous post-authorisation reports of IRRs

Important Potential Risks: Lack of Effect due to Anti-drug Antibodies	
Evidence for Linking the Risk to the Medicine	In nonclinical studies, the prevalence of immunogenicity/ADA was high; however, continuous exposure was maintained for 80% and 50% of animals throughout the 4-week and 26-week toxicology studies, respectively. As cemiplimab is a human antibody, the presence of ADA following cemiplimab administration to cynomolgus monkeys was expected and not considered predictive of the human ADA response to cemiplimab. In the 4 clinical studies presented in this RMP (Study 1423, Study 1540, Study 1620, and Study 1624), the incidence of treatment-emergent ADA was low (2.3%) in all patients receiving cemiplimab 350 mg Q3W. Antibody titers in all ADA-positive patients were all low. Of the patients who developed treatment-emergent antibodies to cemiplimab, none developed NAb. The incidence of persistent ADA was low (0.4%) in all patients receiving cemiplimab. The incidence of treatment-emergent ADA in patients with BCC in Study 1620 (3.2%) was similar to the incidence across all studies and cemiplimab dose regimens. The incidence of treatment-emergent ADA in patients with NSCLC in Study 1624 (2.3%) was consistent with the incidence observed across all studies. Only 1 patient (in Study 1423) showed evidence of altered PK profile with anti-cemiplimab antibody development; this was the only patient in the 4 studies with a moderate maximum titer. The presence of ADA was not associated with significant adverse events or irAEs.
Risk Factors and Risk Groups	Risk factors are unknown. Any patient who receives cemiplimab has a potential risk of developing ADAs.
Risk Minimisation Measures	Routine communication messages: SmPC sections 4.4 and 4.8 Other routine risk minimisation measures beyond the Product Information: Legal status: Cemiplimab is subject to restricted medical prescription and treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

II.C Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorisation:

Cutaneous squamous cell carcinoma

R2810-ONC-1540 - A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6)

Rationale and Study Objectives

Group 6 is conducted within Study 1540 for the purpose of confirming the efficacy and safety among patients with advanced CSCC treated with cemiplimab 350 mg Q3W IV and is intended to fulfill the regulatory requirements associated with conditional approval of cemiplimab. Group 6 is also designed to provide additional exploratory biomarker data.

The primary objective of this additional cohort is to confirm the clinical benefit of cemiplimab monotherapy for patients with advanced CSCC (metastatic or unresectable locally advanced) treated with cemiplimab 350 mg Q3W IV.

Study Design

This is a phase 2, non-randomised, 6-group, multicentre pivotal trial evaluating the efficacy and safety of cemiplimab in patients with advanced CSCC. After a screening period of up to 28 days, patients in Group 6 will receive cemiplimab 350 mg Q3W IV on days 1, 22, and 43 (±3 days for each dose) during each 9-week treatment cycle. Patients will receive treatment until the 108-week treatment period is complete, or until disease progression, unacceptable toxicity or withdrawal of consent. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle; routine safety evaluations will be conducted at each cemiplimab dosing visit.

Screening is up to 4 weeks for all 6 groups. Patients in Group 6 will receive up to 108 weeks of treatment.

Study Population

Approximately 167 patients will be enrolled in Group 6. Group 6 will include eligible patients with metastatic (nodal and/or distant) CSCC and unresectable laCSCC.

R2810-ONC-1540 - A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Groups 1, 2 and 3)

The study included in the RMP, Study 1540, is ongoing and safety data from this study will be used to further characterise the long-term safety profile of cemiplimab and to further characterise identified risk of irARs. The study will provide additional safety data up to approximately 3.5 years of safety data for patients in Groups 1 and 2, and approximately 2.5 years of safety data for patients in Group 3.

Basal cell carcinoma

R2810-ONC-1620 (Group 1, mBCC) - A phase 2 study of cemiplimab in patients with advanced BCC who experienced progression of disease on Hedgehog Pathway Inhibitor therapy or were intolerant of prior Hedgehog Pathway Inhibitor therapy.

Rationale and objectives:

To further confirm clinical 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.

The primary objective of the study was to estimate the ORR for mBCC (Group 1) or unresectable laBCC (Group 2), according to central review, when treated with cemiplimab monotherapy in patients who had progressed on HHI therapy, or were intolerant of prior HHI therapy.

Study design:

This is an ongoing phase 2, non-randomized, 2-group, multicenter study of cemiplimab at a 350 mg dose administered IV Q3W in patients with advanced BCC who experienced progression of disease on HHI therapy, experienced a response no better than stable disease for at least 9 months or were intolerant of prior HHI therapy.

Study population:

The study has 2 groups. Group 1 is for patients with metastatic BCC. Group 2 is for adult patients with locally advanced BCC.

II.C.2 Other Studies in Post-authorisation Development Plan

Not applicable